SUMMARY

at the unequal distribution of the potential medical benefits which generated by genomics research could exacerbate current inequal- the provision of health care among nations are well-founded. h some progress is being made towards improving the situation, roblems remain, particularly in the areas of infrastructure, iological development, patenting DNA, benefit sharing, and the cial implications of large population data collections.

8. ETHICAL ISSUES IN GENETIC RESEARCH, SCREENING, AND TESTING, WITH PARTICULAR REFERENCE TO DEVELOPING COUNTRIES

Contents

8.1 INTRODUCTION

The coming genomics era will raise important ethical issues and challenges. These can and should be addressed in a manner that will allow the health benefits of this new era to be realized. Most of the ethical issues raised by genomics for developing countries are not new, but are found in other areas of biology and medicine. In particular, many of those discussed below, such as informed consent, confidentiality, and stigmatization and discrimination, are not unique to genomics. Nevertheless, even these familiar ethical issues require some specific consideration in the context of genomics and cannot simply be addressed by standard approaches in medical ethics for two reasons.

First, genetic information and potential genetic interventions are different in some important respects from most medical and health information and interventions, in many cases in degree and in others in kind. For example, since genetic information about individuals can be highly predictive of their future health, it has the potential both to stigmatize them and to be used by others such as potential employers and insurers as a basis for discrimination. These issues provide grounds for strong confi-

dentiality protections. In the different context of families, however, there may be reasons to put special limits on confidentiality, since genetic information about an individual is often equally relevant to his or her family members. In the reproductive context, interventions to prevent genetic transmission of serious disease to children often involve abortion which does not simply prevent the disease, as in other branches of preventive medicine, but prevents the birth of a child who would have the disease. At some point in the future it may become possible to manipulate the genetic inheritance of children not just to prevent disease, but to enhance normal functions. Both of these latter kinds of interventions are condemned by some as eugenic and will be addressed later in this section. The history of eugenics in the late 19th and the first half of the 20th centuries more generally casts a shadow over modern genomics and contributes to widespread unease over our expanding potential for genetic control of human nature.

The second reason why these ethical issues require distinct treatment here is the importance of the social context in which the issues arise; in particular, they may be significantly different in developing than in developed countries, as well as among different developing countries. The importance of this point cannot be over-emphasized. The appropriate uses of our new genetic knowledge and capacities, the potential for their misuse or abuse, as well as the kinds of responses needed to prevent such misuse or abuse, all depend critically on social, political, economic and cultural contexts. By way of illustration, in countries without strong cultural and legal traditions of respecting individual reproductive freedom, the potential for coercion of women's reproductive choices for eugenic or other reasons is magnified. In highly patriarchal societies where men traditionally make important decisions for family members, including their wives, women are again especially vulnerable to coercion in making reproductive choices and it will be more difficult to ensure their free and informed consent for genetic services. In countries with significant private health insurance, there is a potential for genetic discrimination by insurers that will not exist in those with a national health service available to all. The populations of very poor developing countries are especially vulnerable to economic exploitation by much richer developed countries or multinational corporations in genetic research or the development and use of genetic databases. Finally, low education levels in some developing countries and limited familiarity with genetic medicine or research present special obstacles to obtaining truly informed consent from the population.

A general feature of many developing countries is a lack of any well-developed regulatory apparatus to deal with either the scientific issues in genetic research and technology, or with the ethical, legal, and social issues (see Section 6). An important priority for many developing countries as genomics becomes more prominent in them should be to develop the necessary regulatory structures to address both the scientific and ethical issues. In some cases broad international guidelines should be created to help to guide the development of genomics and of country-specific guidelines in developing and developed countries. Some of this guideline development has already been done, but much remains to be done and WHO has an opportunity to play a leadership role here.

This Section begins by discussing two central ethical issues that any country should address before engaging in genetic research or initiating genetic screening and testing programmes: informed consent and confidentiality of genetic information to prevent discrimination and stigmatization.

8.2 INFORMED CONSENT

8.2.1 Principles

As a result of past abuses of research participants in many countries, the principle that subjects cannot be enrolled in research without their free and informed consent is well-established in international documents such as the Nuremberg principles and the Declaration of Helsinki, in the law of many countries, as well as in research practice. Unlike medical therapy where the goal is the patient's well being, the goal of research is generalizable knowledge and so there is a potential conflict of interest between the researcher and the research subject (Faden and Beauchamp, 1986). This warrants giving special importance to the informed consent of a potential subject. Genetic research involving human subjects is no different. The consent process employed when developed-country researchers undertake research in developing countries should be sensitive and responsive to local cultural and social beliefs and practices, and it should not violate international standards nor be one that would be ethically unacceptable in their own countries.

The principle, and even more the practice, of informed consent in medical therapy is less well-established and respected than in medical research in both some developed and developing countries. Paternalistic traditions in the medical profession, where it is assumed that physicians are acting for the welfare of their patients, are still powerful in many coun-

tries and result in inadequate informed consent practices. Nevertheless, it is increasingly widely recognized that competent patients should not receive either diagnostic or therapeutic interventions without their free and informed consent. Respecting patients' rights to give or withhold consent respects their self-determination and their right to bodily integrity. When countries implement genetic screening programmes, which by definition are directed at a specific population, individuals should not be included in these programmes without having given their free and informed consent. Even when the screening is only to establish epidemiological data, the informed consent of participants must be obtained.

In some cultural contexts that lack any strong tradition or practice of individual consent, it may be more common for community leaders to give consent for screening or research programmes in their community. While it is appropriate to respect these cultural practices and to seek the agreement of properly identified community leaders to undertake screening or research programmes, it should not substitute for securing the consent of individual participants as well. Research projects in developed countries typically require written consent, but in cultures in which there is reluctance for a variety of reasons to sign a written document, oral consent can substitute for written consent, as it often does for medical therapy that does not carry high risks.

8.2.2 *Genetic testing in health care and research*

Genetic testing is typically targeted at particular individuals at risk for specific disease. As in medical research, medical therapy, and genetic screening, it too should not be undertaken without first securing the individual's free and informed consent. The consent process should include pre-test genetic counselling concerning the condition being tested for, which should be followed by post-test counselling (Nuffield Council on Bioethics, 1993). This counselling is especially important when the level of understanding of genetics and its role in disease is low, yet capacities for high-quality genetic counselling are strained even in developed countries, and are extremely limited in many developing countries. As countries introduce genetic testing programmes, they should simultaneously build capacities for high-quality genetic counseling.

Experience in a number of countries has already demonstrated the potential for coercive pressures from government, society, or family members in genetic screening and testing programmes. For example, in some countries it is now mandatory to have a test for thalassaemia before getting married. While couples are often not pressured to act on the information, in some cases pressure is brought to bear. Health authorities may perceive that prenatal diagnosis for a disease like thalassaemia is effective and much cheaper than treating a child with regular blood transfusions for 20 or 30 years; consequently, pressure may be put on couples to undergo testing and to avoid marriage or terminate a pregnancy when necessary.

Coercive social pressures can also come from potential stigmatization of parents for not using genetic testing. For example, in some countries in which there is a high take up of prenatal diagnosis of thalassaemia, even in apparent absence of explicit pressure put on couples, those who decline testing and have a child with thalassaemia may be strongly stigmatized for doing so. Even when there are strong ethical reasons to prevent the birth of children with serious genetically transmitted diseases, respecting individuals' human right to reproductive freedom requires leaving them free to make their own informed choices. However, these coercive pressures on reproductive choices can be subtle and are often extremely difficult to prevent. Both regulatory and long-term education efforts will be needed to counter them.

When genetic testing services are not a part of universal health services, but instead are available only to those who can pay for them with private funds, the clearly inequitable result could be a concentration of genetically transmitted diseases among the poor in society; this would exacerbate inequalities in those societies by creating a genetic, as well as social and economic, underclass. When genetic testing and screening programmes are introduced in a country, they should be made a part of the universal health care services, available to all and not only in the private health sector where they will worsen health and other inequities.

There are several reasons why informed consent for genetic research, screening, and testing often has special importance in many developing countries. First, in many cases genetic tests are developed before any effective therapeutic intervention exists for those found to have a genetic risk. It is then especially important that individuals understand this fact as well as the potential longer-term psychological, emotional, and social consequences of learning of genetic risks in the absence of therapeutic means for eliminating them. This information can have profound effects on individuals' sense of identity and conceptions of themselves as healthy or diseased. There is also a potential for social misallocation of health resources if genetic tests come into wide use in the absence of cost-effective thera-

peutic interventions necessary to produce health gains for the population tested.

Second, when educational levels are relatively low and potential research subjects have limited familiarity with medical research, the informed consent process is essential so that they can have an adequate understanding of the research and their potential role in it before deciding whether to participate. In the case of genetic screening or testing, low educational levels in many developing countries mean that many potential participants will be relatively uninformed about the nature of the condition being screened or tested for, as well as about the possible implications and uses, both positive and negative, of the information obtained. This places special obligations on investigators or those carrying out genetic screening or testing to ensure that information is provided in a form that is understandable to participants, and appropriate to their educational levels and cultural context. Research is needed, in both developed and developing countries, about how best to provide relevant information.

Third, when only limited medical care is available in a country, participation in research may be the only effective means of obtaining it, creating coercive pressures to participate in the research. Especially in very poor countries, financial incentives to participate in research may also create undue pressures to participate.

Fourth, those performing genetic research in developing countries are often scientists from developed countries or large multinational pharmaceutical or biotechnology companies with research agendas different from the needs of developing countries. Substantial international consensus has developed that research should not be done in developing countries that does not have potential benefits for their populations. Genetic and other research in developing countries should be directed at health problems in those countries. To avoid exploitation, there must be reasonable assurance that the benefits of the research will be available at least to the research participants, and to the broader community in which the research is completed. There is considerable debate about what precisely this "reasonable assurance" responsibility requires; for example, what interventions must be available, from whom, to whom, for how long?, and so forth. The means by which this responsibility will be carried out should be worked out between investigators and representatives of the community in which the research will be done prior to commencement of the research, and should be detailed in the initial informed consent process. In general, there is a high potential for exploitation of relatively poor and uneducated

members of developing countries by outside organizations and corporations whose primary mission is not the health of members of those countries; a meaningful informed consent process is one means of protecting against such exploitation. Some ways in which this complex issue might be addressed are discussed in Section 7.4.4.

8.2.3 *Other approaches to regulating genetic testing, screening and research*

The informed consent process should not be the only means of regulating and controlling genetic research or the use of genetic screening and testing, however, especially in developing countries. Health ministries should develop formal structures for the evaluation of potential genetic screening, research or testing programmes to ensure that the programmes address local health needs in a cost-effective manner. These regulatory structures should also be charged with addressing, on an ongoing basis, the ethical, legal and social implications (ELSI) of genetic screening, research and testing programmes in the country, including the development of appropriate regulations.

Diseases whose cause is largely genetic represent increasing proportions of the disease burden in many developing countries, especially in those in which malnutrition and communicable disease are coming under control. In such cases genetic screening, research or testing focused on those diseases particularly prevalent in the area will often be a cost-effective use of public health resources. In less advanced developing countries where public health and health care resources are extremely limited, other resource uses directed at communicable diseases and basic public health measures may often have greater priority than most or all genetic services. Countries should not leave the introduction of genetic testing programmes to the private sector where profit potential may be the primary motivation and the testing may not represent a good use of limited health resources.

8.2.4 *Genetic databases*

Another form of genetic research in some countries is the development of health information databases (see Section 6.5). Some developing countries, or geographical areas within developing countries, represent desirable opportunities for the development of such databases when the population is relatively genetically homogenous from limited migration in or out of the area and from founder effects. These databases vary in the

extent to which data in them remain individually identifiable, though individual data are typically made non-identifiable to users of the database.

The databases are in some cases developed by public health authorities in the country, sometimes in partnership with private corporations as in the deCODE database in Iceland (Gulcher and Stefansson, 2000), and in other cases predominantly by private corporations. These databases raise a number of ethical issues, including profit sharing with the community from which the data are gathered (see Section 6), but here we focus on informed consent from individuals whose health information is placed in the database.

One central point of debate in the Icelandic project has been whether to employ an "opt-in" consent process, whereby individuals must explicitly consent to information about them being put in the database, or an "opt-out" process where, unless individuals object to information about them being entered into the database, the information will be included. In general, opt-out informed consent processes are not considered adequate for either medical research or therapy. Individuals should have to make a free and informed choice to participate before researchers can enroll them or before therapists can treat them.

In the Icelandic case, supporters of the opt-out consent process have relied mainly on the argument that data will only be drawn from existing medical records, no new genetic information will be gathered from individuals, and data will not be individually identifiable to the users of the database; data will be processed through a double encryption process. Of course, non-identifiability of participants in itself is not sufficient to justify opt-out consent since the results of most research are presented in a form in which individual participants are not identifiable. The database project in Iceland has generated some controversy, but seems to have strong public support and will be under the control of the Icelandic Government, who will grant an exclusive license to a private corporation to operate the database.

Presumed consent with an opt-out procedure should be adopted only with great caution and in special cases, since it is essentially the abandonment of the requirement that individuals must give their free and informed consent for research participation. Presumed consent is not a form of consent, as are written and oral consent, but rather represents a policy that individual consent is not necessary and that individuals will be included in the project unless they explicitly object.

A second important informed consent issue, both for databases and for other genetic research is whether health information or genetic material can be used for other purposes beyond those for which consent was originally given without obtaining additional consent for the new uses. As a general principle, uses of genetic material or information should not extend beyond those for which consent has been given. This problem is best dealt with at the time of the initial consent by specifying clearly the uses for which consent is given; in some cases the consent may be relatively open-ended, permitting as yet unanticipated uses in the future. But if consent is given only for specific and limited uses, then subjects should be recontacted and their consent obtained for any new uses of their genetic material or information.

8.3 CONFIDENTIALITY OF GENETIC INFORMATION TO PREVENT DISCRIMINATION AND STIGMATIZATION

8.3.1 Confidentiality and its appropriate limits

As genetics becomes increasingly integrated into clinical medicine, reproductive decision-making and public health, genetic information will accumulate about the genomes of individuals and groups. This information will often have a far-reaching impact on the individuals and groups in question, and if they are to cooperate freely in the development and use of this information they should have assurance about how the information will be used and who will have access to it (Rothstein, 1997).

Of course, even before the advent of modern genetics, health care systems have faced these issues with other non-genetic health care information about individuals or groups, including information about family history that often had similar predictive import to that of genetic information. In most countries such information is properly treated as confidential and not to be released to others without the patient's consent, although it can be released in therapeutic contexts on a "need to know" basis to others involved in the care of the patient. The legal and professional protections of the confidentiality of health care information vary from country to country and reflect cultural differences, but there is general international consensus on the practice of confidentiality. Does the prospect of increased genetic information pose any new ethical issues about confidentiality for health care and other systems in which that information will exist, in particular in developing countries?

One respect in which genetic information is different than other health care information, in degree if not in kind, is that it is typically not

just about a particular individual who has been screened or tested, but also involves other family members of that individual. Genetic information about a specific health or reproductive risk of a particular individual will often imply a similar risk for other family members. In cases of relatively isolated groups which are unusually genetically homogenous, information about individuals may have implications about the wider group, not just other immediate family members. Second, genetic information is commonly predictive of an individual's risk of developing certain diseases in the future. Sometimes the condition can be predicted with a high degree of certainty, such as with the thalassaemias, but more commonly the information will only indicate different degrees of elevation of risk, as with the breast cancer susceptibility genes, *BRCA1* and BRCA2 (see Section 3.4). The degree to which interventions are possible to reduce or eliminate the health risk also varies greatly.

There are several ethical grounds of the practice of confidentiality of health information generally, and they have implications for how genetic information should be treated in family contexts. First, and perhaps most obviously, maintaining confidentiality typically prevents various possible harms to the patient, such as discrimination in employment or insurance. Second, since the information is obtained only with the patient's consent and cooperation, the patient should control who has access to it. Third, the information is about the patient and so the patient has the greatest interest in it and in who has access to it. Fourth, the medical profession in most countries promises to patients, either explicitly or implicitly, that their medical information will be treated confidentially.

In the case of genetic information with important consequences for family members' reproductive choices or health, it is generally only the second of these reasons that justifies maintaining confidentiality by not providing the information to affected family members without the patient's consent. Providing the information to family members will typically not harm the patient, the information is equally about the family member who consequently has a comparable interest in obtaining it, and confidentiality need not be promised to patients in these circumstances.

Patients can have in such circumstances a moral obligation to provide such information to potentially affected family members, and many believe that it should be permissible at least in some cases for health care providers to do so as well, without the consent of the patient, if necessary. In implementing genetic screening or testing programmes in developing countries, health ministries and professional organizations should consider incorporating this limit on confidentiality to reflect the special feature of genetic information, emphasizing that it is typically about families, not just individual patients. Because there may be special circumstances, either individual or cultural, that may warrant not giving information to affected family members in particular cases, for example if doing so will likely lead to harm or violence to the individual, an institutionalized process should be established to evaluate individual cases of breaches of patient confidentiality without the patient's consent in order to inform affected family members.

8.3.2 *Discrimination and stigmatization*

While there may be reason to limit confidentiality in cases of affected family members, because of the special nature of genetic information, its typically greater potential for discrimination and stigmatization provides reason to develop especially strong protection for genetic information in other contexts before genetic screening or testing programmes are initiated.

As genetic information about particular individuals, and sometimes groups as well, makes it possible to predict individuals' future health problems with varying degrees of probability, the information is potentially valuable to individuals for the prevention of disease, for therapy for the disease, or for planning their lives when neither prevention nor therapy are possible. However, this predictive power makes the information also valuable for others who may use it to wrongly discriminate against or stigmatize the individual in many social contexts. Employers may use the information to deny employment to individuals who may have potentially expensive future health problems. Health insurers may use the information in risk-rated health insurance to increase insurance rates substantially or to deny insurance altogether.

Many of these risks can be expected to increase in developing (and many developed) countries in the future. Responsibilities to provide health care are being shifted from the public sector to the private sector in many countries, where private insurers make use of risk rating for health insurance. As a wider range of genetic tests become available and their cost continues to decline, the incentives and abilities of insurers to use this information to discriminate against individuals with risks of developing serious disease will increase. Since genetic risks are viewed by many, even if often incorrectly, as impossible to reduce or eliminate, they may be given unduly great weight in these contexts.

The stigmatization of people carrying genes creating risks for serious disease can often have serious psychological consequences, not just social consequences with respect to labelling as diseased or unhealthy an individual who remains healthy and who has not yet developed, and may never develop, the disease in question. Being labelled as having "bad" genes can have a variety of serious social and psychological consequences for individuals, and this stigmatization may be stronger and more common where the levels of education and understanding of genetics is low.

Perhaps the most serious worry about genetic discrimination is in health insurance. WHO and many other international and national bodies concur that access to at least a basic level of health care is a human right and a requirement of equity or justice. Basic health care services should be available to all people and not just to those with the ability to pay for them. Since health care services are often expensive, with individuals' needs highly variable and unpredictable, they are difficult to budget for and so are typically provided through some form of insurance; usually social insurance within a national health system, but increasingly in many countries, at least in part, by private health insurance. If individuals are subject to risk rating for health insurance, and increasing amounts of information become available to insurers about genetic risks, many people will face large differences in their health insurance costs from genetic risks; they will be denied health insurance, or be unable to afford it at all. This will seriously undermine the universal provision of health care.

There is a compelling ethical case grounded in equity for community rating of either social or private health insurance in order to spread the costs of individuals' health risks across the larger community. Moreover, genetic risks are a paradigm of risks that are morally undeserved and which should not affect people's cost of or access to health care. Even if individuals may be responsible for some health risks due to their behavior, which is itself problematic, there is no plausible sense in which they are responsible for their genome and the health risks it generates, that is, for their good or bad luck in the "genetic lottery." Rating health insurance by health risks, whether based on genetic or other factors, has the intended, though from the standpoint of the social purpose of health insurance, perverse effect of making it more difficult, or even impossible, for individuals to obtain health insurance who may need it the most.

Genetic screening or testing should not be introduced in a country without first having clear and enforceable legislation prohibiting the use of genetic tests for health insurance or the use of genetic information by

insurance companies in decisions to offer or deny health insurance, or in setting health insurance rates for individuals or groups. A similar ethical case can be made for not allowing use of genetic information in underwriting of disability insurance, at least for reasonable cover.

The ethical case against the use of genetic information in life insurance underwriting, however, is less clear. While individuals who learn that they have a serious genetic health risk should not be deprived of health insurance, they should not be able to amass large amounts of life insurance on the basis of serious health risks of which they, but not their life insurer, are aware. However, life insurance is not always used only for compensation in the case of death. For example, in some countries it is widely used as collateral for loans on a house, without which the rate of interest on the loan would rise substantially. In that context, denial of life insurance on the basis of genetic information results in unfair discrimination in access to housing.

Similar ethical concerns apply to the use of genetic testing by employers or potential employers. Current health problems that would prevent a person from carrying out the duties of employment, even when employers have made reasonable accommodations for illness or disabilities, can justifiably be used in employment decisions. But genetic conditions that constitute risks for future health problems should not be used to bar otherwise qualified people from employment. If and when they prevent the individual from continuing in employment, they can be dealt with appropriately. Nor should people be denied employment because their genetic condition creates a risk of high future health care costs to their employer when health insurance is provided through employment, since this is in effect to deny them both health insurance and employment on the basis of a genetic condition creating future health risks. As in the case of health insurance, countries should not introduce genetic screening or testing without first having clear and enforceable legal prohibitions of the use of genetic information in employment decisions.

In some countries there may be deeper concerns based on religious or other cultural views about the acceptability of genetic screening and testing, often because abortion is associated with the practices but sometimes even when it is not. Countries will make their own decisions about whether these practices are compatible with their particular culture, laws, religion, and traditions, and more generally about the limits they wish to impose on the use of new genetic knowledge and interventions. It is important that this deliberation and decision-making is as open, inclusive,

and democratic as possible. Especially because the potential future health benefits from genomics are substantial, societies should attempt to accommodate reasonable differences among their members on these issues.

8.4 GENDER ISSUES

In societies in which there is deep-seated bias and discrimination against women, genetic information can be withheld or used in ways deeply prejudicial to them (Rothenberg and Thomson, 1994; Davis, 2001). In strongly patriarchal societies, common in many countries, it is especially important to ensure that women are not subject to coercive pressure from within the family or community to pursue or not to pursue genetic testing. Publicly funded awareness and counselling programmes should be established to support women in making decisions about genetic testing on the basis of their own needs and interests. In addition, the consent process should include means to try to identify and prevent any form of coercion. In some countries, similar problems regarding coercion for sex selection of the fetus have arisen which have often proved difficult to prevent (see below). This underscores the special importance of public responsibility for supporting and promoting women's rights in countries without strong traditions of respecting the reproductive freedom of women and with substantial gender inequalities. If this responsibility is not carried out, the introduction of genetic testing has the potential to reduce rather than enlarge women's reproductive freedom. As new options arise, they will not be able to make free and uncoerced choices.

Genetic information can also be used to discriminate or stigmatize in the context of other social practices. For example, in the case of arranged marriages families may seek genetic information about potential spouses of their children. This information can make women unmarriageable if they are known to have genes for serious diseases, or it can subject them to physical and other harms if they give birth to children with diseases for which they are deemed responsible. In countries or cultures with strong discriminatory practices against women, special measures will be needed to protect them against stigmatization or discrimination on the basis of genetic information. Governments and other organizations should undertake an assessment of the special risks to women (and ethnic or cultural groups) in their countries from potential disclosure of genetic information before genetic research, screening, or testing goes forward, so as to limit the harms to those taking part in these programmes.

In many developing countries, abortion services are either not widely available or are prohibited by law except in a very narrow range of circumstances. Post conception genetic testing is typically undertaken with the intent to abort the pregnancy if the fetus is found to have the condition for which it was tested. In the absence of any therapeutic options for the fetus or the child after birth, and where ending the pregnancy is typically either not possible, or possible only under illegal and unsafe conditions, it is problematic whether public resources should be devoted to post conception genetic testing programmes. Moreover, better educated women in such countries are often able to obtain abortion services, despite their illegality, either within their own country or abroad. Genetic testing programmes in such circumstances can be harmful to women who lack the means to act safely on the information obtained.

Genetic information can also be a means to carry out sex selection and thus prevent the birth of female babies. Non-therapeutic sex selection by amniocentesis using chromosomal analysis, or later in pregnancy using sonogram technology, to determine the sex of the fetus, has received public attention and governmental response in several countries. In India, the use of sex selection to avoid the birth of female babies has had a substantial effect on the sex ratio of the population in some areas of the country. The Indian case is instructive because it displays some of the features that can make selection of offspring for non-therapeutic reasons ethically problematic. First, being female is not what might be called a natural disadvantage (indeed, it is a biological advantage in terms of longevity), but is a disadvantage only in the context of substantial prejudice and discrimination against women. Likewise, being male is largely not a natural or biological advantage, but a social advantage only in the context of these unjust social practices. It is the prejudice and discriminatory practices that should be changed, rather than preventing the birth of female babies which can have the effect of reinforcing unjust discrimination against women. Second, a stable sex ratio is a public good which among other things affords members of a monogamic society a reasonable chance to marry; a society can justifiably intervene in even rational individual choices to select for certain traits when doing so is necessary to protect an important public good.

For these reasons, but mainly because it was perceived that sex selection reflects a societal bias against female children, the Indian Government has taken a variety of steps to prevent selection against and abortion of female fetuses, although legal prohibitions have not been strongly enough

enforced to be effective. Professional associations could often do more to regulate their members in this regard and the World Medical Association should exert pressure on its member associations to put more effort into controlling individual physicians' conduct in participating in sex selection.

Recent advances in sperm-selection technology, or "semen sexing," allow the separation of X- and Y-bearing spermatozoa so that fertilization can yield either female or male offspring, respectively. As this procedure advances, sex selection before conception is becoming a realistic option at relatively low cost. Sex-linked diseases can then be prevented before an embryo is conceived and without aborting the embryo or fetus. However, sperm selection can also be used for sex selection that does not prevent disease, but only reflects various social prejudices against women.

Sex selection is a result of deep-seated, entrenched beliefs and values in societies that have long histories of subordinating and devaluing women, and long-term public education strategies will be needed to combat them effectively.

8.5 EUGENICS

The specific ethical issues discussed above, informed consent, confidentiality, and discrimination and stigmatization, are all coloured by broader concerns about eugenics (Paul, 1995). The very power of the genetics revolution for our understanding of the genetic bases of human nature and for prevention or treatment of disease also gives rise to serious concerns in many people. For along with the understanding of our genetic inheritance and the role genes play in determining phenotype may come the potential to control and change human nature. Moreover, the belief that the genetic pool or inheritance of the population could be improved is not new to the Human Genome Project and contemporary genomics. From the 1870s to the 1940s, eugenics movements existed in many countries, and culminated in the Nazi eugenics programme whose unprecedented evils permanently discredited eugenics and largely ended the eugenics movement.

Nevertheless, it is important to understand what the source of the immorality of these historical eugenics movements was in order to avoid their mistakes in the contemporary genomics era. The charge that a particular practice is eugenic is often used to end discussion of the practice without making clear either what is meant by calling the practice eugenic or what precisely makes it wrong. Yet the core concern of eugenicists for human betterment through selection is considered by many people not in itself immoral, although eugenicists' means of achieving it were often

unethical. Of course these historical movements were complex and varied in many ways, but several key features that led to their deeply immoral outcomes can be identified, and must be avoided in contemporary genomics.

One important feature of eugenics movements was a concern with what they believed to be a degeneration of the gene pool, which they sought to reverse by encouraging the "fit" to increase their reproduction and discouraging the "unfit" from reproducing. But the fit and unfit were commonly determined by racial, class, and national prejudices and stereotypes that still persist today in much of the developed and developing world, and that must be avoided in our use of the powers of the new genetics.

A second feature was belief in the heritability of behavioural traits and a biological basis for social problems, and a biological remedy for them. Reproduction was thus seen as having social consequences and hence was a legitimate matter of social concern, which often led to coercive control of reproduction by the state in support of eugenic goals. Between 1900–1910 many thousands of women in countries such as Sweden and the United States were involuntarily sterilized or otherwise coerced in their reproductive choices. Some recent policies in a few developing countries have also had coercive eugenic components. With greater capacity to control reproductive choices and outcomes now, individuals', and in particular women's, right to reproductive freedom must be properly respected.

The eugenics movements also failed to recognize adequately the concept of value pluralism, that is individuals', cultures', and societies' very different conceptions of what constitutes a good person, way of life, and society. As a result, eugenicists tended to favour people like themselves and to be intolerant of different personal and social ideals. With greater control over heredity and the kinds of people there will be, tolerance of different values and ideals will be essential, while also publicly debating appropriate limits on genetic selection.

Some have seen statism, and an active role of the state in reproductive choices and policies, as one of the fundamental wrongs of the eugenics movements. Although state involvement certainly increased the magnitude of the moral wrongs and even horrors of many eugenic programmes, state involvement is not necessary to perpetrate eugenic wrongs, and such concerns cannot be fully alleviated by keeping the state out of reproductive choices and policies. People can suffer harm from the cumulative

effects of uncoerced eugenic choices of individuals, for example in stigmatizing them with particular genetic conditions or leading to discrimination against them in employment or insurance. However, the concern about statism underscores the fact that reproduction always takes place in a social context of unequal political, economic or social power. This hierarchy of power will almost certainly impinge to some degree on practices to achieve eugenic ends. Critical questions about any such practices will therefore include who has the power to select, and who defines such key notions as "better," "defective," or "healthy." The case of sickle cell disease is a useful cautionary reminder that the so-called "bad" gene for this disease is in some circumstances beneficial in protecting its carriers against malaria.

Finally, at the heart of many ethical concerns with eugenics are issues of justice and the sacrifice of some individuals' interests for the sake of some greater social good. Many historical eugenics movements and programmes identified an "underclass" whose genes were not wanted and who, through involuntary sexual segregation, stigmatization and denigration, sterilization, and even murder, paid a heavy and unjust price. The inequalities of social and political power noted above to a great extent made these injustices possible. A major task for contemporary genomics is to ensure that the interests and rights of individuals are not unjustly sacrificed for the benefit of some greater social good.

Some have seen the difference between earlier eugenics movements and contemporary clinical genetics in the different perspectives of each. The eugenics perspective was social, a public health focus on the gene pool and the health and welfare of the population. By contrast, the focus of clinical genetics is typically individual, providing a service to meet the desires of individual parents. But the population perspective is not in itself ethically suspect; there seems nothing ethically wrong, for example, in programmes to eradicate smallpox or polio, or genes that cause serious disease, from the population. The question is rather whether the social goal is ethical and pursued in a just manner.

In seeking to reap the fruits of contemporary genomics the moral failings of the historical eugenics movements must be avoided: race, class, and national prejudices; failure, particularly through state coercion, to respect individuals' human rights to reproductive freedom; intolerance of different views of a "good person," life and society; and abuse of inequalities of power and unjustly sacrificing the rights and interests of individuals for a supposedly greater social good. However, practices should not be dismissed as ethically unacceptable simply on the basis of loose charges that they are eugenic. There is too little unambiguous meaning to that charge and it should be replaced with a clear account of what specific features make the practices wrong.

8.6 THE DISABILITY RIGHTS MOVEMENT'S CHALLENGE TO GENETIC SCREENING AND TESTING

A serious challenge to genetic screening and testing programmes has been raised by members of disability rights movements in many countries (Parens and Asch, 2000). They argue that these programmes do not share the traditional medical goal of preventing or treating disease in individuals, but instead seek to prevent the existence of people with disabilities. Prenatal screening or testing is typically done with the goal of identifying potential parents at risk of genetically passing on serious disease, or identifying an affected fetus so that the pregnancy can be terminated. This is criticized as eugenic, replacing "defective" with "non-defective" individuals, rather than providing therapy to benefit existing individuals. Of course, if replacement were to involve killing people, then there is no dispute that it would be deeply wrong, but here the goal is to ensure that healthy instead of unhealthy people will be born.

Why do many in the disability rights movement view this form of replacement as unethical? They have raised several points. First, the disadvantages of most impairments are due mainly to the failure of society to accommodate disabled persons. Second, typical views about the lives of disabled people are often based on prejudices, stereotypes, and other false beliefs, with the result that disabled people themselves rate their own quality of life higher than the non-disabled rate it. This is in part because people are often able to adjust to their disabilities through processes of adaptation: new learning and skills development that improve their functional performances; coping, adjusting expectations to reflect impaired abilities, thereby increasing satisfaction with their accomplishments; and accommodation, changing life plans to better fit their impaired abilities. Third, only a very few genetic disorders, such as Lesch-Nyhan or Tay-Sachs disease, are so severe as to make the lives of people who have them perhaps not worth living. The vast majority of conditions for which genetic testing is now and will, in the future, be possible are not so severe; they leave an affected individual with a life that from the individual's perspective is clearly worth living, a life valued by the person whose life it is. Fourth, disabled people have made many positive contributions to the lives of others

and to society. Finally, some worry that genetic screening and testing are part of broader undesirable pressures towards normalization, conformity, and intolerance of difference.

How do defenders of genetic testing and screening respond to the disability rights movement's critique? First, although the social disadvantage of many impairments could and should be reduced by changing society to better accommodate people with disabilities, even after doing so there will often still be some residual disadvantage for people with serious conditions. This may be particularly true in countries where resources available to accommodate persons with disabilities are limited. Second, the process of adaptation is typically burdensome and costly for disabled people, and often only partially successful, again, particularly in countries where the availability of health care and rehabilitative services is severely limited. Third, even though some people with disabilities adjust sufficiently to give them as good or even better quality lives than non-disabled people, whether this will be so cannot be known for any individual at the time of genetic testing. So long as a particular disability is a disadvantage for the entire class of people with it, it is reasonable to try to prevent it. Fourth, the process of coping can be ethically problematic when it involves acceptance of a significantly limited life. Though a person may through coping remain satisfied with their life, the life itself may remain significantly limited and diminished; again, satisfaction with one's life as a result of severely limited prospects for improvement is not an adequate measure of how good the life is. Finally, to the extent that treating and accommodating disabilities imposes significant costs and burdens on caregivers as well as on society as a whole, society can reasonably seek to prevent disabilities in order to avoid those costs, particularly in developing countries where resources are often substantially limited. Each of the points made by disability advocates noted above is valid and important. Defenders of genetic testing argue that there remain, nevertheless, good reasons to attempt to prevent serious disabilities through genetic screening and testing.

Disabled people often make another argument against using genetic testing and screening to avoid the birth of disabled individuals. They see society's message in supporting genetic testing for the conditions they have as being that it would have been better if they had never been born, a message that they and others quite understandably reject. Supporters of genetic testing argue that seeking to ensure that children will be born as healthy as possible need not have this message and is not in conflict with recognizing the full and equal moral status of disabled people, including their

right to health care and other services to meet their needs. In this view, the message of genetic testing is directed at the disadvantage or suffering that serious disease or disability can cause, not at persons with the disease or disability. The message is that it would be better if children were born healthy and without the disease; the message is directed at the disability, not at people who have the disability. The desirability of preventing serious genetically transmitted disabilities has no implications for how people with those disabilities can or should be treated, and, in particular, does not justify their mistreatment in any way.

The case for genetic testing and screening to prevent genetically transmitted disabilities may be even stronger in some developing countries, where they often carry greater stigma and can constitute more serious disadvantages because of more limited resources available to treat or accommodate them. The prevention of serious disease through genetic screening or testing appears to many to be a legitimate public health goal, just as the goal of reducing or eliminating serious communicable disease is not an unethical eugenic practice.

8.7 NONTHERAPEUTIC GENETIC INTERVENTIONS: GENETIC ENHANCEMENTS

Historical eugenics movements sought to improve the gene pool principally through encouraging selective breeding. In the modern genomics era the possibility will exist in the future, though how far in the future is unclear, for the exercise of some control over individuals' genetic inheritance not just to eliminate disease, but to enhance normal traits (Parens, 1998). Some have condemned any nontherapeutic use of genetics to select and control the genetic inheritance of children as eugenic and unethical; they support absolute bans on all such uses. Others have taken a more measured position that allows for the possibility of genetic enhancement, if done within specific ethical limits.

Some consider human reproductive cloning a form of nontherapeutic enhancement. It is a point of consensus, even among those who may otherwise disagree about whether human reproductive cloning could ever be ethically acceptable under any circumstances, that at the present time its risks are far too great to permit the practice to take place (see Section 8.8).

Genetics now provides little evidence of links between specific genes and important behavioural traits, but work in behavioural genetics does support a significant genetic as well as environmental contribution to many behavioural traits. While significant genetic enhancement is still a

hypothetical possibility and by no means a near-term prospect, either in developed or developing countries, we address it briefly here because it has been a significant source of public concern about the potential for misuse of new genetic knowledge and powers. If at some point in the future it becomes possible safely to enhance, for example, individuals' memory, intelligence, or immune system, doing so would likely be beneficial to almost everyone in most social contexts. These traits are "all purpose means," useful in nearly any plan of life. Any enhancements of children undertaken by their parents should be of traits like these. Enhancements of specific traits should not be undertaken if they would substantially narrow a person's opportunity when an adult autonomously to choose his or her own way of life.

Some object to any possible use of genetic interventions to select for or to shape and enhance normal traits as "playing God" an improper practice of seeking to design one's children. However, it is hard to see why trying to select against and to intervene to prevent the genetic transmission of disease is not equally playing God, though most people do not object to it in principle. Moreover, parents in nearly all societies are considered to have a responsibility to use a variety of environmental means to help their children develop and enhance their capacities, and they typically have substantial, although not unlimited, discretion in how they raise and shape their children. For example, parents have a responsibility to have their children vaccinated against a variety of diseases; if it became possible instead to use genetic means to enhance their children's immune systems against disease it is hard to see why it would, in principle, be wrong to do so. Of course, sometimes the effect of vaccinations is only for a limited period of time, whereas germ-line genetic interventions would affect future generations as well as the individual. While germ- line interventions cannot be ruled out as always unethical, their greatly increased risks mean that they should not be undertaken until the technology involved is sufficiently developed to provide a clearly favourable risk-benefit ratio (see Section 8.8). In general, interventions to prevent or treat serious disease will have more favourable risk-benefit ratios than most enhancements of normal functions.

It would be a mistake to believe that genetic interventions would change a child's essential identity in some deep way, whereas environmental interventions only bring out a fixed identity that is already present. There is no fixed phenotype that environmental efforts merely bring out; rather a range of phenotypes are possible, according to the different environments that parents might provide. Likewise, particular genetic interventions would also develop the phenotype in a particular direction. It is the nature and goal of the intervention, not whether it is genetic or environmental, that determines its ethical acceptability.

There are a variety of reasons to restrict who could offer genetic enhancements to parents for their children. As noted in the section on eugenics (Section 8.5), concerns about power inequalities are ever present and if governments were to attempt to employ genetic enhancements the potential for abuse — such as enhancements that might have social benefits but not be of benefit to the individual — increases substantially. However, all enhancements of normal function by governments cannot be ruled out in advance as ethically unacceptable; for example, many governments now fluoridate their water supplies in order to enhance their citizens' capacity to resist tooth decay. This enhancement is not ethically problematic merely because it is undertaken by government rather than individuals.

Societies have a moral obligation grounded in equity or justice and human rights to ensure access to health care for their citizens. A fundamental part of the moral importance of health care is its role in maintaining normal function, and in turn helping to secure equality of opportunity for persons that serious disease and disability can undermine. Genetic enhancements of normal function, on the other hand, do not serve justice in this way and if and when they become possible, will almost certainly not be regarded as part of the social obligation to provide health care to all members of society. Instead, they will likely be both available on an ability-to-pay basis, and generally expensive.

This means that enhancements would be available to the rich and not to the poor — the rich would be able to confer on their children not just social advantages, as they do now, but genetic advantages as well. The result could be a substantial widening of inequalities between developed and developing countries, as well as of inequalities within societies between the well-off and the worse-off. Particularly in many developing countries, where there are often very great inequalities between a very small, very privileged minority and a very poor general citizenry, the potential for widening inequalities is substantial.

This is perhaps the greatest ethical concern about possible future capacities to use genetics to significantly enhance important normal human functions — the unfairness of further widening already unjust inequalities of opportunity and well being between the rich and the poor.

The non-therapeutic use of genetic technology for enhancement of normal function may not be inherently unethical, but it raises a number of ethical concerns that must be addressed if and when it becomes possible.

8.8 GENE THERAPY, STEM CELL THERAPY AND HUMAN CLONING

Current approaches to research in human gene- or stem cell therapy are outlined in Sections 3.9 and 3.10, and the problems of regulation of work of this kind are discussed in Section 6.7. These rapidly moving fields are raising a number of ethical issues. Although the issues arising from gene therapy have been widely debated, and there is a considerable degree of agreement about how they should be handled, the position regarding stem cell therapy and its relationship to human reproductive cloning is still in a state of flux.

The distinction between somatic-cell and germ-cell gene therapy is described in Section 3.9. Somatic-cell gene therapy does not raise any fundamentally new ethical issues because, in principle, it is little different to organ transplantation or other therapy. Thus work in this field is based on the ethical principles applied to any form of human experimentation or therapy. Germ-cell gene therapy is different in this respect, principally because it has the potential to alter the genetic make-up of future generations, which would have had no input into the decision-making involved. However, as discussed in Section 6.4, research into human germ-cell gene therapy is prohibited in most countries, mainly on the grounds that since so little is known about the dangers of this procedure, and because there have been so few successes in somatic-cell gene therapy to date, the risks are too great at the moment to allow research in this field to proceed. If and when somatic-cell gene therapy is developed to the stage at which it is both effective and safe, and if there are severe genetic diseases which could only be cured by germ-cell therapy, the ethical issues of this approach may have to be revisited. If extensive animal studies were to show that it is effective, it is difficult to see why it would raise major ethical issues if used to eradicate a lethal genetic disease from a family; some would not even rule out the possibility of germ-line enhancement in the future.

The ethical issues regarding human embryonic stem cell research directed at cell therapy are more controversial. As pointed out in Section 3.10, although a great deal of research is being directed towards obtaining stem cells for therapeutic purposes from different adult tissues, human embryonic stem cells are currently the only cell populations which have

unequivocal potential for developing into the wide range of different adult tissues required for organ repair. Because of the potential of this field for treating a large number of intractable diseases of later life, it has been argued that there is a strong case for pursuing research directed at the properties of human embryonic stem cells. This raises important and complex ethical issues relating both to the moral status of human embryos and to the relationship of the different manipulations that might be used in this work to genuine human reproductive cloning.

The ethical status of human embryos has been widely debated and is controversial (Robertson, 2001). An important distinction revolves around whether objections to research on embryos rest on rights-based or symbolic grounds. Those who view the human pre-implantation embryo as a full person with rights hold that its intentional destruction is equivalent to murder. Although many religious groups and others follow this line it conflicts with other widely held philosophical and moral views which hold that status as a person requires further development, such as at least a nervous system capable of sentience or even self-consciousness. The first sign of the presence of a nervous system is observed at about 14 days of development with the appearance of what is called the primitive streak. Even if lacking rights, the symbolic status of the embryo as the early stage of human development may create ethical issues in how it is treated. Based on these distinctions between rights and a symbolic view of the embryo, some countries, the United Kingdom, for example, have permitted research for specified purposes on embryos of less than 14 days development. Other countries have placed different limits on research on human embryos or banned it completely.

A second set of complex ethical issues in stem cell research arise from the practical problems of its application for organ therapy. As pointed out in Section 3.10, while methods may well be worked out to direct human embryonic stem cells to differentiate into particular cell or tissue types for transplantation and therapeutic effects, since these cells will not be derived from the patient they may well be rejected by the patient's immune system. In this case, one strategy might be to use the patient's nuclear DNA to create an embryo from which embryonic stem cells compatible with the patient could be derived. This would necessitate the transfer of nuclei from the patient's cells into an anucleated egg which would then be activated so that it grew to an early embryonic (blastocyst) stage. This is, in effect, an early step in human cloning, though, of course, it does *not*

amount to true reproductive cloning unless there is the intention of introducing the embryo into a uterus.

This type of research raises a number of ethical issues. First, it would be necessary to create or otherwise obtain large numbers of human embryos which would be destroyed in the process of becoming recipient cells for the nucleus of patients who were to be treated. This would certainly raise ethical problems for those who believe that human embryos should not be destroyed. Even those who accord human embryos some symbolic status often accept the use of embryos "left over" from in vitro fertilization procedures and that would never be implanted. More controversial still is the creation of embryos solely with the intention of destroying them in order to produce cells to be used for activating adult nuclei. Undoubtedly other ethical issues will arise if this field continues to develop. The major problem will be how to obtain sufficient eggs required if therapeutic cloning becomes of widespread clinical value. Certainly this will exceed the numbers that are generated as part of in vitro fertilization. Would it be ethically acceptable to ask, or even pay, unrelated women to undergo repeated cycles of hormone treatment and egg retrieval for therapeutic uses? Would it be acceptable to obtain human eggs from cadavers or aborted fetuses? Even more controversially, would it be acceptable to use bovine eggs in which to develop human nuclei?

Those who do not view early embryos as having inherent moral status that forecloses their destruction may find no significant ethical barrier to obtaining human embryonic stem cells from early pre-implantation embryos for their use in research or therapy. Provided the distinction is maintained between therapeutic and reproductive cloning it may be reasonable to continue to explore different possibilities for generating sufficient eggs necessary for the therapeutic applications of this field. But if embryonic stem cell replacement therapy becomes safe and effective, there will be ethical issues related not just to the supply of eggs, but also to access to treatment for those who would benefit from these potentially revolutionary but extremely expensive forms of therapy.

A second ethical concern is that stem cell therapy, if it were perfected, might lead to genuine reproductive cloning by the replacement of an anucleate egg containing an adult nucleus in the uterus. But there seems little reason to believe that it is necessary to forgo the great potential benefits of therapeutic cloning in order to prevent human reproductive cloning. A much more reasonable position, reflected in both the Council of Europe's Convention on Human Rights and Biomedicine and

UNESCO's Universal Declaration on the Human Genome and Human Rights, is that the line between therapeutic cloning and reproductive cloning is quite clear and that reproductive cloning can be prohibited without impeding cloning for therapeutic purposes. It is unfortunate that the term "therapeutic" cloning has been used to describe work in this field (Vogelstein et al., 2002). While it will undoubtedly generate technology which could be misused for human reproductive cloning the distinction between the two is absolutely clear and would provide no problems for appropriate legislation.

Currently, there is a near universal consensus of opinion that the risks inherent in any attempt at human reproductive cloning at the present time would make doing so clearly unethical. Many also believe that human reproductive cloning would be unethical under any circumstances and that there is no ethical or medical basis for pursuing work on it. This view has been stated by WHO, and many countries have made it illegal to pursue work directed towards this end, or are in the process of doing so.

8.9 SUMMARY

The ethical issues arising from the applications of genome research are extremely complex and constantly changing. But although they present particular problems for different societies depending on their religious beliefs, social structure and cultural practices, they can be based on broad principles which are relevant to every society. Hence there is a major requirement for international leadership in developing a broad framework on which individual countries can develop their own codes of ethical practice as this field evolves in the future.