**GENETIC SCREENING**

**Prior Viewing Recommended**
Video "Genetic Screening"  XMV 55984

**Introduction**
Children are healthier than they used to be. The death toll in the USA around 1900 was 1:40, by 1980 it had dropped to 1:1500. But as the death toll from infectious disease drops, the proportion of children with genetic diseases admitted to hospital is rising. We all possess our share of mutant genes and the Human Genome Project, to be completed by the end of this century, will enable us to identify a very wide range of genetic defects.

Genetic screening is defined as "a search, in an apparently healthy population for those individuals with genotypes that place them or their offspring at high risk of disease". Foetal screening by amniotic examination is feasible at the fourteenth week and chorion villus sampling (CVS) at even the eighth week, but CVS seems very unreliable and was given up at the Foothills Hospital in 1989. Both false positive results and false negative results are known to have been reported.

The history of genetic screening to date shows that it has been successful in alleviating the symptoms of one disease (PKU), and in providing useful genetic counselling for another (Tay-Sachs) but has had no positive results in reducing the incidence of Sickle Cell Anemia. The last two diseases could, if genetic counselling were successfully followed over sufficient generations, be eliminated. This would be an example of negative eugenics - the improvement of the race by the elimination of the unfit. Newly discovered tests for Cystic Fibrosis and Fragile X syndrome are raising moral problems to which no solution has yet been found. And on the horizon looms the challenge of positive eugenics - the improvement of the race by selecting desirable qualities.

A brief history of the application of genetic screening to PKU, Sickle Cell Anemia and Tay-Sachs disease follows.

**PKU**
Phenylketonuria (PKU) is a recessive genetic disease caused by the body's failure to oxidize phenylalanine to tyrosine, because of a defective enzyme. If the disease is not treated early, brain damage may occur leading to mental retardation... The carrier of the defective gene is not affected. It is estimated that 1:60 carry the defective gene, hence the chance of both parents being carriers is 1:3600. Where both parents are carriers, there is a 1:4 chance that a child will be double recessive. The incidence in the USA is 1:40 000 births.

The symptoms can be suppressed by a diet of a special flour and special milk to keep the phenylalanine low. It becomes harder to enforce as the children get older and more independent; on the other hand, there is some evidence that, as children grow older, the brain is less susceptible.

Heel puncture for newborn infants is now routine. A drop of blood so obtained is treated with bacteria that grow faster when phenylalanine is in excess which
indicates PKU. The test is simple and accurate and the treatment is effective. The success of this procedure seems to have engendered a "screening mentality" so that a search is on for other diseases that might be attacked through screening. Sickle cell anemia was one of the first.

**Sickle Cell Anemia**

Sickle cell anemia gives partial protection against death from malaria and hence, through natural selection, it has spread in regions where malaria is, or was at one time, endemic, such as West Africa and the certain marshes in Greece. From Africa it entered the United States through the slave trade. In Greece, the former fisher folk of the marshland are now farming the dried up lake bottom. One child in 50 gets sickle cell anemia. In both the USA and in Greece medical teams attempted to screen the adult population of prospective parents in order to advise them on their chances of bearing children with the disease. In Greece, the only result seems to have been the stigmatization of some women carriers.

The test for sickle cell anemia on adult subjects cannot clearly distinguish between those having "sickle cell trait" i.e. carriers having one good working copy of the gene, and those who have two defective copies. Moreover, amongst those with two defective copies, the expression of the gene varies greatly: some people being very ill and others hardly troubled. The explanation of the test results to the parents therefore presents severe problems, particularly in a population without scientific sophistication.

Nevertheless, under the pressure of activists who claimed that the African-Americans were being discriminated against, screening was introduced for African Americans in the 1970s. It was a failure and generated much ill feeling. Carriers were banned from certain jobs such as aircraft pilots and had their insurance premiums raised.

Tests for sickle cell anemia in foetuses are now available through amniocentesis but are not yet routine.

The problem is greatly exacerbated by race. Only "black" people were to be tested but ordinary medical practice has shown that "In urban centres in the United States, nearly ten percent of patients with various sickling disorders identify themselves as "non-black"." Patients with sickle-cell disease range from individuals with blond hair and blue eyes to those with dark skin and curly black hair.

**Tay-Sachs Disease**

One in thirty Ashkenazi Jews in the USA is a carrier of Tay-Sachs disease. At 3 months a baby with the disease appears normal, but they inevitably die at 3 or 4 years.

A pre-natal blood test using amniocentesis is voluntary, accurate and reliable. The major difference from the sickle cell campaign was that the people understood what they were being tested for and were prepared to abort a diseased foetus. Although genetic screening has prevented the birth of 200 affected children it has probably led to the birth of 500 healthy children who would not have been risked had the parents already had a Tay-Sachs child. However, I see no evidence that the procedure is leading to the reduction of incidence of the defective gene in the population.
**Future candidates for screening**

**Breast cancer**

A gene dubbed BRCA1 plays a major role in the inherited forms of cancer of the breast and ovary (most breast cancers are sporadic, not inherited). The test for BRCA1, when it is ready, will be the first to identify such large numbers of people at high risk for a comparatively common disease - long before their symptoms develop. In both inherited and sporadic breast cancers, the normal copy of the chromosome region that contains BRCA1 is missing from cells, leaving only the copy that contains the altered form. The difference is that in the inherited form the normal copy has never been present. Unfortunately, the options open to a woman identified as being at risk range from early mammography to radical mastectomy.

**Cystic Fibrosis**

In 1989 researchers at the University of Toronto and the University of Michigan pinpointed the tiny genetic defect that causes CF to a gene on chromosome 7. It later transpired that many different mutations can affect this gene and the mutations vary in incidence with race and region. In Britain, more than 85% of CT cases are accounted for by four mutations. In parts of southern Europe as many as 60 mutations account for less than 75% of people with the disease. Screening using 22 different probes detected only 58% of the mutations in the gene among "Hispanic" people with cystic fibrosis. Commercial labs in the United States typically advertise tests on between 6 and 32 mutations. These data indicate that genetic screening for CF is likely to be fraught with difficulty.

CF was regarded as a test case for the application of gene therapy - the introduction of working genes into the body by means of a viral vector. Six years later, the news is not good. Treatments for CT have scarcely benefited patients. In general, inserted genes reach only a tiny portion - maybe 1% - of the target cells. Even those genes that reach their destination work inefficiently, producing too little protein for too short a time to benefit the patient. Patients' immune systems can react badly to the viruses used for delivering the genes; they develop antibodies which destroy the second dose. However, Ron Crystal of the Cornell Medical Center is still optimistic. He says they have learned that they can deliver the genes safely; now they need to get a long, high expression of them.

**Against screening for CF**

Arguments raised against screening for CF, mainly by parents of afflicted children, have some points in common with those of the Finnish disabled advocacy groups, described below, especially with regard to the possible stigmatization of carriers. But they also have their own particular concerns. As we saw above, the mutation picture is very complicated and therefore only a probabilistic diagnosis can be given. Fifteen percent of the mutations cannot be detected at all. The lay person (like many scientists!) has difficulty with the concept of probability and the communication of the test results is consequently very difficult. False positives occur and will cause unnecessary stress during pregnancy. Moreover, the demand for screening is not overwhelming. Many parents do not consider it a serious enough condition for drastic measures; many, when informed of the risks, decide to do
nothing; some would rather not know. To crown it all, there have been cases of positive identification in which neither parent has a mutant gene. Suspicion naturally falls on the paternity of the child although the situation could be explained by a new mutation. This has disruptive social effects.

**Fragile X syndrome**

Blood from newborns could be used to screen for Fragile X syndrome, the most common form of inherited mental retardation. It is caused by a mutation on the X chromosome which prevents the body making a protein called FMRP. Boys with the mutation are certain to be mentally retarded, but only 65% of girls. Picking up the affected males is now easy, but it is hard to interpret the results in girls since they have two X chromosomes. To use the test on girls would "cause too much anxiety". Ethicists argue that the person screened should receive some benefits from the result. The families would benefit from knowing. Mothers might decide to have no more children; affected children would not be penalized as "lazy"; girls might get special schooling.

**Legal and Moral Aspects**

Many fears have been expressed that successful voluntary genetic screening campaigns would eventually lead to coercion. One might ask why not? "Our autonomy as adults to do what we wish, even about ourselves, is not unlimited..." On the other hand, there seems to be no justification for screening if nothing can be done.

There is ambivalence about the use of pre-natal testing. What are the rights and duties of the parents? Do they have the moral right to bring into the world a child whom they know will be diseased? Dr. Joe Fletcher, theologian and moral philosopher, says it is always unjust and therefore immoral deliberately or knowingly to bring a diseased being into the world. It is always wrong to victimize third parties. Genetic defects are no different from communicable disease, about which there has always been legislation. In Fletcher's view, the more artificially we do anything, including reproduction, the more humanly we do it, because what makes us human is to act rationally with some end in view!

**A Finnish Case History**

Disability advocacy groups generally take a contrary view. In Finland they objected to a programme offering free genetic screening to women for foetal defects such as Down's Syndrome on the following grounds:

1. Screening would eventually be compulsory.
2. Women would ultimately be expected to abort abnormal foetuses.
3. Those who carried abnormal foetuses to full term would be judged irresponsible.
4. The human value of people now living with disabilities would be diminished.
5. The tests would not be cost effective.

The following counter arguments have been or could be offered:

1. Who should pay for the care of the congenitally disabled who could have been aborted?
2. What is wrong with taking steps to have a healthy baby?
3. The question of screening should be divorced from our obligation to ensure that people with congenital disabilities are treated with respect and care.
4. The thousands of people and organizations concerned with fund-raising and care giving to the disabled are threatened by cutting off the supply. This may be a subconscious factor in their passionate opposition to screening.
5. At a time when the advanced countries spend millions to keep congenitally disabled children alive, thousands of healthy children in other lands die for lack of simple vaccines. Does our responsibility stop at national boundaries and can we justify morally valuing one life so much more than another? This throws into conflict the deontic and utilitarian attitudes to morality.

Problems with late-onset disease

There are special problems with the identification of late-onset diseases such as cancer and heart disease which may have a genetic contributory factor. The desire of employers and insurers to minimize their risks will put pressure on candidates for employment to demonstrate their "normality" with respect to these conditions. Thus a person may be stigmatized throughout life for a condition to which he may not succumb until after retirement, if at all. Most of these diseases express themselves as a result of a combination of genetic susceptibility and life-style (e.g. smoking, drinking, couch-potato behaviour etc.). A general penalty would seem very unjust.

International Convention on the Human Genome

Over the last few years a group of lawyers has been developing a proposed international convention\textsuperscript{12} for eventual adoption by the United Nations. The study was motivated by a recognition of problems arising out of the Human Genome Project and much of it is relevant to genetic screening. The first two clauses of the convention proscribe germ-line therapy except where there is "indisputable" proof of its benefits. The convention would also prohibit the termination of a pregnancy on genetic grounds if it were possible for the baby to be born alive. This would force parents to bring to term infants with Tay-Sachs and Down's syndromes. This draft convention intrudes into areas where there should be choice and fails adequately to protect the genetic minorities of the world from the exploitation of their rare genetic resources for commercial gain. Matters of this moment should not be entrusted to lawyers.

Conclusion

Arguments for genetic screening have been advanced under the following conditions:
- Adult screening for marriage counselling (Tay-Sachs)
- Post-natal screening for early therapy (PKU, CF)
- Pre-natal screening for compassionate abortion (Tay-Sachs, Downs)
- Pre-natal screening for negative eugenics
- Pre-natal screening for positive eugenics.

In the view of most ethicists, a \textit{sine qua non} of any screening should be some benefit to the individual and/or parents, the reliability of tests, the clarity with which the results are communicated and freedom from coercion. Despite these criteria being
met, some -- or conceivably all -- of the above cases may prove unacceptable to certain people on doctrinal grounds.

Genetic screening is a powerful medical technology which exemplifies many of the characteristics of the technological phenomenon. It *amplifies* the powers we have always had (and, in most previous societies, have widely exercised) to select for survival infants that meet our standards of normality. It is *ambivalent*, in that it offers a reduction of human suffering on the one hand and creates intense moral problems on the other. It is *fascinating*, in that it opens the door to the genetic improvement of the human race and the achievement of eugenics. In other words, it offers us a Faustian bargain on a grand scale! Finally, it offers a test case for the technological *imperative*: Will the legislation under Bill C-47 of the 35th Parliament and the proposed International Convention on the Human Genome be effective in proscribing certain techniques?

**Questions**

1. Describe the ideal conditions for a programme of routine genetic screening and contrast this programme with one which appears ill-advised.

2. What interest groups are involved in advocating the introduction or prohibition of a programme of genetic screening and how are power relations in society likely to be changed as a result of its introduction?

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1 National Academy of Sciences (Perutz rev. of Holtzman)
2 Kome
3 Taber, p.1385.
5 *New Scientist* # 1891, 18 Sept 1993