Mental disorders and genetics:

NUFFIELD COUNCIL ON BIOETHICS

Published by
Nuffield Council on Bioethics
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London WC1B 3JS

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Website: **http://www.nuffieldbioethics.org**

ISBN 0 9522701 3 7
September 1998

To order a printed copy, please contact the Nuffield Council or visit the website.

Designed and printed by RPM Reprographics
2-3 Spur Road
Quarry Lane
Chichester
West Sussex PO19 2PR
01243 787077

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The terms of reference are as follows:

1 to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;

2 to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;

3 in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

The Nuffield Council on Bioethics is funded jointly by the Medical Research Council, the Nuffield Foundation and the Wellcome Trust

Preface

During the two years that it has taken to produce this report, great progress has been made in the field of genetics, and even more concern is now expressed about the treatment of the mentally ill than formerly.

The work has been undertaken in spite of the fact that genetics has not thus far, in its application to mental disorder, led to discoveries which will transform the lives of individuals in the near future. But there are, unfortunately, many misconceptions and fears about potential applications. These are not contributing to a wider understanding of either mental disorders or genetics, and indeed they may be increasing the stigmatisation of those suffering from mental illness.

However, public interest in both genetics and mental disorders is intense and it appeared important to the Nuffield Council for Bioethics that these issues, and their ethical implications, should be examined. This report seeks to encourage wider consideration of the implications for those who suffer, their families, scientists, policy makers and thinking members of society at large. Like previous Council reports the ethical analysis is grounded in as contemporary as possible an exposition of the relevant facts.

It has been a challenging piece of work in the true sense of that word, but at no point have members of the Council or indeed the Working Party, which I have been proud to chair, doubted that our efforts can be justified. It is for others to decide if they have been worthwhile.

We have been pleased at the amount of interest which many individuals have shown in our work and our thanks are duly recorded for specific help that we have received.

Speaking as Chairman, I can say with all sincerity that this report would not have appeared without the tremendous effort and commitment of members both of the Council and also of the Working Party. I should particularly like to single out Chris Barchard who has had the difficult role of constantly reminding us about those to whom this work has been committed; people who suffer from mental illness and their families. The patience and dedication of the Secretariat, and especially of Rachel Bartlett, cannot be commended highly enough, and my gratitude goes to them all.

Dame Fiona Caldicott

Acknowledgements

The Working Party wishes to thank the many organisations and individuals who have assisted its work, particularly those who submitted consultation responses. It is also very grateful to Mr Harry Cayton, Professor Jonathan Glover, the Honourable Dame Brenda Hale, Professor Steve Humphries, Professor Theresa Marteau, Professor Vivienne Nathanson, Professor Chris Thompson and Dr Tom Wilkie who all reviewed an earlier version of the report. Their comments, which contained both far-reaching and detailed criticisms to which we have sought to respond, were extremely helpful.

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Mental disorders and genetics : the ethical context

Terms of reference

1 To survey the current field of research relating to the genetics of mental disorders and to report on recent and prospective advances;

2 In particular, to review:

  a whether there are sufficiently firm criteria for diagnosis;

  b how substantial the evidence is implicating genetic influences.

3 To review the potential clinical applications of the research.

4 To define and consider ethical, social and legal issues arising from work on the genetic aspects of mental disorders and identify those which are additional or complementary to the issues dealt with in the Council's report **Genetic Screening: Ethical Issues.**

  Such matters may include:

  a the ethics of research on the genetics of mental disorders involving human subjects, including particular groups such as children and detained patients;

  b when is it appropriate to translate research findings into clinical or social practice?

  c genetic counselling for mental disorders in the context of adult onset disorders, of children and in prenatal diagnosis;

  d the particular impact of the diagnosis of a genetic risk on the individual, including an individual child or fetus, or on other members of the family;

  e stigma and responsibility: will genetic knowledge increase or decrease the stigma suffered by those with mental disorders and the responsibility perceived by or assigned to relatives?

  f the implications of the use of genetic findings in the courts and other legal proceedings;

  g the implications of the use of genetic findings for access to insurance, employment, education and healthcare.

Executive Summary

This report examines the ethical issues that may arise in the course of genetic research into mental disorders and in the application of that research in clinical and other settings. Some of these issues arise because the conditions are genetic, and others because they relate to mental disorders. A broad and humanistic perspective may be considered to have two basic ethical requirements: respect for human beings and human dignity, and the limitation of harm to, and suffering of, all human beings.

The Working Party considered both rare single gene disorders, focusing on the examples of Huntington's disease and early onset Alzheimer's disease, and common mental disorders, such as schizophrenia and the more common late onset form of Alzheimer's disease, influenced by susceptibility genes and by environmental factors. The ethical issues associated with mental disorders concern the implications for reproductive decisions, the stigma associated with mental disorders and the fact that some disorders may impair the capacity to make decisions.

The Working Party concludes that genetic tests will not be particularly useful in the near future in diagnosing mental disorders with more complex causes, for prenatal diagnosis or for population screening. It is more probable that identifying genes involved in susceptibility to common mental disorders will lead to the development of more effective drug treatments. Even if a number of susceptibility genes were identified for a particular disorder, the report concludes that, without an understanding of their interaction, they would not be adequate for predicting individual risk in a clinical setting.

The Working Party recommends that genetic testing for susceptibility genes which offer relatively low predictive or diagnostic certainty be discouraged, unless there is a clear medical benefit to the patient. The genetic testing of children requires special safeguards and the Working Party recommends that predictive genetic testing and testing for carrier status for mental or indeed other disorders in children be strongly discouraged. Genetic testing for mental and other disorders in adoption raises important and complex issues which require appropriate guidance.

While the best safeguard against new eugenic pressures is freely given, properly informed consent, guidelines for the establishment and maintenance of genetic registers are needed. The report recommends that the confidential nature of genetic information be maintained but recognises that, exceptionally, disclosure to close family members might be justified. Recommendations are also made about the use of genetic information in insurance and employment.

For most people with a mental disorder, arrangements about consent to research participation should not be any different from those required for others. However, for those who are only intermittently competent, consent should be sought only when they are competent. For the incompetent, participation in non-therapeutic research is considered ethical, subject to strict safeguards.

Chapter 1

Introduction

Introduction

1.1 Mental disorders place a heavy burden on individual sufferers, on those who care for them and on society at large. This report examines the ethical issues that may arise not only in the course of genetic research into mental disorders but in application of that research in clinical and other settings. Research into the genetics of mental disorders may lead to a range of potential benefits. It may add to our understanding of their underlying causes; improve diagnosis; enable the development of new drug-based or other treatments; and allow treatment to be tailored more accurately to individuals.

1.2 However, genetics and mental health are both areas which raise significant and sometimes distinctive ethical, social and legal concerns. This report examines the issues that arise when these fields come together. As with other diseases, the development and course of most mental disorders are affected by a complex mixture of biological, psychological and social factors. The focus of the report on the genetics of mental disorders is not intended to imply that genetic research is the only, or even the most important, approach for understanding and treating mental disorders, or that it is the only one to raise ethical issues. The extent of current research into the genetics of mental disorders, however, suggests that it is timely to try and anticipate its consequences.

1.3 The report focuses on schizophrenia, a range of affective disorders (manic depression and depression), dementias (Alzheimer's disease), neurotic disorders (anxiety) and personality disorders. Many of these have complex causes, and any genetic influences are not well understood. So the report also draws on experience of relatively simple single gene disorders, such as phenylketonuria, Huntington's disease and fragile X syndrome. While some of the ethical considerations relevant to these disorders are also relevant to genetically more complex disorders, there are also important ethical differences. Indeed, we should be cautious in regarding these single gene disorders as good models for understanding genetic influences in other more complex conditions.

The whole person and 'geneticisation'

1.4 Some current thinking on genetics suggests that any additional ethical perspective is redundant, as if we could view genetics as basic not only to human biology but also to ethics. We accept, of course, that human behaviour can be viewed from a variety of theoretical perspectives. For example, extreme reductionists think that it is in principle possible to provide an entirely mechanistic explanation of human behaviour, and that given sufficient scientific progress this will eventually be practically possible also. However, even if this were the case, there is no reason to think that these scientific approaches incorporate an adequate ethical perspective. Indeed, there are those, including some respondents to the Working Party's consultation, who are opposed to any research into the genetics of mental disorders on the grounds that it is anti-humanistic. The Working Party does not take that view, though it maintains that the proper object of ethical attention is the condition of the whole human being viewed as a person, that is, as a unified subject of experience, thought and action. This report is primarily concerned with whole persons and not simply with their genes. Present day interest in genetics should not let the molecular complexity revealed by current science distract from the fact that the subjects of study are human beings and their values. Were this inquiry a purely scientific one, our concerns might be otherwise, but it is not and nor should they be. The need for the ethical perspective that focuses on the whole person is inescapable.

1.5 This broad ethical and humanistic perspective may be contrasted with an approach which has been labelled 'geneticisation'.[1] This ungainly term is used to mean an increasing tendency on the part of some, but by no means all, researchers to view human beings essentially as gene carriers, and to characterise issues of nature and functioning, of health and disease, solely in the language of genetics. This tendency has a number of consequences. By giving priority to the study (and manipulation of) genetic structures and effects, other kinds of explanation – such as those which refer to social and physical environments and economic conditions – are given less attention. Genetics may attract a disproportionate share of resources available for research and policy; too little attention and too few resources may be devoted to social research and policy. These issues were of concern to many of those who responded to the Working Party's consultation.[2]

1.6 Paradoxically 'geneticisation', although it focuses on characteristics human beings share, is often linked to an individualistic view of the appropriate treatment for health problems. The genetic defects associated with diseases are carried by individuals, and responsibility for health may then also be ascribed to individuals rather than being seen as something shared by society. 'Geneticisation' is also often associated with a change in attitudes to parenthood and reproduction. The traditional emphasis on the importance of good parenting may become less important, and genetic 'quality' in reproduction more so. People with genetic defects may be made to feel that they are flawed persons; parents may feel that they are expected to have genetically 'perfect' children, if necessary by using prenatal diagnosis and abortion.

1.7 These trends may also be expressed in deterministic or fatalistic attitudes which claim that 'it is all in the genes', and similar attitudes which risk undermining both moral responsibility and social solidarity. The latter is a somewhat neglected, but very important, notion. It involves distributing benefits and losses across society as a whole, so recognising the reality of social existence, deepening a sense of community and expressing equality of respect for persons. Instead of thinking of human life as something to be shaped by individual and social choice, 'geneticising' thinking regards circumstances as given, and classifies individuals and groups according to their genetic potential.

Limiting suffering and having respect for persons

1.8 We take the view that the search for, and availability of, genetic information about mental disorders raises ethical concerns which cannot be answered simply by further genetic inquiry. In exploring such concerns, many approaches regard two ethical requirements as basic. These are the limitation of harm and suffering to humans (even to all sentient animals) and the maintenance of respect for human beings and human dignity.

1.9 Limiting harm and suffering is shown by seeking to cure, to care and not to injure, and so to establish and maintain medical systems that deliver effective, affordable and timely treatment. Respect for persons is shown by treating others as persons who can make their own decisions and lead their own lives; it is expressed in action and procedures that give due weight to personal autonomy and integrity, to human (including patients') rights, and to the obligation of doctors and researchers to seek informed consent, to preserve confidentiality, to respect privacy and to communicate effectively with patients.

1 A term coined by Abby Lippman. See for example, Lippman A (1992) Led (astray) by genetic maps: the cartography of the human genome and healthcare, **Social Science and Medicine** 35:1469–76.

2 For example, the Ethics and Genetic Engineering Network established by the Luton and Leighton Monthly Meeting of the Religious Society of Friends (Quakers), Leeds MIND, Theresa Marteau, Mencap and The Mental Health Foundation.

1.10 Whereas we all have an intuitive idea of suffering, and of the importance of limiting it, the idea of respect for persons is more complex. Persons think and act; they are the agents and recipients of all behaviour, including moral and immoral behaviour. It is only to persons that we ascribe both duties and rights (although some people ascribe rights without duties to other animals). Failure to respect persons is wrong because it threatens or undermines the very sources and possibility of any moral action; this is why respect for persons is ethically fundamental.

1.11 There is widespread agreement that the limitation of suffering and respect for persons are both of fundamental ethical importance. Some philosophical positions place greater weight on one or other of these principles, but this report does not take a stand on this fundamental issue.[3] The practical need is to identify, construct and support institutions, regulatory systems, professional codes and informal practices and ways of life that uphold both principles as thoroughly as possible.

1.12 It is often difficult, however, to establish exactly what the principles of limiting suffering and respect for persons require in practice. Sometimes dilemmas arise when promoting or protecting one value is not fully compatible with promoting or protecting the other; we have not offered ways of resolving all such dilemmas. Even so, it is necessary to recognise that the attempt to achieve ethically acceptable solutions requires that one take account both of the duties of limiting harm and of according respect to persons. There will be few issues that can be resolved in an ethically acceptable way unless both limiting harm, and respect for persons, are taken seriously.

1.13 The genetics of mental disorders raises distinctive issues both for the limitation of (human) suffering and for maintaining respect for persons (and for human dignity). Some of these distinctive ethical issues arise because the concern is with genetic conditions; some arise because (with some exceptions) the concern is with genetic predispositions rather than with gene mutations that have a more predictable effect; some arise because the concern is specifically with the genetics of mental disorders. We shall set out very briefly why these three aspects of our topic raise distinctive ethical concerns.

Genetics and ethics: general issues

1.14 Genetic disorders are distinctive because they affect not merely individuals (as do all diseases), or groups of unrelated persons (as with epidemics), but groups of related individuals. Genetic information about one individual may reveal either certain, or more commonly probabilistic, information about their relatives, including any future children. Yet genetic information can be obtained by testing or treating a single individual. Both individuals and their doctors will then have to decide whether sharing information with relatives to whom it pertains, or its non-disclosure, is the better course of action.

1.15 Even in cases where it is relatively clear whether disclosure or non-disclosure would better limit suffering, it is often difficult to decide which would better express respect for persons. Would withholding knowledge from relatives about the possibility that they too might have a genetic mutation that could lead to a disorder be acceptable? Relatives might use that information in

3 Utilitarians, who maintain that an action is right to the extent that it promotes happiness, have argued that respecting persons (special cases of which are respecting patients' rights to privacy and confidentiality) is just another aspect of limiting harm and suffering. Other approaches, such as versions of Kantian thinking (which emphasise principled action), religiously inspired views (which view ethics as based on divine command or on the sacredness of life), and rights-based approaches, all argue that limiting suffering is just one aspect of respect for persons, and not invariably the most important. Finally, there are other philosophical positions which view the limiting of harm and suffering and showing respect as distinct and mutually independent goals.

making decisions about their lifestyle or their medical treatment, or about whether to have children. Would withholding information be a form of paternalism that denied them the possibility of making their own well-informed decisions? In that case, would respect for others require relatives or doctors to communicate what they knew about the results of genetic tests, or other genetic information? Or should genetic test results be treated as confidential to individuals, like other medical information? Can we think of a 'right to know' – or of a 'right not to know'– in purely individualistic terms in the case of genetic knowledge? Or does genetic knowledge challenge the basis of our usual individualistic understanding of medical confidentiality? Does respect for others require doctors or researchers to seek consent for genetic investigation from all who might be affected? Even if these questions can be resolved, and they are legal as well as ethical questions, showing proper respect for persons may make complex demands in seeking consent for investigation and treatment of genetic conditions.

Genetics and ethics: single gene disorders and predispositions

1.16 Experience of genetic counselling and testing so far has been mainly concerned with single gene disorders, where a genetic test result may offer a high degree of certainty as to whether an individual will or will not develop a certain condition.[4] For example, prior to testing or screening, individuals who know that the Huntington's disease mutation is present in their family can often be given quite clear information about their own risk and relatives' risk of suffering from the disorder. If they then choose to have a genetic test, the result will allow a very confident prediction of who will and who will not suffer from the condition. For gene mutations of this sort information can be clearly established and communicated, and the difficult ethical questions are about whether and when to seek such information and whether, when and how to communicate it.

1.17 These issues are much more complex for gene variants which are associated with relatively slight predispositions to a disorder, rather than those which impose a near certainty of suffering from a disorder.[5] For example, a variant of the apoE gene (called the apoE4 allele) is associated with a predisposition to Alzheimer's disease, but a genetic test result can indicate no more than a somewhat increased susceptibility. Knowing that one has a gene variant associated with a predisposition to a disorder might nevertheless be useful (for example, if some medical or lifestyle change could reduce the susceptibility or the severity of the disorder) or alternatively harmful (for example, if it become a source of anxiety and there were no known way of reducing the susceptibility). It is often difficult to decide whether having information of this sort or lacking it might be more likely to cause suffering.

1.18 Showing respect for others may also make complex demands in the case of genetically-based predispositions. In particular, doctors have to determine whether and how to offer information about genetic tests for predispositions, whether to advise patients to take tests, how to disclose the results of any tests that are taken and how to explain the degree of risk to those tested (and to any relatives) without causing undue alarm. Those who choose to be tested and learn their own test results (adverse or otherwise) have in their turn to decide whether and how to inform their relatives.

4 Nuffield Council on Bioethics (1993) **Genetic Screening: Ethical Issues**, Nuffield Council on Bioethics, London.
5 Where a variant (or allele) of a gene is associated with only a slight predisposition we have used the term **susceptibility gene**.

Mental disorders: integrity, reproduction and stigma

1.19 The range of ethical issues raised by genetic information expands when the information concerns mental disorders. Some of these additional issues cluster around the notion of personal well-being, of how one views oneself and is viewed by others; others concern reproductive decisions and some arise from the fact that mental disorders are often stigmatised.

1.20 A wide range of cognitive and emotional capacities are relevant to a person's identity, integrity and rationality; their absence may impair abilities to function as a person, may reduce personal well-being and may even lead to severe dysfunction. Genetic information which might be used to diagnose, or suggest susceptibility to a mental disorder, might raise questions about an individual's ability to function as a whole person and about their personal relationships. It might also undermine or weaken a person's sense of integrity and well-being, even when they are not suffering from any manifest difficulty or disorder. In the most vulnerable cases, acquiring genetic information about a predisposition to some mental disorders might cause great anxiety and even precipitate the feared condition.

1.21 A second area in which information about genetic susceptibility to mental disorder might raise difficult questions is that of reproductive choice. Even in the absence of genetic information, reproductive decisions can be hard for people with mental disorders. Some respondents to the Working Party's consultation who had suffered from mental disorders described the difficult considerations they had faced in deciding whether to marry or to have children; many had in fact done both successfully. At the same time there will be some individuals for whom such information may be helpful both as relevant and as a reinforcement of a decision already arrived at. For a few, rare single gene disorders, prenatal testing may provide definite information about the fetus; if information is both certain and adverse and the law permits it, termination is possible, and sometimes chosen. However, where genetic influences are slight (as for many mental disorders) and prenatal tests cannot provide accurate predictions, the relevance of genetic tests to reproductive decisions may also be slight.

1.22 Nevertheless, concerns have been expressed that new genetic technologies could be used for eugenic purposes. The concerns are often linked to the fact that in the past some eugenic abuse was directed at people whose behaviour was considered socially unacceptable, including those with mental disorders. The possibility that genetic information relevant to mental disorders might be misused to influence reproductive choices, or for other forms of genetic abuse, cannot be simply dismissed.

1.23 A third distinctive group of ethical problems raised by mental disorders is that those afflicted often have to suffer not only their disease, but also the associated stigma. Relatives caring for a patient with mental disorder may also have to cope with the stigma of having an afflicted relative. Stigma is a distinctive form of suffering in which a person experiences shame, and is the object of blame, often for matters which were in no way avoidable. There is little shame suffered, or blame apportioned, for most physical injuries and illnesses. Broken legs, measles and heart attacks will attract sympathy and concern; patients are not usually blamed for their sufferings; their relatives are not usually stigmatised. Many mental disorders, however, are a matter of shame for those affected and for their relatives and, far from attracting sympathy, are a source of avoidance, criticism or even of blame by others. It is important, therefore, to consider whether the availability of genetic information will increase or decrease the stigma associated with mental disorders, and whether fear of stigma will affect reproductive decisions.

1.24 The requirement to limit suffering makes similar demands on those treating and caring for persons with mental and with physical disorders. The requirement to respect persons is more complex in the case of mental disorders, however, and makes distinct and difficult demands. Mental disorders frequently disrupt cognitive processes and capacities for social interaction; sufferers may have difficulty in making decisions, in giving consent to the investigation or treatment of their conditions, in assimilating the implications of genetic counselling and in communicating relevant information to relatives. If the limitation of suffering were the sole ethical requirement, then a purely paternalistic perspective, directed solely towards promoting the welfare of those with mental disorders, would suffice. If people with a mental disorder are to be respected as persons, however, their autonomy must be supported (even when it is greatly reduced), they must be given accurate information (even when they are having difficulty in following it), their concerns must be treated with due confidentiality, they must be offered privacy like other patients and, above all, informed consent must be sought if they are to be subject to investigation and treatment. All of these can prove demanding, not least because of the need to observe legal as well as ethical duties.[6]

1.25 Because these requirements cannot be met in all cases, separate legal and medical procedures have been established which permit paternalistic investigation and treatment undertaken in the 'best interests' of the patient. This may take place in circumstances where the attending doctor has formed the view that the patient lacks capacity to consent,[7] or under the provisions of the Mental Health Act, on the certification (normally) of two doctors that the person comes within the terms of the Act. Even at its worst, however, mental disorder is rarely a matter of comprehensive incapacity; it is commonly a matter of impaired or intermittently impaired capacities. Most people with a mental disorder can continue, throughout the duration of their disorder, to take all decisions for themselves with no more assistance than a person without mental disorder. Accordingly, no general case can be made for those suffering mental disorders to be exceptions to the usual requirements for consent, or to other aspects of respect for persons. Care and sensitivity are needed if due respect is to be shown to mentally disordered persons, particularly if they are detained and subject to compulsory treatment. In some circumstances it can be very hard to meet these ethical demands; but this is no reason to overlook or deny them.

Science and ethics: genetic research

1.26 Everybody recognises that ethical considerations must govern the treatment of patients but some think that research itself, including genetic research, does not raise difficult ethical questions. For example, it is sometimes argued that scientific inquiry itself is value neutral, and that any attempt to direct or evaluate basic or applied research by using ethical norms may frustrate the principal goal of research, which is the acquisition of knowledge, and may even lead to the very abuses it was intended to avoid. This argument has several flaws. Science is, by definition, committed to certain values. Systematic investigation of the natural order is an expression of the desire to understand, and involves a commitment to the value of knowledge as such as well as to certain standards of inquiry: honesty in data gathering; accuracy in reporting results; fairness in using others' work and so on.

6 Law Commission Report (1995) **Mental Incapacity**, Law Com No 231, HMSO, London; Nuffield Council on Bioethics (1995) **Human Tissue: Ethical and Legal Issues**, Nuffield Council on Bioethics, London; The Lord Chancellor's Department (1997) **Who Decides? Making Decisions on Behalf of Mentally Incapacitated Adults**. Cm 3803, HMSO, London.

7 See *Re F* [1989] 2 All ER 545 (HL) as regards adults and *Re W* [1992] 4 All ER 627 as regards children.

1.27 Current scientific practices clearly rely on further ethical norms. Science funding is provided by state and private sponsors allocating scarce resources. Their priorities and decisions will rightly reflect various principles and values, and scientists seeking funding will point out the intrinsic worth and the other benefits of particular proposals. The question is not whether values underlie scientific research, but which values are most significant, how conflicts between them are to be weighed, and what they may show about the importance of supporting, of refusing to support or even of restraining certain types of research. Scientific research, like any other activity, is subject to discussion about the best way to proceed in the light of principles and values.

1.28 This conclusion contrasts with the view that once something is scientifically or technically possible, it will invariably be done. It indicates how important it is to distinguish between questions about what can be done, about what will be done and about what should be done. Scientific possibilities do not of themselves determine policies, which may and should reflect ethical, legal, social and economic considerations as well. Doing science is not a way of escaping moral responsibility. There may be no simple rules whose automatic application will yield acceptable solutions and, as respondents to the consultation have pointed out, the "*current paucity of information on genetics and mental disorders suggests that it is too early to try to develop detailed ethical frameworks*." [8] Even so, scientific and medical researchers cannot abrogate moral responsibility for their own investigations, or for the ethically significant issues which their work may create for society. Scientific possibility is one thing, moral permissibility another and moral obligation a third.

1.29 In summary, this report has two main aims: to describe the current possibilities for diagnosis and treatment based on genetic research into mental disorder, and to consider the ethical and legal reasons for supporting, for regulating or for setting aside these possibilities. It is not the purpose of the report to speculate about long-term social trends, or to resolve fundamental philosophical questions about human nature. However, as has been noted, the orientation of this and subsequent chapters is at odds with that of 'geneticisation'.

8 Response by the Royal Society to the Working Party's consultation. The response continues, *"None the less it is important to identify the issues that may arise."*

Chapter 2

Definition and study of mental disorders

Introduction

2.1 Although there is no universally accepted characterisation of mental disorder, widely used definitions are those of current international systems of classification. Thus, to quote, mental disorder "*is not an exact term, but it is used to imply the existence of a clinically recognizable set of symptoms or behaviour associated in most cases with distress and with interference with personal functions. Social deviance or conflict alone, without personal dysfunction, should not be included in mental disorder as defined here.*" [1] Most psychiatrists diagnose mental disorders only when an individual is unable to achieve realistic personal goals due to psychiatric symptoms. But several respondents to the Working Party's consultation pointed out that, while not wishing to underestimate the suffering that such conditions can and do cause, people who are perceived as having mental disorders may also contribute great gifts of the spirit.[2] One respondent, describing himself as schizophrenic, argued that "*Mental illness is also emotional distress and experience of darkness and distress that we will all experience. Is that necessarily so bad? All our lives we strive to improve and make easier our lives – where would we be without that struggle?*"

2.2 The report does not address criminal behaviour since this is defined in relation to systems of law and jurisdictions, and not in terms of personal dysfunction. It does, however, discuss personality disorders and these sometimes give rise to profoundly anti-social behaviour which in some circumstances may constitute criminal action. The Working Party recognised, of course, that to the extent that criminal law is concerned with responsibility, mental disorders are relevant, for example, to a plea of diminished responsibility or of insanity. The issues raised, however, go much wider than a consideration of the relationship between genetics and mental disorder. The principal concern is the decision whether to attribute culpability. While medical and scientific evidence is relevant, it is not determinative, in principle or in practice. Ultimately, it remains a decision for the Court and so goes beyond our concerns here.

2.3 An important category within international systems of classification of mental disorder is that of mental retardation and the Working Party has used as examples conditions which are relatively well understood, such as phenylketonuria and fragile X.[3] Issues such as the ethics of genetic research into mental retardation or intelligence within the normal range, or its applications or implications however, fell outside the Working Party's terms of reference. Recently, concerns have been expressed about the ethics of genetic research into conditions involving mild mental retardation and its implications for the understanding of intelligence in the normal range. The Working Party considers that there are issues in this area, such as the criteria of intelligence, the dangers of illusory perfectionism, and the possibility of increased pressures for selective abortion, which would merit future consideration.

Definition and diagnosis of mental disorders

2.4 A criticism of definitions of mental disorder is that they reflect judgements linked to social circumstances. It is still the case that many features of mental disorder are defined in terms of

1 World Health Organisation (1992) The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines, World Health Organisation, Geneva, p5. Although many mental disorders constitute a spectrum, ranging from severe through mild to 'normal', the prime focus of the scope of this study is mental disorder as defined by these criteria.

2 Response by the Ethics and Genetic Engineering Network established by the Luton and Leighton Monthly Meeting of the Religious Society of Friends (Quakers).

3 In the UK, mental retardation is now more usually known as learning disability. The Working Party has adopted the term mental retardation on the basis that it is currently used in international systems of classification. It accepts, however, that this is neither a universally accepted, nor an ideal, term.

difference or deficiency as compared with a standard defined within a social context. Assumptions about what is standard, and hence about what differs from standard, will vary over time and according to cultural context.

2.5 Another criticism is that diagnosis of mental disorders is hampered by imprecise definitions and lack of consistency.[4] Although there have been problems of this sort in the past, current clinical definitions of mental disorders such as schizophrenia or manic depression are now no less precise than those for some non-psychiatric medical disorders. If modern diagnostic criteria are used, there should be agreement about diagnosis between any two trained assessors. This said, individual cases can vary greatly in the symptoms displayed and their relative severity, sometimes resulting in inconclusive or conflicting diagnoses. Also, as in other areas of medicine, criteria and diagnostic categories are themselves liable to be modified as knowledge grows.

2.6 The real problem is that, in most cases, little is known about the underlying causes of mental disorders. Thus psychiatric diagnoses represent operational definitions, or working hypotheses, rather than well-understood entities. Unlike other diseases, there are few biochemical, radiological or physiological tests to assist in a clinical diagnosis based on history and current presentation. Nevertheless, a measure of validity may be inferred from the fact that, in many cases, it is possible to give an indication of probable outcome (prognosis) on the basis of a diagnosis and to predict to a certain extent the likely response to treatment and other clinical interventions.

Can mental disorders be explained in physical terms?

2.7 As in every other branch of the subject, the philosophy of mind and the philosophy of psychology are characterised by significant disagreements. Philosophical consensus is rare and generally not long-lasting. Even so current philosophical thinking about the nature of psychological phenomena is broadly anti-reductionist.[5] That is to say, while most philosophers believe in the physical basis of the mind, they do not suppose that psychological features are reducible to physical ones in the sense that they might be wholly describable or explicable in terms belonging to physical theory. The relationship between the mind and its physical basis remains unresolved, and no easy resolution is in prospect, but, given the correlation between the two, it makes sense to consider the influence of physical factors, including genetics, on mental states. The identification and explanation of mental states, however, is taken to proceed by reference to *psychological* criteria. Any attempt to explain the psychological in terms of the purely physical will fail if, according to the predictions of the favoured physical theory, a person 'should' be in a state of depression, but he or she is patently untroubled as judged by *psychological* criteria. The psychological evidence is decisive in medical diagnoses as in ordinary life: someone is anxious if, and only if, they feel anxious and/or their behaviour expresses anxiety. This truth holds good whatever underlying physical basis there may be for the psychological condition. We have much to learn from the physical sciences about the structure and activity of the brain, but physics does not purport to be an account of persons as psychological subjects.

4 Professor Bill Fulford, University of Warwick, in his response to the Working Party's consultation argued that difficulties of definition can lead to practical difficulties and dangers. *"Much abusive practice has arisen from, on the one hand, people who are not mentally ill being treated as such (eg the institutionalised abuses of psychiatry in the former USSR), and, on the other, people being denied treatment for mental illness on the grounds that they are 'merely socially' deviant (this has become an increasing problem with shrinking resources)."*

5 For contrasting surveys and assessments of the current state of the subject, see Churchland P (1986) The Ontological Problem (the Mind-Body Problem) Chapter 2 in **Matter and Consciousness**, MIT Press, Cambridge, Mass & London; and Searle J (1992) What's Wrong with the Philosophy of Mind? Chapter 1 in **The Rediscovery of the Mind**, MIT Press, Cambridge, Mass & London; and, for a brief overview designed for non-philosophers, see Haldane J (1998) The Philosophy of Mind in **Encarta Encyclopedia**, Websters, London.

2.8 There is also a growing consensus within philosophy and the social sciences that human beings only develop fully within a social context which allows interaction with others. For example, it is widely accepted that language is intimately connected with thought. While human beings may have a natural potential for language, this can only be fulfilled in an environment in which others' use of language can be experienced. It is also generally supposed that the notion 'I' can only be applied by a being that has a concept of others ('you', 'him', 'her') and the capacity to view him or herself as an object of attention and interest to others. In short, my ability to think of myself as a psychological subject is linked to my ability to think of others as such, and to think of them as regarding me as an other.

2.9 There are generally held assumptions about what someone ought to think or feel in various circumstances. These constitutive norms relating belief, intention and action vary relatively little across cultures and time. Less logically rigid, but no less important, are society-specific expectations about what constitutes normal psychology. These are much more prone to vary across cultures and with time. For example, certain forms of statistically uncommon sexual behaviour regarded at one stage in social history as disordered or pathologically deviant may come to be viewed as legitimate expressions of sexuality. In clinical practice, the impact of society-specific expectations can be minimised by bearing in mind the definition of disorder adopted in this report (paragraph 2.1). According to this definition, statistically unusual sexual preferences would be classed as mentally disordered only if they were associated with personal distress or personal dysfunction.

2.10 One need not endorse all of the claims made under such headings as 'the social construction of normality' to see that what counts as reasonable or unreasonable, regular or deviant, healthy or morbid may differ across societies and with time. The period since the Second World War has, it seems, been one of many changes in assumptions about normality. It is as well to remember this when thinking about mental disorders. Certainly, one needs to be mindful that conditions now regarded as involuntary pathologies may come in time to be viewed as legitimate lifestyles.

2.11 We end this chapter by emphasising related points made in Chapter 1 about the human perspective of this report (paragraph 1.4) and in this chapter, about the relation between the mental and the physical (paragraphs 2.7–2.10). In reflecting upon standard styles of description, explanation and evaluation of human psychology it is important to recognise that the proper and primary subject of study is the person. It is also necessary to be aware that contrasting notions of order and disorder and of normality and deviancy are at least partly rooted in social norms and expectations which may vary over time and across cultures. In the domain of human psychology there are few if any timeless truths and the significance of those that are recognised is often evaluated differently at different times.

Chapter 3

What do genetic studies of mental disorders tell us?

Introduction

3.1 Genetic studies of mental disorders attempt to address the following questions:

- Is there an inherited component to mental disorders? If so, to what extent?
- If genetic influences are important for certain mental disorders, can the specific gene variants involved be identified?
- What are the environmental influences that may be important in explaining these mental disorders?
- How do genetic and environmental influences combine and interact?

3.2 This chapter briefly describes the main approaches being used in genetic research, together with their strengths and weaknesses. It illustrates their application to mental disorders and some of the main conclusions that can be drawn. The techniques are described in more detail in Appendix 1.

3.3 Historically, genetic studies of human characteristics and diseases have involved either families or populations. In general, a person's genes occur in pairs, one inherited from the mother and one from the father. In turn, one or other of each gene pair is passed down to every offspring. Studies of family histories (or pedigrees) have been used to establish whether or not the pattern of occurrence of a disorder within the family is predictable in terms of the inheritance of a single pair of genes (Mendelian inheritance). Such studies may suggest that a disorder is recessive, dominant, or sex linked. Once such a pattern is established, family linkage studies can be used to identify the gene mutation involved. This involves comparing the DNA of unaffected and affected family members. The aim is to find a region of DNA which differs between affected and unaffected individuals. This might contain a gene mutation which contributes to the development of the disorder. The region is narrowed down and, eventually, the gene isolated and different mutations characterised.

3.4 This procedure is now well established and gene mutations causing Mendelian disorders are rapidly being isolated. The genetic mechanisms vary in different diseases. For example, phenylketonuria is a recessive condition in which both copies of the relevant gene need to occur in a mutated form before the condition develops (Box 3.1). In contrast, Huntington's disease is a dominant condition; it will develop if only one of the two copies of the person's gene occurs in the mutated form (Box 3.2).

Variable expressivity

3.5 In some disorders, a single major gene is involved but the effect of the mutation varies in different people in terms of timing of onset, severity and manifestation. This phenomenon is called variable expressivity. It occurs, for example, in tuberous sclerosis, a single gene disease in which some people develop seizures and mental retardation whereas others do not, although they usually exhibit other features of the disorder. The reason why the same mutation may have variable effects in different individuals is poorly understood, although it is generally attributed to interaction with other genetic and environmental factors. For some disorders, such as myotonic dystrophy and Huntington's disease, the molecular basis of variable expression and penetrance is known to be related to lengths of repeated DNA of varying size (Box 3.2). Even in such cases, there is variable age of onset for a given repeat size, so that it is not possible to define phenotypes solely in terms of the gene mutation. Moreover, mutations in single genes for major disorders may sometime have no discernible effect, a phenomenon termed 'non-penetrance'.

3.6 Single gene disorders are, however, relatively rare; few mental disorders show such simple patterns of inheritance and few families are affected by each disorder. Many common mental disorders appear to be more complex. Their development is affected by a number of factors (multifactorial), which may include several genes (oligogenic) or perhaps many genes (polygenic) as well as environmental factors. Consequently, such disorders do not have a simple Mendelian pattern of inheritance. Studies of families, of twins and of people who have been adopted away from their birth families are used to estimate *heritability*. This is a statistic that estimates how much of the variation within a population for a characteristic can be attributed to the influence of genetic factors rather than the environment (Appendix 1, paragraphs 12–17).

Box 3.1

Phenylketonuria (PKU)

1 Clinical features: if people who are affected eat food containing phenylalanine, a component of most proteins, severe mental handicap results. With rigorous dietary control, development can be normal. This demonstrates two important points: first, that even for conditions in which a mutation in a single gene is sufficient to cause the disease, there can be effective treatments or environmental interventions. Second, that genetic information can be useful for identifying when such interventions are needed.

2 Genetic mechanism: the PKU gene contains the information needed to produce an enzyme that metabolises the nutrient phenylalanine. Everyone has two copies of the PKU gene in their genetic material. If a person has two defective or mutant copies of the PKU gene, phenylalanine cannot be metabolised and substances build up which damage the activity of the central nervous system. PKU affects about 1/10,000 births in the UK and children are screened for the condition at birth (the Guthrie test).

3 The genetic causes and mechanisms of PKU are well understood: two normal genes and you are unaffected, two mutant genes and you have PKU, one of each and you are a carrier – unaffected but with the potential to pass the mutant gene to your children. The way in which PKU is inherited follows a clear pattern known as Mendelian inheritance (after Mendel who described it). Thus, if the genetic make-up of the parents is known, the chances that any children will inherit the condition can be calculated very accurately. Because the effect of a mutant gene is counteracted by a normal gene, PKU is known as a recessively inherited disorder.

4 This example also illustrates another important point – everyone has two copies of the PKU gene but only certain mutant forms of the gene cause the disease.

3.7 If heritability studies suggest that there is a substantial genetic contribution to a complex mental disorder, the next step is to try and identify the specific gene, or genes, that may be involved. The main approaches used are described in Appendix 1. They include association studies on candidate genes and genome searches using pairs of siblings. These techniques are being used in the study of schizophrenia, manic depression, depression, anxiety disorder, obsessive-compulsive disorder and personality disorder. The search for gene variants associated with complex conditions, however, is characterised by many claims but few confirmations. There are several possible explanations for this. For example, such disorders may involve several interacting genes of varying effects, there may be groups of related disorders (paragraph 3.8), and there are likely to be variations in the way different researchers use diagnostic criteria. These

difficulties are further compounded by the particularly complex developmental processes, often including social and environmental influences, which seem to be typical for mental disorders. Despite these problems, genetic research is beginning to increase our understanding of some mental disorders, as described below.

Box 3.2

Huntington's disease

1 Clinical features: progressive degeneration of the central nervous system leading to involuntary movements, loss of motor control and dementia. Symptoms usually begin to appear when people are between 40 and 50, with death occurring 15–20 years later. At present, the disease cannot be prevented, treated or cured. This is a rare disorder affecting about 1/10,000 people in the UK.

2 Genetic mechanism: Huntington's disease is caused by mutations in the Huntington's gene, on chromosome 4. It is a dominantly inherited condition. That is, if one gene has a mutation, even though the other is normal, the person will develop the condition. If one parent has the Huntington's gene mutation, there is a one in two chance that that parent will pass on that gene to his or her child. This means that even though the other parent is unaffected, there is a one in two chance that any child of that relationship will inherit the condition.

3 The mutation is the expansion of a small region of the gene. This region is called a 'trinucleotide repeat' (because the expanded region consists of three base pairs or nucleotides). The size of the repeat correlates with the age of onset of the disorder: large numbers of repeats are associated with earlier onset. Sometimes the repeats increase in size from one generation to the next so that the disease gets more severe in successive generations, a phenomenon known as 'anticipation'.

4 The function of the Huntington's disease gene when not mutated is not understood. The gene contains the information required to make a protein known as 'huntingtin'. The trinucleotide repeat region of the huntingtin is able to bind other proteins including an enzyme involved in energy production. The extra repeats in the mutant forms of the gene and, in turn, in the huntingtin protein may promote cell death and/or impair energy production, and it has been suggested that this ultimately leads to neurodegeneration.

Some mental disorders are a cluster of related disorders

3.8 Genetic studies indicate that some mental disorders may in fact be groups of related disorders. This appears to be the case for Alzheimer's disease (Box 3.3). In certain rare families which show an earlier age of disease onset, gene mutations have been identified that have a major effect and which are inherited in a Mendelian fashion. Although such mutations may account for only a small fraction of the total number of cases of Alzheimer's disease, studying them has been very informative.[1] Other mental disorders, such as schizophrenia, may also be groups of related disorders with different causes.

1 Other forms of dementia, with brain pathology distinct from Alzheimer's disease, largely determined by single genetic loci are being found; for example, frontotemporal dementia and parkinsonism linked to chromosome 17 (McInnes L, Reus V and Freimer N (1998) Mapping genes for psychiatric disorders and behavioural traits, **Current Opinion in Genetics and Development**, 8:287–292).

Box 3.3

Alzheimer's disease

1 Clinical features: progressive decline in memory, initiative and intellect, leading to generalised dementia and death usually within five years. At post mortem, the brain shows characteristic features under the microscope.

2 Genetic mechanism: research into Alzheimer's disease reveals that it is a cluster of dementias, involving different genetic mechanisms.

3 About 1% of cases of Alzheimer's disease show a Mendelian pattern of inheritance and have an early age of onset. These are due to dominant (autosomal) single gene mutations. Either the amyloid precursor protein (APP) gene, the presenilin 1 gene or the presenilin 2 gene may be defective.

4 The majority of cases of Alzheimer's disease have a later age of onset and do not show an obvious tendency to run in families. A gene has been identified, called the apoE gene, which occurs in different variants (alleles). A person's likelihood of developing Alzheimer's disease depends in part on which apoE alleles they possess (E2, E3 or E4). Each individual possesses two apoE alleles in their genetic material. Studies show that there is an elevated risk of Alzheimer's disease in groups of people who carry one E4 allele and that the risk is even higher in people who carry two E4 alleles. However, E4 alleles are best thought of as normal variants, not mutations of the Mendelian type which are much rarer. In addition, these alleles are much more weakly associated with the disease than the mutations involved in Mendelian disorders. In fact, about 15% of the general population has at least one E4 allele and many do not develop Alzheimer's disease, whereas perhaps as many as 50% of people who do develop the disorder do not carry an E4 allele. This indicates that other factors are involved: almost certainly other genes and also environmental factors (for example, diet and head injury).

5 Thus the situation with the apoE gene is very unlike that for single gene disorders in two major respects. First, genetic testing offers an approximate estimate of risk rather than a certain answer because it does not take additional, individual risk factors into account. Second, the apoE4 allele that is associated with increased risk occurs at much higher frequency in the population than the very rare single gene mutations.

6 Genetic studies of Alzheimer's disease have provided new insights into the underlying causes of the disease. Amyloid precursor protein, the product of the APP gene, is converted into beta-amyloid. Beta-amyloid is the main component of the plaques seen in Alzheimer's disease and mutations of the APP gene lead to increased levels of beta-amyloid. Understanding these processes offers new possibilities for treatment.

Most common mental disorders probably involve variations of several genes

3.9 As already mentioned, most common disorders, and this includes physical diseases as well as psychiatric ones, are probably influenced by variants in several or many genes with each individual gene variant having a comparatively small effect. A good example is so-called type 1 diabetes mellitus, the form of diabetes that starts early in life and responds to insulin treatment.

The risk of the disorder is about fifteen times higher for the brother or sister of an affected child than for the general population. One of the genes involved is on chromosome 6 in a part called the HLA region. Having a particular HLA variant can increase the risk of diabetes by three- or four-fold. Another is a variant of the insulin gene on chromosome 11. This confers roughly a doubled risk. Other genes have also been reported which confer somewhat smaller increases in risk of type 1 diabetes. A pair of affected siblings, therefore, would have to share several 'high risk' gene variants if the sibling recurrence risk of fifteen-fold over normal were to be explained solely by genetic susceptibility.

3.10 One way of looking at disorders like this is to assume that susceptibility (or liability) to a disorder is variable in the population with some having low susceptibility, some having high susceptibility and most people being somewhere in the middle.[1] It is also assumed that susceptibility results from a combination of predisposing genes and environmental risk factors. Only those individuals with a high susceptibility, which at some point exceeds the threshold for becoming ill, actually show the disorder. This type of model accounts for a number of features of common disorders that would be puzzling if we were to try and explain them with a simpler Mendelian model:

- Common conditions may show a broad range of severity, and in some, for example depressive disorder, the milder forms may shade into normal low mood, with no clear boundaries except that, by definition, a disorder tends to result in impairment.
- The gene variants conferring susceptibility are likely to be common in the population. Many people will carry one or more alleles associated with raised risk (for example the apoE4 risk allele for Alzheimer's disease) but never develop the disorder.
- A disease may seem to `appear from nowhere'. That is, a person may develop the condition even though there is no family history. This may be because an individual's chance inheritance of a high number of susceptibility genes results in the disorder, even though their parents and other family members carry a combination of these genes that is below the threshold for being affected. Alternatively, it may be that some people with a high susceptibility are not exposed to the relevant environmental factors which also affect the development of the mental disorder.

Some genetic influences affect more than one disorder

3.11 Some psychiatric disorders appear to be genetically distinct from one another. For example, there appears to be no genetic overlap (contrary to what was once thought) between schizophrenia and autism. By contrast, depression and anxiety often occur in the same patients and it has recently been inferred from twin studies that there is a considerable overlap between the genetic factors that confer susceptibility to these two sets of symptoms.

3.12 Such findings again point to a continuum of susceptibility underlying mental disorders and suggest that the same genes that contribute to individual differences in normal personality may be relevant to disease. Thus, genetic studies may reveal information about normal traits which, at the extreme, result in a disorder. Again, this is not confined to psychiatric illness but also is

2 The theoretical models that are most useful in conceptualising this complicated type of inheritance are known as liability-threshold models. Height or weight are good examples of characteristics that show a bell shaped normal distribution in a population. The idea that a continuum of liability underlies common diseases suggests that these, like characteristics that are more obviously continuous (eg height, weight, personality dimensions), can be regarded as quantitative traits (Appendix 1).

relevant to common physical diseases. For example, the level of cholesterol in the blood is a characteristic which varies throughout the population and high levels at the extreme end of the range may contribute to the development of coronary heart disease. In support of this, it has now been firmly established that lowering cholesterol by the use of drugs in subjects with high cholesterol levels significantly reduces their risk of having a heart attack.

3.13 A recent, and still preliminary, example relevant to mental disorder involves the dopamine receptor DRD4. This gene has different forms, depending on how often a particular region is repeated. The most common forms, or alleles, have four repeats (short allele) and seven repeats (long allele). Two studies have shown that the long allele is associated with significantly higher levels of the personality trait of novelty seeking.[2,3] Novelty seeking is regarded as a normal personality trait, not a disorder. As both alleles occur at high frequencies in the population, the long allele cannot be thought of as a mutant or defective gene. Rather it is a normal variant or polymorphism. Moreover, the association accounts for only 4% of the normal population variation in scores on a novelty seeking questionnaire, so the gene variant has only a very small effect.

3.14 While novelty seeking is a normal personality trait, subsequent studies have found that the association of DRD4 with novelty seeking may also be correlated with susceptibility to several mental disorders. There is preliminary evidence that the long allele *is over-represented* in samples of people with attention deficit-hyperactivity disorder (ADHD) and is *under-represented* in people with major depression. Note, however, that these associations are still controversial and, in any case, so weak that they do not allow useful predictions to be made. Table 3.1 gives further examples of genetic variants (alleles) thought to be associated with different disorders or traits.

Table 3.1:

Some examples of genes thought to be associated with different disorders or traits

Gene	Alleles	Associated disorder or trait
Dopamine D4 receptor (DRD4)	Long	ADHD[4]
Serotonin transporter (5-HTT)	Short	Neuroticism[5] Manic depression[6]
Serotonin 2a receptor (5-HT2a)	C polymorphism	Schizophrenia[7]

3 Ebstein R, Novick O, Umansky R, Priel B, Osher Y, Blaine D, Bennett E, Nemanov L, Katz M and Belmaker R (1996) Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of novelty seeking. **Nature Genetics** 12: 78–80.

4 Benjamin J, Li L, Patterson C, Greenberg B, Murphy D and Hamer D (1996) Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. **Nature Genetics** 12: 81–84.

5 Lahoste G, Swanson J, Wigal S, Glabe C, Wigal T, King N and Kennedy J (1996) Dopamine D4 receptor gene polymorphism is associated with attention-deficit hyperactivity disorder. **Molecular Psychiatry** 1: 121–124.

6 Lesch K-P, Bengel D, Heils A, Sabol S, Greenberg B, Petri S, Benjamin J, Muller C, Hamer D, and Murphy D (1996) Association of Anxiety-Related Traits with a Polymorphism in the Serotonin Transporter Gene Regulatory Region, **Science** 274:1527–31.

7 Rees M, Norton N, Jones I, McCandless F, Scourfield J, Holmans P, Moorhead S, Feldman E, Sadler S, Cole T, Redaman K, Farmer A, McGuffin P, Owen M and Craddock N (1997) Association studies of bipolar disorder at the human serotonin transporter gene, **Molecular Psychiatry** 2: 398–402.

8 Williams J, McGuffin P, Nothen M, Owen M and the EMASS Collaborative Group (1997) Meta-analysis of association between the 5-HT2a receptor T102C polymorphism and schizophrenia, **The Lancet** 349: 1221.

What do genetic studies of mental disorders tell us about normal behaviour?

3.15 It is apparent from some of the above examples that genetic studies of mental disorders may reveal information about normal traits if the disorders blend into the extreme end of the normal population. This carries an implication that susceptibility genes which predispose to mental disorder may also confer identifiable *advantages* for the individual. For example, it has been suggested that manic depression (bipolar affective disorder) arises at the extreme end of variation in a trait associated with energy and creativity.[8] This adds a further dimension to the debate about whether it is possible to draw a line between disorders regarded as pathological and legitimate territory for medical interventions and those behaviours within the normal range that are not.

Many mental disorders involve genetic and environmental factors

3.16 Considerable energy continues to be expended on trying to demonstrate that *either* biological *or* environmental factors are of prime importance in the development of mental disorders. Some diseases are indeed due largely to one or other of these factors. For example, the eating disorder bulimia nervosa is familial but there appears to be a negligible genetic contribution to bulimia symptoms, suggesting that environmental influences are of prime importance.[9] Conversely, in Huntington's disease, inheriting the genetic defect is necessary and sufficient for development of the condition. Even for this condition, however, there is considerable variation in severity and age of onset, some of which is likely to be due to environmental factors.

3.17 Epidemiological studies suggest that, for most of the common mental disorders, both genetic and environmental influences are likely to be important. This concept is familiar from studies of familial hypercholesterolaemia, a genetic disorder present in one in 500 individuals that causes high cholesterol in the blood. The extent to which this predisposes to illness (heart attack) is raised if a person smokes, and is lower in women than men because hormonal influences protect women from hardened arteries until after the menopause.

3.18 A drawback of many studies, however, is that they tend to treat genetic and environmental influences as independent factors. But in the more complex mental disorders, genetic and environmental factors *interact* to a great extent and so are difficult to separate. For example, at first glance, traumatic life events might seem to be environmental occurrences over which individuals have little control.[10] Studies have suggested, however, that genetic differences between individuals affect whether particular events have a traumatic effect. In other words, people differ in their vulnerability to life events.[11] One way of viewing this finding is that genetic susceptibility influences the way in which a person reacts to the environment. In spite of having similar experiences individuals might, or might not, become mentally ill.

3.19 Moreover, the occurrence of events is not always randomly distributed across the population. This has led some to suggest that genetic differences between individuals may affect their behaviour

9 Jamison K (1995) **An Unquiet Mind: A Memoir of Moods and Madness**, Picador, London; Goodwin F and Jamison K (1990) **Manic-Depressive Illness**, Oxford University Press, Oxford.

10 Rutherford J, McGuffin P, Katz R, and Murray R (1993) Genetic influences on eating attitudes in a normal female twin population, **Psychological Medicine** 23:2, 425–36.

11 This and subsequent examples taken from Rutter M and Plomin R (1997) Opportunities for psychiatry from genetic findings, **British Journal of Psychiatry** 171:209–19 and Plomin R, DeVries J and McClearn G (1990) **Behavioural Genetics: A Primer**, Second edition. Freeman, USA, pp250–2.

12 Put another way, differences in individuals' genetic make-up may lead them to experience the same environment differently. For example, it has been suggested that neuroticism is influenced by genetic factors and that neurotic individuals are more susceptible to environmental stress and depression than others.

and hence the events they experience. Factors often thought of as environmental, including parenting, may also reflect genetic influences. If there is a family history of mental illness, for example, a child's susceptibility may be influenced by an affected parent in two ways. First, the child may also have an increased genetic risk. But second, the parent's mental disorder may also produce a more high-risk environment for the child.

3.20 There are important practical implications of evidence that genetic and environmental influences contribute to development in a mutual and interconnected fashion:

- Research studies need to be able to study variation in a number of different genes that are involved in susceptibility to the disease, as well as measuring, with as much accuracy as possible, a number of different environmental risk factors which might be important in contributing to the development of the disease. Measuring such risk factors might be carried out, for example, by detailed questionnaires of life history and lifestyle.
- Even if the genetic influences affecting a disorder are well understood, there is likely to be a degree of variability in the symptoms and outcomes observed.
- Even if the genetic contribution to the development of a disorder is substantial, environmental interventions may still be effective. For example, height is estimated to have a high heritability of 90% but there have been big increases in average height this century due, probably, to improved nutrition. Another example is that of phenylketonuria, in which the consequent neurodevelopmental defects can be overcome by modifying the diet (Box 3.1). This illustrates the point that people with certain single gene disorders can do well if the environment is changed. Thus even strong genetic effects can be environmentally dependent. In the context of more common mental disorders it has been suggested that genetic influences may increase a person's vulnerability to environmental risks. An important question, then, is whether these are risks that it will be practical for people to avoid.

Criticisms of the genetic study of mental disorder

3.21 Given the strong evidence for a genetic contribution to many mental disorders (see Appendix 1), the difficulty of identifying specific susceptibility genes came as a surprise to many. Early results, highly publicised, of linkages of schizophrenia to chromosome 5 and bipolar disorder to chromosomes 11 and X, were followed by numerous failures of confirmation in independent samples. Conventional scientific explanations for these problems revolve around issues such as sample size, diagnostic criteria and statistical interpretation.[12] Theoretically, all of these problems can be overcome by collecting more data or employing association studies.

3.22 2 An alternative interpretation is that there is something fundamentally wrong with the methodology of the statistical approach to genetics involving the calculation of heritabilities. It has been argued that the conceptualisation of factors predisposing to illness into two categories – genes and environment – is not a helpful model of biological and social development. Critics have put forward alternative models[13] accommodating multiple interconnections and hierarchical organisation from societies through individuals to cells and their chemical constituents. As Gray

13 Risch N and Botstein D (1996) A manic depressive history, **Nature Genetics** 12:351–3; Moldin S (1997) The maddening hunt for madness genes, **Nature Genetics** 17:127–9.

14 Alternatives to the genes–environment dichotomy known as constructionism, epigenesis or the developmental systems approach have been suggested by authors such as Lewontin (see Lewontin R (1993) **The Doctrine of DNA: Biology as Ideology**, Penguin, London); Oyama (see Oyama S (1985) **The Ontogeny of Information**, Cambridge University Press, Cambridge and Oyama S (1991) Bodies and minds: dualism in evolutionary theory, **Journal of Social Issues** 47:27–42); and Gottlieb (see Gottlieb G (1991) Experiential canalization of behavioral development in theory, **Developmental Psychology** 27:4–13).

(1992) states, "*the effects of both genetic and environmental differences are contingent on the context in which they occur . . . The impact of an environmental factor will vary depending on the developmental state of the organism and, reciprocally, the effect of a gene being activated will depend on the state of the rest of the developmental system*".[14]

3.23 As with many other accounts drawing upon a large number and wide range of factors, the construction and testing of such a hypothesis is liable to be complicated. For this reason, some would argue that, while the traditional model is undoubtedly an oversimplification, approaches such as partitioning of variance are undoubtedly useful and similar to the study of human beings in terms of their nervous, cardiovascular and gastrointestinal systems.

3.24 That said, the widely used short-hand of 'genes for' so-called traits such as schizophrenia, intelligence, criminality, or even divorce, by some scientists and some elements of the media, is both inaccurate and unhelpful. Critics argue that speaking of a 'gene for' something suggests a deterministic one-to-one relationship between the gene and the characteristic: between genotype and phenotype. We agree that such oversimplifications have great potential to do harm and are to be discouraged.

Conclusions

3.25 Because of its inaccessibility, the brain is not an easy organ to investigate and our understanding of normal brain function is still quite limited. Therefore it is not surprising that it has been very difficult to study the abnormal function of the brain in mental disorders. One great attraction of a genetic approach (and this is well established in other fields of medicine) is that it allows indirect access to processes that are otherwise difficult to study in living people. Thus genetics allows the possibility of inferring the biochemical and functional abnormalities that lead to disease once the underlying changes in DNA have been identified.

3.26 Despite considerable effort to date, genetic research has so far yielded little practical help in limiting the suffering of those with mental disorder. Almost every susceptibility locus identified for the complex disorders listed in Chapter 1 (paragraph 1.3) is still the subject of scientific controversy. However, the difficulty of reproducibly identifying gene loci in common mental disorders represents a key scientific discovery in its own right. It indicates that disorders such as schizophrenia and manic depression are rarely, if ever, caused by simple dominant or recessive mutations analogous to those in rarer disorders such as Huntington's disease or phenylketonuria.[15] This has important implications for application to clinical practice, as outlined in Chapter 4.

3.27 Methodology for genetic research is progressing rapidly due, in part, to the impact of the Human Genome Project. There seems little doubt that, over the next ten years, susceptibility loci will be identified and some of these will hold up to robust scientific scrutiny. These discoveries will certainly improve understanding of the causes of mental disorder, probably more by small incremental steps than major revolutions. The full potential of these discoveries can only be realised if accompanied by a well-integrated and rigorous research programme covering social, developmental and other biological approaches to the understanding of mental disorder.

15 Gray R (1992) Death of the gene: developmental systems strike back, in Griffiths P (ed), **Trees of Life**, Kluwer,The Hague pp175–6.
16 Moldin S (1997) The maddening hunt for madness genes, **Nature Genetics** 17:127–129.

Chapter 4

Clinical applications

Introduction

4.1 This chapter reviews potential clinical applications of genetic research into mental disorders. These include improvements in:

- classification and diagnosis;
- risk assessment for genetic counselling;
- drug treatments;
- preventive medicine; and
- possibly in the more distant future, gene therapy.

4.2 In the case of disorders largely determined by alterations in single genes, genetic information is already being used for classification and diagnosis, genetic counselling and preventive medicine. The pitfalls in these relatively straightforward situations illustrate the many potential difficulties that lie ahead in translating genetic research findings relevant to the more complex mental disorders into useful clinical applications. As such applications have not yet been developed for these mental disorders, the analysis in this chapter is based on two sources of information; first, extrapolations from single gene disorders such as Huntington's disease, second, experience gained in multifactorial disorders for which some of the susceptibility genes have been identified, such as Alzheimer's disease and the non-psychiatric examples of diabetes and familial hypercholesterolaemia.

Classification and diagnosis

4.3 An important distinction between psychiatry and most other branches of medicine is that, although psychiatric diagnoses made by different practitioners show a high level of agreement, little is yet known about any underlying physical changes. Consequently, laboratory tests to confirm or refute diagnoses are generally unavailable. It is possible, therefore, that some psychiatric diagnoses include distinct disorders with different causes. This variation may be due to the interaction of different genes, to the interaction of genes with specific environmental factors, or to the existence of separate disorders in which the same symptoms occur, but genetic predisposition plays little or no role.

4.4 Developments in our understanding of genetics may allow psychiatrists to define subtypes of mental disorders with different underlying causes (paragraph 3.8). Such developments are more likely to result in modification rather than the complete revision of systems of psychiatric classification, but may be very important for understanding the causal mechanisms of disorders.

4.5 The discovery of genes with different mutations has had profound implications for the diagnosis of many single gene disorders. For example, the characterisation of a particular type of mutation called expanded triplet repeats in diseases of the nervous system such as Huntington's disease (Box 3.2) and Friedreich's ataxia has important implications for diagnosis and prognosis. This may occur either in the context of a person who is already ill, for whom a genetic test may confirm or refute a particular diagnosis; or it may predict the later development of an illness in an apparently healthy person or fetus (presymptomatic or prenatal test). However, even single gene disorders are affected by other genetic and environmental effects, so that, for example, age-of-onset and severity in such diseases may be quite variable (paragraph 3.5). It may sometimes

be difficult to establish whether a particular alteration in a gene is pathological or not and, even in single gene disorders, different mutations may have different qualitative and quantitative effects on disease severity.[1] So it is never possible to predict the complete clinical picture from knowledge of mutations in a single gene.

4.6 For disorders with more complex causes susceptibility genes play a role but are neither necessary nor sufficient to cause the disease. This limits the usefulness of genetic tests in either a diagnostic or a predictive context. In familial hypercholesterolaemia (FH), for example, diagnosis by the presence of a specific gene variant is of no better predictive value than a cholesterol assay. Moreover, the development of heart disease is strongly influenced by many factors in addition to FH, including environmental factors (diet and smoking) and other disorders such as obesity, diabetes and hypertension, making prediction of disease risk by genetic testing for FH impracticable for most individuals in the population.

4.7 An example relevant to psychiatry is late onset Alzheimer's disease (Box 3.3). The finding that a gene variant called the apoE4 allele is more common in patients with Alzheimer's disease than healthy controls has shed new light on the biochemical basis of the disease, but the effect of the gene variant accounts for only 15% of susceptibility to the disease. About 50% of all affected patients do not possess an apoE4 allele. Recent studies have concluded that, while apoE4 testing may be important for research, it is not appropriate either for diagnosis or for prediction in members of the population as a whole,[2] although debate on this issue continues.[3] Given the findings from genetic linkage studies (paragraph 3.21) it is likely that few, if any, susceptibility genes associated with mental disorders will make a larger contribution to susceptibility than apoE4 does for Alzheimer's disease. If this turns out to be correct, the usefulness of these loci for either diagnostic or predictive genetic testing will be limited. A positive ratio of benefits to risks of any potential test would need to be demonstrated and replicated in a research setting before routine clinical implementation could be recommended.

4.8 It is perhaps more likely that the identification of susceptibility genes could lead to a better understanding of disorders and hence the development of useful diagnostic tests. Type 1 diabetes (the form of the disorder that occurs early in life and is treated with insulin) is an example. Although a number of susceptibility genes have been identified, notably the HLA and insulin genes, the genetic tests have low predictive power. But by measuring an intermediate clinical feature, the presence in the blood of autoantibodies, healthy siblings of diabetics can be identified who have a greater than 90% risk of developing diabetes within ten years.

4.9 Genetic tests open up the possibility of prenatal diagnosis of the fetus and, assuming that a termination of pregnancy in such circumstances would come within the terms of section 1(1) (d) of the Abortion Act 1967,[4] termination of pregnancy. Prenatal diagnosis is offered in the UK for serious single gene and chromosomal disorders such as fragile X and Down's syndrome that are generally associated with mental retardation from birth and for which a cure appears unlikely.

1 Kahn P (1996) Coming to grips with genes and risk, **Science** 274:496–8; Humphries S, Galton D and Nicholls P (1997) Genetic testing for familial hypercholesterolaemia: practical and ethical issues, **Quarterly Journal of Medicine** 90:169–81.

2 American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer disease (1995) Statement on use of Apolipoprotein E testing for Alzheimer disease, **Journal of the American Medical Association** 274:1627–9; Lovestone S with UK Alzheimer's Disease Genetics Consortium (1995) The genetics of Alzheimer's disease, **International Journal of Geriatric Psychiatry** 10:1–7.

3 Post S *et al.* (1997) The clinical introduction of genetic testing for Alzheimer Disease, **Journal of the American Medical Association** 277:832–6.

4 See the discussion in Kennedy I and Grubb A (1994) **Medical Law: Text with Materials**, Second Edition, Butterworths, UK pp 877–8.

By contrast, the uptake of prenatal diagnosis for single gene disorders that predominantly affect adults, such as Huntington's disease, has been relatively low.[5] In other nervous system disorders such as neurofibromatosis the demand for prenatal diagnosis is even lower.[6] Pre-implantation genetic testing is now feasible for couples at risk for transmitting an identified single gene disorder to their children. To date, uptake has been limited by the technical difficulty, expense and low rate of completed pregnancy associated with the procedure. However, this option may become more popular if these technical hurdles are overcome.[7]

4.10 For mental disorders of complex aetiology any one susceptibility gene is very unlikely to be necessary or sufficient to cause a disease, making it difficult to predict its future occurrence and severity in a fetus or child with any certainty. Unlike Huntington's disease, many mental disorders already have reasonably effective treatments and there is every prospect that those treatments will improve further in future decades. Quite apart from the ethical and legal considerations discussed in Chapter 5, therefore, prenatal diagnosis for the common mental disorders is unlikely either to have sufficient predictive value to be indicated medically or to be demanded by families.

Genetic counselling

4.11 The Working Party adopted a broad definition of genetic counselling as "*the process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it and of the ways in which this may be prevented, avoided or ameliorated*."[8] Adults may want to confirm the diagnosis of an existing disorder or to explore their own risk of developing a disorder and its likely severity. Genetic counselling in relation to children may have the same aims but it raises additional issues of consent if genetic testing is contemplated. In addition, adults may seek genetic information about themselves, their partners, their children or a fetus in order to help them make reproductive decisions.

4.12 In the UK, genetic counselling is a specialist service for individuals and families provided by clinical geneticists and other trained professionals in regional centres. At present, genetic counselling for complex mental disorders occurs fairly rarely. It has been said that families show a thirst for knowledge,[9] and it is generally thought that the demand for genetic information is likely to increase.[10]

4.13 Genetic counselling depends on two types of risk figures, *empiric* and *calculated*. *Empiric* risk figures are based on gathering data on the frequency of a disorder in a population. Thus the empiric risk of schizophrenia in the UK population is about 1%. Such figures 'average out' differences in actual risk between individuals. If the empiric risk figure is relatively low (less than 2%) this may often provide reassurance in a situation where people overestimate risks and assume the worst. However, the empiric risk figures for first-degree relatives of individuals

5 In one study of Huntington's disease, for example, only 7 out of 38 (18%) of couples eligible for a prenatal test decided to proceed. Optimism about the discovery of a cure was the predominant reason given for not considering prenatal testing (Adam S, Wiggins S, Whyte P, Bloch M, Shokeir M, Soltan H, Meschino W, Summers A, Suchowersky O, Welch J, Huggins M, Theilmann J and Hayden M (1993) Five year study of prenatal testing for Huntington's disease: demand, attitudes, and psychological assessment, **Journal of Medical Genetics** 30:549–56).

6 Ponder M, Murton F, Hallowell N, Statham H, Green J. and Richards M (1998), Genetic counselling and future reproductive intentions of people with neurofibromatosis type 1 (NF1), **Journal of Genetic Counselling**, in press.

7 Schulman J, Blake S, Handyside A and Nance W (1996), Preimplantation genetic testing for Huntington's disease and certain other dominantly inherited disorders, **Clinical Genetics** 49:57–8.

8 Harper P (1993) **Practical Genetic Counselling**, Fourth edition, Butterworth-Heinemann Ltd, Oxford,.

9 Office of Technology Assessment/Congress of the United States (1994) **Mental Disorders and Genetics: Bridging the Gap Between Research and Society**, OTA-BP-H-133, US Government Printing Office, Washington DC, p36.

10 McGuffin P (1994) Genetics, Chapter 4 in Paykel E and Jenkins R (eds) **Prevention in Psychiatry**, Gaskell Press, London.

affected by certain mental disorders of complex basis are often considerably higher. For example, the sibling and offspring risks for individuals affected by schizophrenia are around 10% (Appendix 1, Figure 1). The usefulness of empiric risk figures in genetic counselling for the occurrence of mental disorders in relatives has never been evaluated but making decisions based on such low risks is often very difficult.

4.14 *Calculated* risk figures are based on objective criteria, including knowledge of the specific mode of inheritance and/or the results of blood tests, X rays or genetic tests, to modify empiric risks. In some cases this will result in an increased or decreased individual risk figure. Arguably, the value of genetic counselling depends on the possibility of categorising an individual's risk on objective, rather than empiric criteria. To what extent, then, will genetic testing for complex mental disorders make it possible to provide individualised risk figures?

4.15 Individual risk figures that combine a knowledge of the family history with the results of single locus testing can be obtained by a type of mathematical reasoning called Bayesian theory.[11] It can be shown that this approach works fairly well in predicting risks for relatives of affected individuals even when the risk contributed by each susceptibility gene is comparatively small.[12] For example, the risk of developing schizophrenia if one has a first-degree relative (parent, brother or sister) already affected is about ten times the general population risk, or about 10%. Genetic research is beginning to identify potential susceptibility genes for schizophrenia and one of these is a variant in the serotonin receptor (5HT2a) gene which, one study has shown, occurs in about 70% of people with schizophrenia in the UK (Table 3.1). The variant also has a high frequency in healthy controls (about 55%) but the difference between the frequencies in people with schizophrenia and controls is statistically significant.[13] What would be the risk of developing schizophrenia for someone who already had a brother affected by schizophrenia and who tested positive for the serotonin receptor variant? The answer (using the Bayesian method) is 12.3%, in other words, only a little higher than the 10% empiric risk figure. Such an increase is unlikely to be clinically significant given evidence that reduction in uncertainty is one of the most common reasons given for undergoing a DNA test.[14]

4.16 Despite such examples, it has been claimed that gene identification will be very valuable in personalising risks, and that the increase in precision provided by the ability to calculate risks on an individual basis will be of enormous clinical benefit.[15] Evidence to support such claims, however, is lacking. There is currently very little provision, or demand for, genetic counselling in any of the common multifactorial disorders such as cardiac disease and diabetes, even where tests are available that would allow the calculation of individual risk. Indeed, no objective study of genetic counselling in these diseases has been undertaken. One possible reason for this is that, in the absence of effective therapeutic interventions for people found to be at high risk, such studies have not been considered either ethically acceptable or cost-effective. Studies are now being contemplated (for example, in diabetes), however, and their findings might have important implications for the management of mental disorders and for genetic counselling.[16]

11 This takes into account an individual's initial risk (the so-called prior probability) of disease and then allows a calculation of the modified risk once the result of a test is known (the posterior probability).

12 It is possible to take the empiric risk as the prior probability and use genetic marker data to calculate the posterior probability of becoming affected.

13 Williams J, Spurlock G, McGuffin P, Mallet J, Nöthen M, Gill M, Aschauer H, Nylander P, Macciardi F and Owen M (1996) Association between schizophrenia and T102C polymorphism of the 5-hydroxytryptamine type 2a-receptor gene. European Multicentre Association Study of Schizophrenia (EMASS) Group, **The Lancet** 347:9011, 1294–6.

14 Marteau T and Croyle R (1998) Psychological responses to genetic testing, **British Medical Journal** 316:693–6.

15 Rutter M and Plomin R (1997) Opportunities for psychiatry from genetic findings, **British Journal of Psychiatry** 171:209–19.

16 British Diabetic Association (1996) Ethical issues in research into prevention of insulin-dependent diabetes mellitus (IDDM), **Diabetic Medicine** 13:399–400.

4.17 In type I diabetes, a number of preventive strategies are theoretically feasible for healthy siblings of diabetics who are identified by autoantibody measurement as at risk of developing diabetes. Placebo-controlled trials are under way to determine whether these strategies delay or prevent the onset of diabetes.[17] Here, prediction and prevention (or at least, its possibility) are being offered hand-in-hand in a research setting. Such studies allow the evaluation of the psychological effects of risk alteration and genetic counselling for common multifactorial diseases.

4.18 The value of genetic counselling in the common multifactorial mental disorders will depend on two principal criteria: the ability to calculate individual risks and the ability to identify preventive measures to reduce risk in individuals at high risk.[18] It is difficult to predict the extent to which these criteria will be met but, given the difficulty of identifying convincing susceptibility genes over the past ten years, it seems likely that only a small proportion of individual risk will be predictable even when multiple susceptibility genes can be tested. The 15% contribution that apoE4 makes to variance in risk for late onset Alzheimer's disease is probably the maximum contribution we can expect for individual susceptibility genes for most mental disorders; a more typical figure would be the 4% variance in novelty-seeking behaviour apparently explained by the DRD4 genotype (paragraphs 3.13–3.14).

4.19 The lack of usefulness of apoE4 testing for genetic counselling has already been highlighted (paragraph 4.7). The value of testing for most mental disorders will be still weaker if the genetic susceptibilities are lower. Even if sufficient susceptibility genes were identified to explain say, 30% of the variation in risk between different people in a population, without an understanding of the interactions between the genes, and between genes and environment, it would still be difficult to predict accurately the risk for an individual (paragraph 4.21).

4.20 To summarise, genetic testing in complex mental disorders is unlikely to improve on the empiric risk figures (paragraph 4.13) by more than a modest extent. Nevertheless, it is important to study genetic and environmental susceptibilities and their correlation and interaction, since this may shed further light on causal mechanisms and suggest novel therapeutic or preventive strategies. Empiric risk figures for recurrence of mental disorders in relatives already exist, yet their value in genetic counselling has never been evaluated. Similarly, no data are available on the value of genetic testing and counselling for common diseases (heart disease, diabetes) in which susceptibility genes have already been identified.[19] In mental disorders, direct investigation using brain imaging of how brain mechanisms are disrupted may yet be more convincing and have greater clinical implications than genetic approaches.[20]

4.21 If developments in genetics continue at the present rate, however, some possibilities that currently seem unrealistic, such as testing simultaneously for large numbers of susceptibility genes and examining combined risks, may become feasible. One obstacle to the potential usefulness of genetic tests for multifactorial disease is that we do not know how many susceptibility genes are involved nor how they combine and interact. For example, we do not know whether carrying several 'high risk' variants in different genes has a simple additive effect or whether the situation is more complicated.[21] Estimating the predicted risk where two predisposing genes are thought to be involved is not possible using the Bayesian method (paragraph 4.15) because the interactions between the genes are not known. Empirical research will be needed, examining the effects of

17 Alberti K (1993) Preventing insulin dependent diabetes mellitus, **British Medical Journal** 307:1435–6; Palmer J (1994) What is the best way to predict IDDM? **The Lancet** 343:1377–8.

18 Rutter M and Plomin R (1997) Opportunities for psychiatry from genetic findings, **British Journal of Psychiatry** 171:209–19.

19 Boerwinkle has pointed out the difficulties of attempting to derive estimates of genetic risk on the basis of retrospective or cross-sectional studies, and has emphasised the need for prospective studies to address these questions (Boerwinkle E (1996) A contemporary research paradigm for the genetic analysis of a common chronic disease, **Finnish Medical Society DUODECIM, Annals of Medicine** 28:451–7).

20 A point made by Professor Guy Goodwin, University of Oxford, Department of Psychiatry, in advice to the Working Party.

21 In other words, the effect of variant *a* and variant *b* may be *a* x *b* rather than *a* + *b*.

the genes of interest in large samples. Again, it must be emphasised that, even if all the susceptibility genes involved and their interactions were known, there are limits to the predictive certainty. Even if a pair of relatives are alike at all of the relevant genes and the first member of the pair develops schizophrenia, the second will not necessarily become affected too. We know this because the concordance rate for identical twins (who are 'natural clones' sharing 100% of their genes) is just under 50% indicating that non-genetic influences are also important (Appendix 1, Figure 2).

Development of new and better targeted drug treatments

4.22 Although many pharmacological and behavioural treatments have been identified for mental disorders, their therapeutic efficacy for a given individual can be unpredictable. To a degree, drug development for psychiatric disorders has been a question of trial-and-error. There is great optimism that a better understanding of brain chemistry in mental disorders will lead both to new treatments and to treatments that are better tailored to individual requirements, with fewer side effects. Finding specific alterations in susceptibility genes for mental disorders may provide a better understanding of the biochemical pathways of disease. Knowledge of these pathways may suggest entirely new drug treatments.[22]

4.23 Work to reduce the side effects of drugs which already exist is rather further advanced. The gene variants that influence whether a person suffers from side effects may be concerned with the general metabolic handling of the drug and, as such, may be distinct from the susceptibility genes associated with mental or other disorders. For example, a gene that codes for a type of enzyme called p450 determines the efficiency with which certain drugs are metabolised by the liver.[23] In most cases, this variation will be present throughout the population, rather than being confined to individuals with the disease. Such information may enable doses of medicine to be tailored more accurately to the individual so that therapeutic levels are achieved, rather than the patient being under or over medicated.

4.24 The pharmaceutical industry has been investing very heavily in genomics over the past few years and is optimistic about developing drugs which are targeted to specific patients. "*In clinical efficacy trials, genomics provides an increasingly sensitive tool to devise a novel framework for specific diagnosis, selective therapy and prediction of non-responders.*" [24] However, it should be emphasised that optimism about 'pharmacogenomics' is largely based on supposition, rather than on what has already been achieved. So far, the real contribution of molecular genetics to the production of medicines has not come from new gene discovery. Rather it has come from using recombinant DNA technology to turn organisms such as bacteria into 'chemical factories' by introducing known human genes, for example the insulin gene, and harvesting the gene product.

22 For example, the detailed causation of cystic fibrosis remained obscure until the identification of mutations in the CFTR gene in 1989. Subsequent studies showed that the CFTR gene is responsible for a chloride channel, a protein on the membrane of cells, that is involved in controlling chloride levels. If the gene is abnormal this particularly affects some parts of the body, such as the linings of the lungs and the intestines. This finding in turn has spurred an explosion of work on the biochemical pathway within which this chloride channel lies and hence the identification of 'weak points' which might be targeted by novel drugs. (Delaney S and Wainwright B (1996) New pharmaceutical approaches to the treatment of cystic fibrosis, **Nature Medicine** 2:392–3). An additional point to emerge from this work is that different therapies would be appropriate for different cystic fibrosis mutations. Such a refined approach to development of new medicines would have been inconceivable in the pre-genomic era. Nevertheless, it must be emphasised that, nearly a decade after the discovery of the CFTR gene, these new potential therapies are still some way from being applied clinically.

23 Another example of a situation in which part of the variation in response to medication is attributable to genetic factors is apoE in the context of familial hypercholesterolaemia (FH). In a study of the efficacy of the lipid lowering drug probucol in FH patients, apoE genotypes significantly influenced how well patients responded, but had no influence on hypercholesterolaemia not attributable to FH. (Nestruck A, Bouthillier D, Sing C and Davignon J (1987) Apolipoprotein E polymorphism and plasma cholesterol response to probucol, **Metabolism** 36:743–7.)

24 Shaw G (Chairman) (1995) **Human Genetics: The Science and Its Consequences, House of Commons Science and Technology Committee Third Report, Session 1994–95, Volume II Memoranda received up to January 31st 1995**, 41-II, HMSO, London, p81 submitted as part of the response by SmithKline Beecham to the Working Party's consultation.

Improved preventive measures

4.25 There is ample evidence that genetic background is usually not sufficient to cause mental disorder, and that interaction with environmental factors may be crucial for disease to occur. The identification of susceptibility genes would enable this relationship to be studied in a more sophisticated fashion. This might enable the identification of specific environmental triggers that cause disease in genetically susceptible individuals. For example, boxers show wide variation in their susceptibility to neurological damage. Preliminary evidence suggests that boxers with the apoE4 allele are more likely to suffer neurological damage than those without.[25] Even if this result is confirmed, however, the Working Party would caution against any suggestion that apoE4 testing should be used to enable boxers to assess their risk of suffering neurological damage more precisely, not least because this might lead people without apoE4 alleles to underestimate the risks of what is always a highly dangerous activity. This example illustrates the complexity which arises when variants of susceptibility genes are both relatively common in the population and associated with more than one disease or characteristic (paragraph 5.20).[26]

4.26 Many preventive measures for medical conditions require positive intervention, such as changes in diet (phenylketonuria), vitamin supplementation (neural tube defects) or hormonal replacement (congenital hypothyroidism). The risk/benefit ratio of such measures needs to be evaluated very carefully. For example, two drugs in the Coronary Drug Project secondary prevention trial had to be discontinued before completion of the study because of excess mortality.[27] The risks of such interventions are even more pertinent if individuals are susceptible to a disorder, but there is no certainty that the condition will develop in the absence of treatment.

4.27 There is preliminary evidence that a common variation in the dopamine receptor DRD4 allele is weakly associated not only with variation in a behavioural dimension (novelty seeking), but also with a number of pathological states such as attention deficit hyperactivity disorder, drug dependence, and major depressive disorder (paragraphs 3.13–3.14). It has been argued that these findings may suggest specific preventive measures, for example, avoidance or behavioural therapy. However, any use of targeted environmental modification may be unrealistic given that the health care and social welfare system has not eliminated simple, basic inequalities of service delivery which themselves contribute substantially to ill-health. Moreover, avoiding environmental triggers is not always realistic, especially if a number of family members suffer from a mental disorder.

25 Jordan B, Relkin N, Ravdin L, Jacobs A, Bennett A and Gandy S (1997) Apolipoprotein E 4 associated with chronic traumatic brain injury in boxing, **Journal of the American Medical Association** 278:136–40.

26 Indeed, another study has suggested that, while smoking is a strong risk factor for Alzheimer's disease in individuals without the apoE4 allele, it has no effect in people with this allele (Ott A, Slooter A, Hofman A, van Harskamp F, Witteman J, Van Broeckhoven C, van Dujin C and Breteler M (1998) Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: The Rotterdam Study, **The Lancet**, 351:1840–3).

27 Levine G, Keaney J and Vita J (1995) Cholesterol reduction in cardiovascular disease, **New England Journal of Medicine** 332:512–21.

Gene therapy

4.28 Gene therapy has received wide publicity in recent years but its clinical efficacy remains highly speculative. A report by a US National Institutes of Health Working Party (reviewed by Touchette[28]) criticised the standard of current gene therapy protocols and emphasised that therapeutic efficacy had not been demonstrated for any disorder. The report highlighted the mismatch between the poor knowledge of basic mechanisms of gene regulation and the mechanisms by which diseases are caused, and the ambitious nature of the therapeutic measures being attempted. Until there is evidence that gene therapy for technically more straightforward metabolic or haematological disorders is effective, it should not be applied to mental disorders. This is likely to take at least a decade. Even once this has been achieved, additional problems in treating mental disorders, such as the difficulty of modifying neural tissue which is both highly inaccessible and composed of non-dividing cells, will need to be overcome.

Conclusions

4.29 Developments in genetics may allow psychiatrists to define subtypes of mental disorders with different causes but this is more likely to result in modification rather than complete revision of systems of psychiatric classification. Identification of genes involved in susceptibility to common mental disorders is unlikely to lead directly to the development of diagnostic tests but may do so indirectly by improving understanding of abnormal biochemical processes.

4.30 Because of their complex aetiology, it is unlikely that genetic tests will be of much use for the diagnosis of most common mental disorders. Hence it is even less likely that genetic testing for common mental disorders will be useful for general population screening for susceptibility to mental disorders. Further research will be required before it can be known whether genetic testing will prove useful in the genetic counselling of individuals who are known to be at high risk because of a family history of mental disorder.

4.31 An improved understanding of biochemical processes resulting from genetic research provides long-term potential for the development of more specific and effective drug treatments. There may be potential for preventive measures once genes conferring susceptibility to common mental disorders have been confidently identified. However, preventive strategies are likely to be less clear cut than those for single gene disorders.

4.32 The usefulness of gene therapy in single gene disorders has so far been disappointing. Although the application of gene therapy to common mental disorders at some point in the future cannot be discounted, it would not be appropriate to formulate an approach until general principles have been validated in the technically more straightforward single gene disorders.

28 Touchette N (1996) Gene therapy: Not ready for prime time, **Nature Medicine** 2:7–8.

Chapter 5

Clinical applications of genetic information about mental disorders: ethical and legal issues

Introduction

5.1 In this chapter we consider the range of ethical and legal concerns, outlined in Chapter 1, that may arise for individuals, their families and their physicians when genetic information about mental disorders is sought or used in a clinical context. We begin with a discussion of genetic counselling, since this is often the prelude to, and a component of, any genetic investigation.

Genetic counselling

5.2 Genetic counselling is defined in Chapter 4 (paragraph 4.11). It may be undertaken when individuals are seeking information about a condition which may be inherited or about methods of risk reduction where this is possible: when they are considering having genetic tests; when they are being treated for genetic disorders; or when they are making reproductive decisions. Genetic information creates difficulties in two senses. It may be technically difficult for many people to understand and its implications for an individual's own future and for a family's future may be emotionally difficult to accommodate.

5.3 There are already accepted ethical standards which genetic counselling must meet.[1] Those who provide it have responsibilities:

- to ensure that genetic counselling is voluntarily undertaken;
- to provide accessible and accurate information both about patterns of inheritance and about the condition;
- to ensure confidentiality and to explain to those receiving counselling if there are good reasons for them to share the information with other relatives;
- to emphasise at each stage of counselling that consent to counselling or to a genetic test (if available) does not constitute consent to take any advice that is offered, to take any reproductive decision or to terminate a pregnancy.

5.4 For a few conditions, such as Huntington's disease, it is possible to give very precise figures about the risk of occurrence on the basis of a family history (Box 3.2). For complex disorders such as schizophrenia, all that can be offered by genetic counsellors is an estimate of average risk based on studies of families with the condition. Because the common mental disorders involve a variety of genetic and non-genetic causative factors, and are likely to involve variation in several (or many) genes, the contribution to risk of any one susceptibility gene may be small. While counsellors must convey risks accurately they must also make clear the limitations of current scientific knowledge, in particular about the interaction of different environmental and genetic factors.

5.5 Accuracy in genetic counselling is profoundly important where mental disorders are concerned because anyone left with a misleading view of their risk may suffer additional trauma to their personal integrity and additional fear of stigma. Those providing genetic information about mental disorders must bear in mind that many "*people with psychiatric problems have low self-esteem and they may conclude that the results of a genetic test confirm their low opinion of themselves.*"[2] In particular, before embarking on counselling, they must judge carefully whether

1 See, for example, Nuffield Council on Bioethics (1993) **Genetic Screening: Ethical Issues**, London, Nuffield Council on Bioethics; Harper P and Clarke A (1997) **Genetics, Society and Clinical Practice**, Bios Scientific Publishers, Oxford, and British Medical Association (1998) **Human Genetics: Choice and Responsibility**, Oxford University Press, Oxford.

2 Response by Dr Katherine Rimes and Dr Paul Salkovskis, Univeristy of Oxford, Department of Psychiatry, to the Working Party's consultation.

providing information might not add to patients' difficulties. An exaggerated perception of the degree to which genetic influences determine an individual's health and future is widespread. For individuals with psychiatric problems, as for those with other conditions, "*an increased risk result may cause fatalistic attitudes towards their current problems and decrease their motivation to try to resolve their difficulties.*" [3] For these reasons counselling about genetic factors making a slight contribution to risk should never be urged on individuals who do not clearly want it.

5.6 In view of these points it might be thought that there is little to be gained from genetic counselling for those in families with complex disorders. However, it seems that some people value the opportunity to learn about and discuss their risks. Since there is often a tendency to perceive risks as higher than the evidence confirms, genetic counselling can be reassuring in some cases. Moreover, a complaint not infrequently made by members of families, where individuals suffer from mental disorders, is that they find it difficult to get clear and accurate information about the possible inheritance of the disorder, and that this information is often not available from general practitioners.

5.7 The impact of genetic counselling on people who are not themselves ill but are in a family with a history of mental illness must also be considered. Genetic counselling has the potential to affect family dynamics adversely and to trigger anxiety and even illness if it involves giving information about an individual's risk. Stress may also arise if counselling cannot predict a precise level of risk, leaving individuals in a state of uncertainty. There is as yet little precise evidence about the effects of genetic counselling for mental disorders; caution is indicated. **The Working Party recommends that research is undertaken to clarify the appropriate aims and outcomes of genetic counselling for mental disorders and to assess the response of individuals and families to counselling. Such research should investigate the expertise and training needed by those undertaking counselling for various conditions and purposes.**

5.8 Counsellors must be aware that, in consenting to counselling, individuals and families have not consented to any subsequent course of action. Although it may be impossible to provide wholly non-directive counselling, the aim should be to enable those counselled to make their own decisions at each stage of the process. This may be particularly demanding for genetic counselling involving mental disorders because, as noted, genetic information is cognitively and emotionally demanding and mental disorders are distressing to patients and their families. The mental health charity and service provider MIND, for example, was concerned that genetic counsellors "*may have little experience of mental health problems, and see a life with, say, manic depression as necessarily tragic and a 'burden'.*"[4]

Provision of genetic counselling

5.9 If genetic counselling is to be conducted in an ethically acceptable manner, thought needs to be given to its provision. At present, very few centres provide genetic counselling for mental disorders in the UK. This reflects the fact that mental disorders due to mutations in single genes are extremely rare and that, as yet, there is little information about the susceptibility genes associated with the common mental disorders. The future demand and need for genetic information and counselling is difficult to predict but, as more knowledge about genetics becomes available, demand may well increase.[5]

3 Ibid.
4 Response by MIND to the Working Party's consultation.
5 McGuffin P (1994) Genetics, Chapter 4 in Paykel E and Jenkins R (eds) **Prevention in Psychiatry**, Gaskell Press, London.

5.10 Analogies with genetic counselling for other disorders may be helpful.[6] Some breast cancer clinics are developing a useful method for coping with increased demand for genetic information and assessing whether specialist counselling is needed. Those referred to a clinic are interviewed over the telephone by a genetic nurse. The individual's risk is estimated according to guidelines developed at consensus meetings. For most referrals, specialist counselling is not appropriate and a letter is sent to the GP containing the information needed to inform and reassure the patient.

5.11 For the common mental disorders, susceptibility genes are unlikely to increase an individual's risk to a degree which would merit specialist counselling, at least for the purpose of discussing genetic testing. So, beyond the small number of people with rare, single gene disorders, the need for specialist counselling should be low. If this turns out to be the case, it will be important to balance any inappropriate demand for specialist genetic counselling against other healthcare priorities. There is, however, an ethical obligation to identify the few who genuinely need specialist genetic counselling and to provide any useful information to those who do not. Such information will be most needed by primary healthcare teams which undertake 90% of the care of those with mental disorders. These teams, however, cannot, and should not, be expected to provide specialist counselling or advice. Psychiatric nurses trained in genetic counselling would be well placed to provide a link between primary care teams and genetic clinics offering specialist counselling. For those who do provide specialist counselling, a multidisciplinary approach will be needed, drawing both on clinical geneticists' expertise in interpreting complex genetic information and counselling for the rare single gene disorders, and on psychiatrists' experience in diagnosis and care of those with mental disorders. It has been suggested that the basics of genetic counselling could usefully be covered in general professional psychiatric training.

5.12 It is important to take a considered view of the resources available, in genetics, in mental health and in primary care. In 1991, the Royal College of Physicians recommended that there should be two consultant clinical geneticists per million population. Although the number of geneticists has been rising, this target has yet to be met in any centre, despite the steadily increasing demand for genetic counselling services.[7] In 1997, the Royal College of Psychiatrists warned of "*the current crisis in mental health services.*"[8] There is evidence that some psychiatric patients do not receive basic information even about contraception, or counselling about relationships. In such circumstances, it is unlikely that they will receive information or counselling about genetics, even if it might be of benefit. Finally, a general practitioner (GP) who responded to the consultation considered that GPs lack appropriate premises, equipment and staff and, as such, "*general practice is ill-equipped to deal with the challenges of the present day, let alone those that will come with the completion of the human genome*" project.[9] It was of concern to many who responded to the consultation that genetic research and services might divert resources from the provision of more immediate help and support for those with mental disorders.[10] Provision for genetic counselling and related services for psychiatric patients should be proportional to the urgency with which they are needed. **The Working Party recommends that the British Society for Human Genetics and the Royal Colleges of General Practitioners, Nursing, Psychiatrists and Physicians consider arrangements for the education, training and support both of primary health care teams providing genetic information about mental disorders and of those providing specialist genetic counselling.**

6 The results of the Confidential Enquiry into Counselling for Genetic Disorders will be published in late 1998.
7 Royal College of Physicians (1996) **Clinical Genetics Services into the 21st Century: A Report from the Clinical Genetics Committee of the Royal College of Physicians,** Royal College of Physicians, London, p5.
8 The Royal College of Psychiatrists (1997) **A Manifesto for Mental Health: Rebuilding Mental Health Services for the 21st Century**, London.
9 Personal response by Dr Robert Lefever to the Working Party's consultation.
10 For example, responses to the Working Party's consultation from a Mental Health User Consultant and the Christian Medical Fellowship.

Genetic testing

5.13 One outcome of initial clinical consultation or of genetic counselling, may be that a patient is offered, and chooses, genetic testing. At present genetic tests have been developed only for a small number of diseases. Where genetic tests *are* available patients may ask a number of questions, which the physician, or where appropriate the genetic counsellor, must seek to answer while keeping to the standards outlined in paragraph 5.3. These include:

- How serious is the disorder in question? How variable is it in its effects? What are the therapeutic options?
- If the test result is adverse, how likely are they to suffer from the relevant disorder? If they do suffer, how severe is it likely to be?
- If the gene mutation or variant is inherited, how likely are their children to suffer from the disorder?
- How reliable is the test?
- How will they be told about test results, and what will be done with the samples after the test?
- Might genetic test results reveal unexpected or embarrassing information, for example about paternity?
- What are the current requirements for disclosure of information to insurers and employers?

5.14 As with counselling, there are two broad categories of mental disorder for which testing may have to take quite different approaches. We shall contrast rare single gene disorders, using Huntington's disease and early onset Alzheimer's disease as examples, with conditions for which one gene variant is likely to alter risk only slightly, using late onset Alzheimer's disease as an example.

5.15 There is now almost a decade of experience of predictive genetic testing for Huntington's disease, first by linkage and since 1993 by direct testing.[11] The number of people seeking testing for Huntington's disease is far lower than was initially predicted. Studies prior to the identification of the disease gene suggested that about three-quarters of those at risk of inheriting the Huntington's disease mutation from a parent would seek testing. It was widely believed that the apparent advantages of resolving uncertainty and having a clearer basis for planning lives would make testing the usual choice of family members. In the event probably less than 10% of those with a parent with Huntington's disease have decided to have counselling about the possibility of a test, the majority apparently preferring the hope that uncertainty preserves. Of those considering testing who are counselled, about two-thirds opt to be tested.[12]

11 68 The protocol that is generally adopted for Huntington's disease testing involves two, usually hour-long, counselling sessions before written consent is obtained and blood is drawn for testing (Craufurd D and Tyler A (1992) Predictive testing for Huntington's disease: protocol of the UK Huntington's Prediction Consortium, **Journal of Medical Genetics**, 29:915–18.) The first session covers such matters as Huntington's disease and its inheritance, reasons for requesting testing and present and future ways of coping with Huntington's disease. The second session which is held after an interval of several weeks for reflection and perhaps discussion with friends or family members, covers questions arising from the first session, reviews support networks and the practical arrangements for giving results. In addition to a clinical geneticist, a second person, sometimes a genetic counsellor or a psychiatrist with special skills in the area, is present at one or both of the sessions. Assuming the individual decides to proceed with testing there is a briefer session at which results are given and four further follow ups – a telephone contact a week later, a home visit by a counsellor at one month, a further telephone contact at three months, if required, and a clinic visit for mutation carriers after a year. (Madigan J (1996) in Marteau T and Richards M (eds) **The Troubled Helix**, Cambridge University Press, Cambridge, pp 7–22, provides a description of this process from the perspective of someone seeking testing.)

12 69 Richards M (1998) Annotation: Genetic research, family life, and clinical practice, **Journal of Child Psychology and Psychiatry**, 39: 291–305.

5.16 For the small self-selecting group who are tested, the benefits of knowing their genetic status seem to outweigh the drawbacks. However, adverse reactions, including periods of depression, have been reported for some of those who received either favourable or unfavourable results. The adverse reactions reported for some of those who are found not to have the mutation have been explained as a kind of survivors' guilt, or as a need to adjust their sense of identity after a long period spent living in the shadow of the disorder.[13]

5.17 Similar points can be made about the rare early onset form of Alzheimer's disease which often develops when people are in their early 50s. Mutations in three different genes have so far been identified in families with this form of Alzheimer's disease. These are dominant and so have a 50% chance of being passed on (Box 3.3). It is likely that other such genes will be identified in the future so that most, if not all, of the very small number of families who carry this early onset form of Alzheimer's disease can be offered genetic testing. For these families the situation is very similar to that for families with Huntington's disease. The mutations are highly penetrant so that most of those who carry them will develop Alzheimer's disease. While, as with Huntington's disease, there are currently no proven measures for the prevention of Alzheimer's disease, three licensed drugs are available which may be of benefit in the early stages of Alzheimer's disease. There are also various life planning steps that individuals may wish to take. Early indications are that very few members of families that carry early onset Alzheimer's disease wish to have a genetic predictive test.[14]

5.18 An important conclusion from research so far is that reactions to the availability of genetic testing are specific to particular conditions. Different uptake rates for testing and outcomes have been reported for a number of adult onset conditions.[15] These may depend on the perception of the disease and of the distress it may cause, on the age and certainty of onset, on the options for prevention and treatment, and finally on the implications for health care and life insurance. Uptake may also depend on the way testing is offered, for example by letter or in person.[16] This variability shows that as further genetic tests for mental disorders become available, research will be needed into the response of individuals and families to genetic testing for mental disorders.

Genetic testing for susceptibility genes

5.19 Most of the mental disorders considered in this report do not follow the simple Mendelian pattern of inheritance seen if a single gene mutation is associated with a disease. Late onset Alzheimer's disease (Box 3.3) illustrates the ethical issues which arise. Within populations, the slightly increased average risk of Alzheimer's disease associated with one, or even two, copies of the apoE4 allele is of limited value for diagnosis or prediction of individual risk for two reasons. First, the alteration in risk is small and second, it is calculated for the whole population, and does not take into account individual genetic and environmental variation. Testing for such genes would produce false positives and negatives and might unnecessarily burden NHS services. Given the very low predictive power of apoE4 tests the Working Party concurs with others that there is no case for testing for apoE4 alleles to provide predictive or diagnostic information for Alzheimer's disease.[17] **It recommends that genetic testing for susceptibility genes providing predictive**

13 Spijker A and Kroode H (1997) Psychological aspects of genetic counselling: A review of the experience of Huntington's disease, **Patient Education and Counselling** 32:33–40.

14 Personal communication. Professor Daniel Pollen, University of Massachusetts Medical Centre.

15 Dudok de Wit A (1997) To Know or Not to Know: The psychological implications of presymptomatic DNA testing for autosomal dominant inheritable late onset disorders, doctoral thesis, University of Utrecht, Utrecht.

16 Marteau T and Croyle R (1998) Psychological responses to genetic testing, **British Medical Journal** 316:693–6.

17 American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer disease (1995) Statement on use of Apolipoprotein E testing for Alzheimer disease, **Journal of the American Medical Association** 274:1627–9; Lovestone S with UK Alzheimer's Disease Genetics Consortium (1995) The genetics of Alzheimer's disease, **International Journal of Geriatric Psychiatry** 10:1–7.

or diagnostic input of certainty comparable to, or lower than, that offered by apoE tests for Alzheimer's disease should be discouraged unless and until the information can be put to effective preventive or therapeutic use. It must be borne in mind that, for many of the common mental disorders, evidence even of weak associations between gene variants and the population occurrence of a disorder has yet to be confirmed. While there may well be public health reasons for determining the frequencies of some genetic variants in populations, such screening should be carried out on an anonymous basis.[18]

5.20 ApoE testing was first undertaken in the context of the diagnosis and treatment of heart disease since different apoE variants are associated with variation in levels of lipoprotein. Even in the context of heart disease, apoE testing is less useful than more direct biochemical measurement of cholesterol and lipoprotein levels. Nevertheless, the question has been raised whether patients who have undergone apoE testing in connection with the treatment of heart disease, or who may do in the future, should be informed about any slight increase in their risk of Alzheimer's disease. As susceptibility genes are identified which may influence a number of conditions, it is more likely that genetic testing will reveal additional medical information about a patient (paragraphs 3.11–3.15). The possibility that additional information will be revealed should be discussed with the patient before the test is undertaken. **The Working Party recommends that the duty of physicians to discuss and disclose any possible increase in risk revealed by genetic tests for conditions other than that under investigation be considered equivalent to the duty to do so for other, non-genetic, types of information.**

Direct marketing of genetic tests

5.21 It has been predicted that the range of genetic test kits marketed directly to the public will increase rapidly over the next five years. These self-test kits, sometimes known as over the counter (OTC) tests, may be marketed by mail order or over the Internet. It has been suggested that while "*susceptibility screening may be bad science, it is likely to be excellent business. Screening tests applicable to the general population will hold out promise of enormous profits for those corporations that can develop and patent tests and techniques ahead of their competitors.*" [19] These commercial pressures might lead to promotion of susceptibility testing even where this would not be advisable or appropriate. In the UK, the Advisory Committee on Genetic Testing has introduced a voluntary code of practice for directly marketed tests and has recommended that the development of such tests be restricted to those which determine carrier status for inherited recessive disorders where such status carries no significant direct health implications for the carrier individual.[20] However, tests for apoE status are already commercially available to the public in the United States and others will follow. The Working Party endorses the position of the Advisory Committee on Genetic Testing, but considers that the present voluntary system of approval is likely to prove unworkable. **The Working Party recommends that the Advisory Committee on Genetic Testing monitors the uptake of directly marketed tests and the consequences of their use. If, in the light of such monitoring, adverse consequences become apparent, it recommends that the UK government seeks stronger national or international regulation of directly marketed tests**.

18 Khoury M and the Genetics Working Group (1996) From gene to public health: the application of genetic technology in disease prevention, **American Journal of Public Health** 86:1717–22.

19 Clarke A (1997) The genetic dissection of multifactorial disease: The implications of susceptibility screening, Chapter 7 in Harper P and Clarke A, **Genetics, Society and Clinical Practice**, Bios Scientific Publishers, Oxford, p100.

20 Advisory Committee on Genetic Testing (1997) **Code of Practice and Guidance on Human Genetic Testing Services Supplied Direct to the Public**, Health Departments of the United Kingdom, London.

Consent and impaired capacity

5.22 As set out in Chapter 1, an important principle in ethics is respect for human beings, their autonomy and dignity. This ethical principle underlies the legal requirement to seek consent prior to any genetic counselling or testing of adults; any invasive procedure undertaken without consent will be illegal. These consent requirements apply to individuals already suffering from a mental disorder as well as to those who may seek counselling or testing to discover if they are at increased risk. In most cases neither current mental disorder nor risk of future mental disorder will impair capacities; even when there is impairment it is often no more than intermittent. The Law Commission has recommended that statutory force should be given to the existing common law presumption that an adult has full legal capacity unless it is shown that he or she does not.[21]

5.23 Because of the significance attached to consent, the ethical principles have been developed in some detail in law. The law requires that, in determining if a patient has the necessary capacity to decide whether or not to consent to a procedure, the psychiatrist or other responsible medical officer must be satisfied that the patient:

- possesses the capacity to make a choice;
- understands what the procedure is, that somebody has said that he, or she, should have it and why it is being proposed;
- understands in broad terms the nature of the procedure;
- understands the principal benefits and risks of the procedure;
- understands the consequences of not receiving the procedure. [22]

5.24 Different decisions require different levels of understanding and an individual may be capable of making one decision but not another. This will depend partly on the relative complexity of the issues involved. It has already been argued that decisions about genetics are particularly complex, because of the extensive family involvement and the difficulty of interpreting the implications of findings in a field where genetic influence is generally only one of many (Chapter 1). The level of understanding required for any procedure might, in practice, be expected also to depend in part on its risks and benefits. The greater the potential benefits and the less the risk of harm, the more flexibility might be allowed in relation to an individual's consent; the less the benefit and the greater the risk, the more stringent the requirements should be.

5.25 Even for individuals able to give consent, fully informed consent is an unattainable ideal. "*The ethically significant requirement is not that consent be complete but that it be genuine.*"[23] Obtaining genuine consent requires health care professionals to do their best to communicate accurately and in an understandable and appropriate way the purposes and implications of the procedure as well as its risks. They should respect the limits of individuals' understanding and capacity to deal with difficult information, and allow time for them to ask questions. It may be helpful for consent to be sought in the presence of another person – perhaps, in the case of

21 The Law Commission (1995) **Mental Incapacity**, Law Com No 231, HMSO, London. As regards children (those under 18) it may be that the legal presumption is somewhat weaker for those aged 16–18, even though, where medical treatment is involved, they are to be regarded as if they are adults (s.8(1) Family Law Reform Act 1969) and there are other contexts in which they may be regarded as having the necessary capacity to give valid consent. As regards children under 16, though they may have the necessary capacity to consent (see *Gillick* v.*West Norfolk and Wisbech Area Health Authority* [1985] 3 All ER 402), the presumption should, perhaps, be reversed.

22 See the Department of Health and Welsh Office (1993) **Code of Practice: Mental Health Act 1983**, HMSO, London, paragraphs 15.8 to 15.24; *Re C* (*Adult: Refusal of Treatment*) [1994] 1 WLR 290; *Re MB* (*Medical Treatment*) [1997] 2 FLR 3 and Lord Chancellor's Department (1997) **Who Decides? Making Decisions on Behalf of Mentally Incapacitated Adults**, Cm 3803, Lord Chancellor's Department, London.

23 Respect for human lives and the human body, Chapter 6 in Nuffield Council on Bioethics (1995) **Human Tissue: Ethical and Legal Issues**, Nuffield Council on Bioethics, London, paragraph 6.20.

someone with a mental disorder, their key worker – so that the individual feels supported and any questions or concerns that arise can more easily be addressed. It can be helpful to offer leaflets or other written information presented in a clear, balanced and non-technical way with translations and interpreters available where English is not the first language.

5.26 For an adult person deemed mentally incompetent to make his or her own treatment decisions, a doctor must act in that patient's 'best interests'.[24] There are difficulties, however, in translating from the general principle to the specific case. 'Best interests' may vary according to the nature and degree of certainty of the information, the person's capacity for understanding and acting on the information and his or her wishes, social and family context and needs. Often 'best interests' can only be determined after prolonged consultation, and even then a certain amount of subjective judgement may be involved. However, unless it is necessary for there to be an application to the Courts, 'best interests' are a matter for the judgement of the appropriate doctor or other responsible health authority.[25]

5.27 The Mental Health Act 1983 does not refer to genetic testing with or without consent. It follows, therefore, that genetic testing of patients without consent who are subject to that Act is only permissible if the testing forms a part of, or is itself, therapeutic treatment authorised by the patient's responsible medical officer (see also paragraph 7.13).

The genetic testing of children

5.28 By section 8(1) of the Family Law Reform Act a child between the ages of 16 and 18 may give valid consent to treatment as if he or she were an adult, provided, of course, that he or she is otherwise competent. Furthermore, a child below the age of 16 may also give valid consent to medical treatment if able fully to understand what is involved in the proposed medical treatment or procedure.[26] The emphasis in both situations is on treatment, thus the issues are comparable to those raised by the genetic testing of adults in circumstances in which testing contributes to treatment. It is probable that only diagnostic testing and perhaps, very rarely, carrier detection would be so regarded.

5.29 Different issues arise when the testing of children is proposed for purposes other than diagnosis or treatment.[27] There are difficult lines to be drawn where children are concerned, particularly where the child is considered to be competent to make a range of decisions but the wishes of the child and parent/guardian do not coincide. For example, parents may want the child to be tested to resolve uncertainty, although they know that there is no treatment (paragraph 5.31). The child, although competent, may disagree, or not even be consulted. Older children may wish to be tested on their own initiative, for similar reasons, but their parents may object. It has been said the parental right yields to the child's right to make his or her own decisions when he or she reaches a sufficient understanding and intelligence to be capable of making up his or her own

24 In the case of an incompetent child, the doctor can ordinarily look to the parents to establish the child's best interests. Once again, these ethical principles find more detailed expression in law. See, for example, *Re F* (*mental patient: sterilisation*) [1990] 2 AC 1; *Airedale National Health Service Trust* v. *Bland* [1993] 1 All ER 821 (HL) and *L* v. *Bournewood NHS Trust* (HL), **The Times**, 30 June 1998.

25 For recent guidelines laid down by the Court of Appeal, see *St George's Healthcare NHS Trust* v. *S*(*No.2*), **The Times**, 3 August 1998.

26 Following the decision of the House of Lords in *Gillick* v. *West Norfolk and Wisbech Area Health Authority* [1985] 3 All ER 402.

27 A great deal of the recent discussion of genetic testing has concerned children and there is already a considerable literature on the topic. These are reviews of ethical issues (Wertz D, Fanos J and Reilly P (1994) Genetic Testing for Children and Adolescents: Who decides? **Journal of the American Medical Association** 272:878–81; Chapple A, May C and Campion P (1996) Predictive and carrier testing of children: Professional dilemmas for clinical geneticists, **European Journal of Genetics and Sociology** 2:28–38); legal issues (Mclean S (1995) Genetic screening of children: The UK position, **Journal of Contemporary Health Law and Policy** 20:113–30); and research issues (Michie S and Marteau T (1996) Predictive genetic testing in children: The need for psychological research. **British Journal of Health Psychology** 1:3–14). The proceedings of a major conference are soon to appear (Clarke A (ed) (1998) **Genetic Testing of Children**, Bios Scientific Publishers, Oxford, in press).

mind on the matter requiring decision.[28] However, testing of the kind under discussion here may fall in a novel category raising such complex issues of benefit and possible harm that additional caution should be exercised before leaving the decision solely to the child (particularly if the child is below the age of 16). On the present state of the authorities it is unclear whether, in the case of children under the age of 16, they would be regarded as capable of giving reliable, valid, consent to testing which is of no diagnostic benefit and cannot be categorised as treatment.[29]

Diagnostic testing

5.30 The law permits the testing of children unable to consent only when it is in the child's best interests. When effective interventions are available, the issues raised by genetic testing are not, in principle, different from those related to any kind of medical test or treatment which involve issues of consent [30] and understanding.[31] With rare exceptions such as phenylketonuria (Box 3.1) effective interventions for mental disorders in children (most commonly mental retardation) are not available. Nevertheless, the use of genetic tests to help establish a diagnosis may be viewed as being in the child's best interests since a firm diagnosis will enable a clearer prognosis and management plan for the child. It may also benefit the parents (but not the child) by relieving uncertainty and providing information which they can use in deciding whether to have further children and in some situations the child's interests might best be served by permitting testing to benefit the family as a whole.

5.31 In the context of screening, the ethical arguments are more finely balanced (see also paragraphs 6.32–6.35). For example, diagnostic screening for fragile X syndrome in children with mental retardation is feasible. But a positive diagnosis may have limited management implications for the child, whilst the genetic implications for the family will not necessarily be welcome if the information is unexpected. We would emphasise the importance of obtaining fully informed consent from the family unit, if consent from the child is not possible, before diagnostic testing occurs.

Predictive testing

5.32 Where genetic tests offer some degree of predictive certainty, professional opinion amongst clinical geneticists has been against the testing of children for adult onset conditions, on the grounds that this has no benefit for the individual during childhood, denies him or her the chance of making their own choice as an adult, and could lead to discrimination within the family.[32] Some parents and patient groups have argued, to the contrary, that parents have a right to know about their children's genetic make-up and, in the case of Huntington's disease, that they would

28 See Lord Scarman in *Gillick* v. *West Norfolk and Wisbech Area Health Authority* [1985] 3 AII ER 402, and contrast, for example, Lord Donaldson MR in *In re R* [992] Fam. 11.

29 See the views of the Law Commission referred to at footnote 21 above. If a child, whether or not below 16, is considered as having a right to know his or her own genetic makeup, then the answer to the problem may be simpler – that, if the child is otherwise competent and is capable of understanding the information, it should not, perhaps cannot, be prevented from agreeing to be tested.

30 King N and Cross A (1989) Children as decision makers: Guideline for paediatricians. **Journal of Pediatrics** 115:10–16; Alderson P (1990) **Choosing for Children: Parents' Consent to Surgery**, Oxford University Press, Oxford; and Alderson P (1992) In the genes or in the stars? Children's competence to consent, **Journal of Medical Ethics** 18:119–24.

31 Richards M (1999) The genetic testing of children: adult attitudes and children's understanding, in Clarke A (ed) **The Genetic Testing of Children**, Bios Scientific Publishers, Oxford, in press.

32 Clarke A (Chairman) (1994) **The Genetic Testing of Children: Report of a Working Party of the Clinical Genetics Society**, Clinical Genetics Society, London.

rather know than have to live with the uncertainty of not knowing if their children had inherited the disorder.[33] It has also been suggested that parents may want to use testing to ensure that they have at least some children who are free of the disease. Given that the great majority of adults at risk of Huntington's disease choose not to be tested, however, it is hard from an ethical point of view to justify parents' requests to have their children tested. It would be even more difficult to do so for tests for the common mental disorders which are likely to offer less predictive certainty. Moreover, whatever the ethical arguments, such testing if not carried out explicitly to serve the best interests of the child, would not be permissible in law. **The Working Party recommends that, for children unable to give consent, predictive genetic testing should be strongly discouraged unless there are implications for clinical intervention in childhood**. This would include situations in which a child is currently asymptomatic for a disorder which may begin in childhood and for which there may be a family history.

Carrier detection

5.33 Carrier detection tests for young children are sometimes proposed when an affected sibling is diagnosed. An example is genetic testing of healthy girls who have siblings with fragile X syndrome. It is sometimes suggested that early carrier tests are helpful to children who can then have the implications explained progressively and as appropriate through childhood so that they are well prepared before they need to make any choices about partners or reproduction; for some children this may be earlier than 16. However, the Working Party considers that, as with childhood predictive testing, this denies children the possibility of making their own decisions at a later date. **The Working Party recommends that children should not be tested for carrier status for mental, or indeed other, disorders until they are competent to make their own decisions.**

Directly marketed tests

5.34 It may be very difficult to ensure that children are being tested out of concern for their best interests if genetic tests are marketed directly to the public. Guidance from the Advisory Committee on Genetic Testing suggests that testing should not be offered to those under the age of 16 and that persons under the age of 16 should not be tested presymptomatically for adult-onset conditions for which there are no clinical treatments.[34] It is not clear, however, how a company would determine whether a sample had in fact come from a child. This difficulty adds to the reasons for monitoring the uptake of directly marketed tests (paragraph 5.21).

33 Block M and Hayden M (1990) Opinion: predictive testing for Huntington's disease in childhood: Challenges and implications, **American Journal of Human Genetics** 46:1–4.

34 Advisory Committee on Genetic Testing (1997) **Code of Practice and Guidance on Human Genetic Testing Services Supplied Direct to the Public**.

Adoption

5.35 Genetic testing of children might also be considered during adoption. Placing children born to parents with mental disorders for adoption is not uncommon since severe mental disorders may be a reason for a parent to give up a child for adoption voluntarily or as a result of a Court Order. Requests to perform genetic tests before children are adopted have already been encountered in other contexts: the Tuberous Sclerosis Association has received inquiries about genetic tests from adoption agencies with the purpose of informing prospective parents if there is a possibility that a baby available for adoption will inherit tuberous sclerosis.[35] The stigma associated with mental disorders might encourage prospective parents to insist on testing.

5.36 Adoption regulations require that all children have medical examinations before they are adopted: the issue is what those examinations are for and what, therefore, they should contain. They were originally designed to ensure that the child was 'adoptable': prospective adoptive parents were assumed to want healthy babies with no recognisable liability to illness. Nowadays, all children are regarded as potentially adoptable. The law would once again insist that a test may only be carried out on a child incapable of giving consent if it can be shown to be in the child's best interests to do so. But it is not in a child's best interests to be adopted if there is a risk that he or she will later be rejected because the adoptive parents had an incomplete understanding of the child they were adopting. Most good adoption agencies would probably want to address the issue of mental illness in the birth family, just as they would want to address issues of physical disability, HIV status, sexual abuse or any other matter which might impact upon the full integration of that child into the adoptive family. In very rare situations, this might involve genetic testing of a child. Indeed, agencies may now run the risk of being sued by the adoptive parents if they do not properly inform them about the child they are adopting. **The Working Party recommends that, given the importance and complexity of the issues, the Health Departments, in consultation with the appropriate professional bodies, provide guidance on the pre-adoption use of genetic testing.**

5.37 It is also worth considering whether an adoptive child should have access to information about possible family histories of disease so that, from early adulthood, they may make informed decisions about seeking genetic counselling or testing or other forms of investigation or treatment. It would seem unfair to deprive adoptive parents and adopted children of information about family histories of disease which would be available to birth parents and their children. At 18 years of age, adopted children may ask to know the identity of their birth parents and this might be an appropriate time at which to provide this kind of additional information.

Genetic information and reproductive decisions

5.38 One of the most important uses of genetic information is to inform reproductive choices. Many people with mental health problems, or a family history of them, have chosen to have children and have not encountered any difficulties. But reproductive choices may be complicated even when there is no relevant genetic information. The consultation responses indicated that, for some people, decisions about whether to marry or have children had been influenced by what they knew of their family history. One woman, who had helped to care for her brother since he was diagnosed as having schizophrenia forty years ago wrote that "*I have led a reasonably*

35 Response by the Tuberous Sclerosis Association to the Working Party's consultation. Tuberous sclerosis is a rare single gene disorder which results in abnormal tissue growth. The symptoms, and their severity, vary but can include autism, seizures, learning difficulties and early death.

healthy, normal (but not married and no children – mental health considerations may have entered into this) and successful life." [36] For others the decision had either not been easy or had been one which they felt they had to justify. Some had been subject to pressure from others about the choice they should make. One respondent to the consultation wrote "*I am personally very glad that accurate genetic counselling was not available when I was pregnant with any of my three children. Medical reasoning at the time seemed to be along the lines of 'Well, you could be carrying another schizophrenic: and, even if you aren't, you'll never be able to be a fit mother anyway.'*" [37] Many respondents referred to the history of eugenic abuse and expressed concern about the possible use of genetic information for eugenic purposes.[38]

5.39 Genetic information is used by those making reproductive choices in three main ways: before they marry or enter long-term relationships (prenuptially), before they have children ('preconceptionally') or during pregnancy (prenatally). An example of prenuptial decision-making is the requirement that Cypriot couples take carrier tests for thalassaemia before they can marry in the Orthodox church. Another example is found in some Jewish communities in which the results of carrier tests for Tay–Sachs disease are available only to matchmakers. This allows young carriers to avoid entering relationships with other carriers and, at the same time, to avoid the stigma and damaged self-esteem that can be associated with knowledge of carrier status. Although this consideration may be particularly important in mental disorders where stigma is especially great, the circumstances under which pre-nuptial testing might be employed appear to be very limited.

5.40 Prenatal genetic testing may lead to information which bears on a decision to seek abortion. The starting point for consideration of the option of abortion must be the Abortion Act 1967, including S.1(1)(d) which provides that an abortion may be carried out where there is a substantial risk that if the child were born it would suffer from such physical and mental abnormalities as to be seriously handicapped. Experience to date of prenatal genetic testing indicates that decisions to abort for these reasons are not made lightly. Where a test can reveal with some certainty the presence of a severe, early onset disorder for which no treatment is known, genetic testing and abortion may be accepted by many parents. In principle, this would apply to mental, as well as physical, disorders. However, when even one of these factors is missing, the relevance and acceptability of prenatal genetic testing is lower. In effect, this means that, for the common mental disorders, prenatal genetic testing and termination will be less likely to meet the criteria of the Abortion Act as well as being less acceptable and accepted by parents. Table 5.1 provides details of some common single gene conditions for which prenatal testing may be offered. Most of the mental disorders considered in this report are not associated with mutations of a single gene, but with more weakly predictive susceptibility genes. For the reasons already given, genetic testing for predictive reasons for these conditions is unhelpful at present and such testing is not offered prenatally (paragraph 5.19).

36 An individual's response to the Working Party's consultation.
37 An individual's response to the Working Party's consultation.
38 Including the Christian Medical Fellowship, Oxford Hearing Voices Group and several individual respondents to the Working Party's consultation.

Table 5.1:

Factors affecting the uptake of prenatal testing for different single gene conditions

Disease	Age of onset	Severity	Treatable?	Predictive certainty of test (% of people developing condition with adverse result)[39]	Uptake of test
Tay-Sachs	From birth	Fatal	No	100%	High levels of uptake in counselled couples in certain communities; many do not seek counselling.
Huntington's	Middle age	Fatal	No	100% but some variation in age of onset (see Box 3.2)	18% uptake in counselled couples.[40] Very low overall.
Phenylketonuria	From birth	If not treated, severe mental handicap results.	Yes	100% (see Box 3.1)	All testing is neonatal. National screening programme.
Neuro-fibromatosis	Child-hood	Variable	Some complications treatable	100% for NF1 but severity varies	1/60 families[41]
Fragile X	From birth	Variable	No	Prognosis may depend on the mutation present	Some at least but epidemiological data unavailable.[42]
Early-onset Alzheimer's disease	Middle age	Severe	Potential treatments currently being explored.	100% for the APP or presenilin 1 or 2 genes (see Box 3.3)	Low uptake of predictive testing for early onset forms.[43]

5.41 Genetic information will not be particularly helpful in making reproductive decisions for many with a family history of a common mental disorder. The reasons underlying reproductive decisions are always varied and personal. Some people are reluctant to terminate fetuses because they may share the condition that affects a parent or other members of the family. This may be one reason for the very limited use of prenatal diagnosis and abortion in Huntington's disease. One respondent to the consultation wrote: "*Schizophrenia has become a part of me – it defines who I am . . . I cannot divide my experiences into illness and health – they all feel to be part of me. Therefore when I hear of moves to try to eradicate schizophrenia it feels like an attack on my status as a full human being.*"[44] While prenatal testing for schizophrenia or any of the other common mental disorders is not possible at present, or likely in the near future, this comment captures a common view. Optimism about future treatments or cures may also contribute to a

39 Predictive certainty depends both on the amount risk increases, and on variability in prognosis.

40 Adam S, Wiggins S, Whyte P, Bloch M, Shokeir M, Soltan H, Meschino W, Summers A, Suchowersky O, Welch J et al. (1993) Five year study of prenatal testing for Huntington's disease: demands, attitudes and psychological assessment, **Journal of Medical Genetics** 30:549–56.

41 Ponder M, Murton F, Hallowell N, Statham H, Green J and Richards M (1998), Genetic counselling and future reproductive intentions of people with neurofibromatosis type 1 (NF1), **Journal of Genetic Counselling**, in press.

42 Murray J, Cuckle H, Taylor G and Hewison J (1997) Screening for fragile X syndrome: information needs for health planners, **Journal of Medical Screening** 4:60–94, pp81–2.

43 Personal communication. Professor Daniel Pollen, University of Massachusetts Medical Centre.

44 An individual's response to the Working Party's consultation.

reluctance to undergo prenatal testing and abortion. Yet some people are anxious that their children should not have to suffer a disease that they, or other family members, have suffered and several studies have found that parents are more likely to countenance prenatal testing and abortion for mental, rather than physical, disability.[45] For those reasons **the Working Party recommends that people making reproductive decisions in the light of a family history of a mental disorder should have access to genetic counselling**.

5.42 In practice, there is evidence that some decisions about abortion may be made without adequate and impartial information.[46] Pregnant women may be led to think that they would not be offered a test unless there was a clear and proven benefit; they may not have appreciated at the time of testing that abortion would be the only intervention available; they may take tests in order to gain reassurance and not have been adequately prepared for an adverse result.[47] If an adverse test result is received, they may feel that abortion is expected and the only course of action. Indeed, in one study, over one third of a sample of obstetricians said that they generally require a woman to agree to termination of an affected pregnancy before offering prenatal diagnosis.[48] There is certainly a widespread impression among many of those who counsel women that, in choosing to abort a fetus that has been diagnosed with an abnormality amounting to a serious handicap, a parent is making the obvious choice. It is essential that access to genetic tests is not tied to conditions which might prejudice individuals' abilities to accept or refuse tests, such as willingness to consider abortion as a condition of prenatal genetic testing. That said, pregnant women should certainly be alerted to the risks associated with fetal genetic tests which they may prefer to avoid if they do not wish to consider abortion in the light of an adverse test result and no other intervention is available. They should also be aware that, if they do have such a test, any child born will not have the option of deciding not to be tested.

5.43 In their consultation response, MIND argued that there may be social pressure on parents not to burden themselves or society with 'affected' children and emphasised that real reproductive choice will "*necessitate political and social commitment to providing opportunities (like the chance to work), and support where necessary for people who do develop mental health problems.*"[49] In this context, government measures to integrate health and social service initiatives in tackling mental health are welcome but, even if social provision were to improve far beyond what is currently available, parents and their affected children will still face problems that cannot be alleviated by social means. In the face of these considerations, it has been argued that some parents may not be in a position to make independent reproductive choices.

5.44 The ideal of 'non-directiveness' in genetic counselling has been widely endorsed and the failure to meet this ideal equally lamented. The Working Party questioned the clarity and feasibility of 'non-directiveness' as a universal aim and noted the importance of enabling individuals to make their own informed decisions at each stage of the process. These important issues will need to be included in the consideration of education, training and support for those providing genetic information and counselling recommended in paragraph 5.12. The adequacy of genetic counselling also has to be judged against the realities of situations in which termination decisions

45 Green J and Statham H (1996) Psychosocial aspects of prenatal screening and diagnosis, Chapter 6 in Marteau T and Richards M (eds) **The Troubled Helix**, Cambridge University Press, Cambridge.

46 For a general discussion see Clarke A (1997) The process of genetic counselling: Beyond non-directiveness, Chapter 13 in Harper P and Clarke A, **Genetics, Society and Clinical Practice**, Bios Scientific Publishers, Oxford.

47 Green J and Statham H (1996) Psychological aspects of prenatal screening and diagnosis, Chapter 6 in Marteau T and Richards M (eds) **The Troubled Helix**, Cambridge University Press, Cambridge, p143.

48 Green J (1995) Obstetricians' views on prenatal diagnosis and termination of pregnancy: 1980 compared with 1993, **British Journal of Obstetrics and Gynaecology** 102:228–32.

49 Response by MIND to the Working Party's consultation.

have to be made quickly, in the light of difficult information and emotionally fraught circumstances. The available evidence indicates that, in any case, reproductive intentions are seldom changed by genetic counselling and the main outcome seems to be that couples feel confirmed in whatever they planned to do beforehand.[50] **The Working Party notes the need for further debate about the appropriateness of non-directiveness in genetic counselling and recommends that further research to establish appropriate aims and outcomes for genetic counselling is undertaken**.

Eugenic programmes

5.45 There have been concerns that the growing deployment of new genetic technologies will lead to a 'new eugenics'.[51] Professor Peter Harper, for example, has pointed out that the existence of genetic predictive tests and the feasibility of keeping computerised genetic registers could provide the information required for serious abuse and has argued that at "*a time when psychiatric and behavioural genetics are again entering controversial areas, everyone involved should be fully aware of the long shadow that is still cast by the abuse of genetics in these disorders.*" [52]

5.46 In the first three decades of this century eugenic programmes were set up in many industrialised countries. In both Britain[53] and the United States[54] programmes were targeted at those with mental handicaps and criminal behaviour; they also covered many with the mental disorders that are the subject of this report. In Britain there was legislation allowing the confining of individuals in institutions for reasons that some would regard as eugenic, while in the United States and elsewhere there were extensive programmes of compulsory sterilisation.

5.47 In Nazi Germany, Huntington's disease was specifically listed as one of the nine categories of disorder suitable for compulsory sterilisation under the German law of 1933.[55] It has been suggested that there could have been 3,000–3,500 sterilisations of those from families with Huntington's disease.[56] Later there were countless killings of persons with mental handicaps and psychiatric conditions including schizophrenia.[57]

5.48 Eugenic programmes were originally designed to change the genetic characteristics of a population either by preventing or discouraging those with the (inherited) characteristics held to be undesirable from having children or by encouraging those with characteristics held to be desirable to have more children. Subsequently, eugenic programmes in many countries had compulsory elements and a degree of coercion or the restriction of individual choices.

5.49 A number of distinct issues underlie concerns about the possibility of a new eugenics. There is a possible cause for concern over the development of genetic registers and research studies of the general population where DNA samples are collected. Genetic registers have been set up to collect information about individuals and families who carry particular genetic disorders both for

50 Michie S and Marteau M (1996) Genetic counselling: some issues of theory and practice, Chapter 4 in Marteau T and Richards M (eds) **The Troubled Helix**, Cambridge University Press, Cambridge.
51 Duster T (1990) **Backdoor to Eugenics**, Routledge, Chapman and Hall, London.
52 Harper P (1997) Huntington's disease and the abuse of genetics, Chapter 17 in Harper P and Clarke A, **Genetics, Society and Clinical Practice**, Bios Scientific Publications, London, pp227–8.
53 Mazumber P (1992) **Eugenics, Human Genetics and Human Failings: The Eugenics Society, Its Sources and Its Critics in Britain**, Routledge, London.
54 Kevles D (1985), **In the Name of Eugenics**, Knopf, New York.
55 Muller-Hill B (1988) **Murderous Science**, Oxford University Press, Oxford; Burleig M (1991) **Death and Deliverance, 'Euthanasia' in Germany 1900–1945**, Cambridge University Press, Cambridge.
56 Harper P (1997) Huntington's disease and the abuse of genetics, Chapter 17 in Harper P and Clarke A, **Genetics, Society and Clinical Practice**, Bios Scientific Publications, Oxford.
57 Meyer J (1988), The fate of the mentally ill in Germany during the Third Reich, **Psychological Medicine** 18:3108–14.

research purposes and to target specialist genetic services. Such registers, where they are kept on a computer, are regulated in Britain by the Data Protection Act which requires their registration and allows access by individuals to their recorded information. Clearly, release of such information to third parties could be very damaging to the individual concerned. Other problems may arise when an individual who has set up and maintained a register moves to a new position and there may be no one to take over responsibility for it. Clear guidelines are required for the establishment and maintenance of registers whether or not they are kept on computers. These could usefully draw on the principles set out in the recent **Report on the Review of Patient-Identifiable Information.**[58] **The Working Party recommends that the British Society for Human Genetics explores mechanisms for the development of guidelines for the establishment and maintenance of genetic registers in the new NHS**.

5.50 Concerns have been raised about the existence of genetic testing, and the provision of genetic services more generally, for conditions that some regard as differences rather than disabilities. In the case of achondroplasia (an inherited condition with short stature) for example, disabled rights groups have argued that the existence of genetic testing is intrinsically eugenic and medicalises a socially constructed disability. Clearly, such issues could potentially arise in the field of mental disorders, though this seems relatively unlikely given the limited role for genetic testing in this field.

5.51 Individual choices about having children can alter gene frequencies in future populations. If those who carry mutations related to a dominantly inherited late onset condition such as Huntington's disease restrict their own reproduction or use techniques (prenatal diagnosis and abortion or preimplantation diagnosis) in order to avoid producing children with the mutation, those mutations will become rarer in future generations. We see no reason not to welcome such reductions.

5.52 For recessively inherited conditions, current practice may limit the numbers of affected children born, but not of those who are carriers. Hence, such practice ensures the continuation of the current frequencies of carriers in populations. Indeed, there may be benefits from continued genetic diversity in the population for conditions where carriers have selective advantage in certain situations. For example, resistance to malaria is found for carriers of some inherited blood disorders. In the case of common polymorphisms such as the susceptibility genes for some complex disorders, there may well be population advantages for the existing genetic diversity. Assessment of any potential testing programme for such susceptibility genes should include public health considerations.

5.53 Cost–benefit arguments are widely used in the evaluation of medical interventions. In the case of genetic screening programmes, the cost of the programmes may be set against the potential economic savings in the reductions of births of individuals who may require extensive medical and social services. In a rationed health care system there are likely to be pressures to deploy screening programmes which may result in cost savings for services. But as we have seen, the scope for genetic screening programmes related to mental disorders is limited. However, such a programme has been advocated for fragile X syndrome. Whilst a programme designed to provide choice for parents might, through their collective actions, reduce the number of children born with fragile X, in itself such a programme would not be eugenic as its aim would be to provide choice.

58 The Caldicott Committee (1997) **Report on the Review of Patient-Identifiable Information** Department of Health, London.

5.54 Again, with regard to pregnancy screening for Down's syndrome, the intention is to provide the possibility of choice for parents. If parents exercise the choice not to proceed with a pregnancy when a fetus with Down's syndrome is detected, costs may be saved, but it is important not to conflate arguments about financial savings with eugenic intentions. One study has shown, however, that a small minority (13%) of a sample of obstetricians agreed with the statement, 'The state should not be expected to pay for the specialised care of a child with a severe handicap where the parents had declined the offer of prenatal diagnosis of the handicap.' [59] It is not uncommon for the argument to be put that the cost of a genetic screening programme would be covered by the savings resulting from the prevention of affected births. It has been further suggested, though we are unaware of evidence to support the point, that services available for those with a disability may be reduced if that condition is seen to be preventable through the use of prenatal diagnosis and abortion. Clearly, the reductions of such services might provide indirect pressures for parents to choose testing and selective abortion and such pressures should be resisted as unethical. We believe that parents should make their own decisions whether or not to proceed with a pregnancy, if a fetus is diagnosed as having Down's syndrome, and should be supported in whichever choice they make. In conclusion, the Working Party considers that the present use of genetic testing for reproductive choice in the UK cannot be regarded as eugenic. It takes the view that the best safeguard against any new eugenic pressures is properly informed, freely given consent.

Confidentiality and disclosure

5.55 An area of great concern is the use that might be made of genetic information about an individual's mental health. The use of information for non-medical purposes is discussed in Chapter 6. But one of the unique aspects of genetic information is that it is likely to be common to, and therefore relevant to, other family members. This raises distinctive issues about confidentiality: who should have access to genetic information derived from one individual if it is of relevance to another family member, yet the individual tested does not wish it to be disclosed?

5.56 In brief, of prime importance is the doctor or hospital's obligation of confidentiality.[59] If that is not assured, individuals may not agree to provide information or to be tested, exposing themselves to the unexpected and unchecked development of mental disorder. It must be a matter for the individual concerned to agree to the disclosure of information about his or her genetic make-up, unless there are strong public interest justifications for disclosure.

5.57 The confidentiality of genetic information is protected in a number of ways, involving the common law, statute, professional codes of practice and contracts of employment. It must be accepted, however, that there will be situations in which the public interest in disclosure will override the public, and private, interest in confidentiality. There is an obvious analogy with information about a person's HIV status. In relation to serious communicable diseases, the General Medical Council has advised that disclosure is justified "*in order to protect a person from risk of death or serious harm.*" [60] Thus the duty of confidentiality is not absolute. In the Council's

59 Green J (1995) Obstetricians' views on prenatal diagnosis and termination of pregnancy: 1980 compared with 1993, **British Journal of Obstetrics and Gynaecology**, 102: 228–32.

60 The arguments have been extensively discussed elsewhere. See, for example, Nuffield Council on Bioethics (1993) **Genetic Screening: Ethical Issues**, Nuffield Council on Bioethics, London; Shaw G (Chairman) (1995) **Human Genetics: The Science and Its Consequences, House of Commons Science and Technology Committee Third Report, Session 1994–95, Volume I Report and Minutes of proceedings**, 41-I, HMSO, London; British Medical Association (1998) **Human Genetics: Choice and Responsibility**, Oxford University Press, Oxford; and Genetic Interest Group (1998) **Confidentiality and Medical Genetics**, Genetic Interest Group, London.

61 General Medical Council (1997) **Serious Communicable Diseases**, London, General Medical Council, p 9, paragraph 22; and see also W v. Egdell

report **Genetic Screening: Ethical and Legal Issues** it was argued that "*When genetic screening reveals information that may have serious implications for relatives of those who have been screened, health professionals should explain why the information should be communicated to other family members . . . in such circumstances health professionals should seek to persuade individuals, if persuasion should be necessary, to allow the disclosure of relevant genetic information to other family members.*" [61] Both the law and professional guidelines provide for exceptional circumstances, when an individual cannot be persuaded to inform family members with a legitimate right to know, though there are those who hold a contrary view.[62] If a risk is real and serious a doctor has discretion, but not a duty, to inform others exposed to that risk and this disclosure will not be regarded as a culpable breach of confidentiality.

5.58 Problems of non-disclosure, already rare, are likely to be even less pressing where the common mental disorders are concerned, since genetic information is unlikely to lead to such significant modification of risk that non-disclosure would have serious consequences. Many mental disorders are relatively late onset and some are treatable. Any genetic information may well indicate increased susceptibility rather than any degree of certainty that a particular disorder will develop.

The right not to know

5.59 A further complication is that some family members may wish not to be presented with information. There are three possible scenarios:

- Relatives are aware of a family history and have the opportunity to participate or not in genetic counselling.
- Relatives do not wish to participate in genetic counselling but genetic testing of another family member would reveal information about them.
- Relatives are not aware of a family history. Should they be informed and asked if they want counselling, or does this action deprive them of the possibility not to know?

5.60 Arguments about disclosure to other family members who may be aware of inherited risks are finely balanced. Some would see it as a duty for the doctor or genetic counsellor to break confidentiality and provide the information for a family member in situations where the members who have the information cannot be persuaded to pass it on. Others would argue that an individual has a right to have confidential information kept secret whatever his or her reason. Breaking confidentiality in such situations may serve to further undermine the already fragile concept of medical confidentiality and bring genetic counselling into disrepute. It may be argued that the disinclination of a family member to pass on information should be respected since they are likely to be better informed about their own family than an outsider. We should be wary of breaking confidentiality in a context where professionals are much keener to provide services than many family members are to use them. **The Working Party recommends that the confidential nature of genetic information should be maintained. It can conceive of exceptional circumstances in which, in the absence of the consent of the individual, disclosure to close family members might be justified, if there are serious implications for them. Such decisions should be judged on a case by case basis**.

62 Nuffield Council on Bioethics (1993) The results of genetic screening and confidentiality, Chapter 5 in **Genetic Screening: Ethical and Legal Issues**, Nuffield Council on Bioethics, London, p53, paragraph 5.43.

63 Brown J and Gannon P (1996) Confidentiality and the Human Genome Project: a prophecy for conflict? in McLean S (ed) **Contemporary Issues in Law, Medicine and Ethics**, Dartmouth, Aldershot.

5.61 Although doctors owe an obligation of confidence to competent adult patients, there is some doubt whether there is a similar legal obligation owed to those who lack mental competence to form a confidential relationship with doctors. The unsatisfactory outcome (if the doubt is valid), could be that the confidentiality of those who are most vulnerable is not subject to any legal protection. In practice this is unlikely to be a significant problem. Where the lack of mental competence is temporary, the issue of disclosure is more straightforward than in, say, infective conditions. The decision about whether to disclose information can and must be deferred until the individual has regained sufficient competence for the matter to be discussed. Where the lack of mental competence is likely to be permanent and they are unable to consent to the disclosure of information to other family members, we assume that the requirement to act in their best interests would extend to disclosure of information to others.

Chapter 6

Wider use of genetic information about mental disorders:

Introduction

6.1 Genetic information about mental disorders raises ethical issues which extend beyond those arising from its clinical applications (discussed in Chapter 5). It may affect the ways in which those with mental disorders are viewed by others, and in particular the stigma that they suffer. It might also be invoked to argue for different treatment, or unacceptable forms of discrimination towards those who suffer, or are deemed likely to suffer, mental disorder, particularly in areas such as insurance, employment, education and health care.

Mental disorder and stigma

6.2 As noted in Chapter 1, stigma is a notable and pervasive feature of mental disorder. In the words of one person with schizophrenia "*there is nothing more devastating, discrediting, and disabling to an individual recovering from mental illness than stigma, which Webster's (in an older edition) defines as 'the scar or brand left by a hot iron on the face of an evil-doer'. This brand is a mark of disgrace, of shame. It signifies that an individual is different, someone to be avoided.*" [1] One US study found that mental illness is one of the most highly rejected conditions, clustering with drug addiction, prostitution and ex-convict status rather than with cancer, diabetes and heart disease.[2] The degree of stigma differs for different mental disorders. Depression evokes considerable sympathy; schizophrenia frequently leads to social isolation.

6.3 Stigma has several different elements. In part, it may be an understandable, if regrettable, response to some of the behaviour of people with mental disorders. People may find such behaviour frightening or disturbing, and deal with their fear by segregating those with mental disorder, by viewing them as alien and by trying to exclude them from society.

6.4 In large part, however, stigma results, not from experience of difficult behaviour by the mentally disordered, but from ignorance and misconceptions about mental disorders. According to one recent US study perhaps "*the most pernicious of all myths is that of the dangerousness of psychiatric patients. While less than 3% of mentally ill patients could be categorized as dangerous, 77% of mentally ill people depicted on prime-time television are presented as dangerous.*" [3] Public fear of random attacks by mentally ill patients, prompted largely by two or three highly publicised cases of so-called 'care in the community killings', has led to research into the matter.[4] The study of people convicted of homicide found that those with no symptoms of mental illness were more likely to have killed a stranger than those with symptoms (although the risk to relatives of the mentally ill was higher). A recent US study found that over half of respondents in a large survey believed that weakness of character was a likely cause of both depression and schizophrenia, and were inclined to blame those with mental disorders for their condition.[5] A history or label of mental disorder can even lead to stigma in the absence of any behaviour that differs from the norm.

1 Leete E (1992) The stigmatised patient, Chapter 4 in Fink P and Tasmai A (eds) **Stigma and Mental Illness**, American Psychiatric Press Inc, Washington DC, p18.

2 Albrecht G, Walker V and Levy J (1982) Social distance from the stigmatized: A test of two theories, **Social Science and Medicine** 16:1319-27 cited in Link B, Cullen F, Mirotznik J and Struening E (1992) The consequences of stigma for persons with mental illness: evidence from the social sciences, Chapter 9 in Fink and Tasman (eds), **Stigma and Mental Illness**, p91.

3 Dubin W and Fink P (1992) Effects of stigma on psychiatric treatment, Chapter 1 in Fink and Tasman (eds), **Stigma and Mental Illness**, p3.

4 Appleby L (1997) **Progress Report of the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness**, Department of Health, London.

5 Jorm A, Korten E, Jacomb P, Christensen H, Rodgers B and Pollitt P (1997) Public beliefs about causes and risk factors for depression and schizophrenia, **Social Psychiatry and Psychiatric Epidemiology**, 32:143-8.

6.5 These attitudes are evidence of lack of understanding, lack of sympathy and lack of respect for suffering fellow human beings. Many respondents to the Working Party's consultation highlighted the problems caused by stigma.[6] Stigma also affects the families of people with certain mental disorders. This may be due partly to fear that contact with the family will result in contact with the affected person; but it runs wider than this. Families are sometimes regarded as tainted with the patient's deviance, and may even be blamed for their relative's mental illness.

6.6 Stigmatising mental disorder may injure and harm people in two ways. Firstly, those who stigmatise represent sufferers in ways that demean and debase them, so damaging their reputation and sense of self: stigma **constitutes** an injury to self even if it has no further effects. Secondly, those who stigmatise may **cause** further injury or harm to sufferers, for example, by unfair and even discriminatory action in areas such employment and housing.[7] In so far as stigma **constitutes** an injury, it resembles practices of defamation on the basis of race, ethnicity or gender, which may injure even when those affected are not, or not fully, aware of the fact, or accept their demeaned status. Such lack of due respect for persons is wrong even when it leads to no further harm. For example, a racist who provides material goods to those whom he regards as despicable, or a child pornographer who looks after the material welfare of his victims, may injure greatly without causing additional harm. More typically, stigmatising others not only **constitutes** injury but also causes further harm. Proper treatment of those with mental disorder must work to eliminate both the injury which stigmatisation **constitutes** and the harm which it **causes**. In general, constitutive injury may be deeper and less easy to rectify.

6.7 The serious injury and harms constituted and caused by the stigmatisation of mental illness make mental disorder an object of fear. This fear can in turn have a range of further effects; in particular it may deter people from seeking psychiatric treatment. This avoidance may be partly because they share the negative perceptions of mental illness held by many in the population, but also because they fear the consequences of being labelled as mentally ill and suffering the associated stigma. Taken together, "*Patients' willingness or unwillingness to be treated, the inability to pay for treatment, and the unwillingness of people to have mentally ill persons living near them or working in their companies have combined to form the most powerful anti-therapeutic forces that mentally ill individuals face*." [8]

6.8 Some people argue (or hope) that increased knowledge of genetic information relevant to mental disorder might help to reduce the stigma those with these disorders now face. Evidence that mental illness has a physical basis might help to counter traditional notions that mental illness reflects weakness of character, and put mental illness on a par with other, physical illness. The stigma associated with Alzheimer's disease, for example, has decreased, and this may be because understanding of its biological basis has increased. There is also greater familiarity with the disease, both because its incidence has increased and because it is more widely discussed.[9] But others have noted the possibility that linking mental illness with genetic differences might reinforce the idea that the mentally ill are fundamentally different.

6 Including the National Council of Women of Great Britain and individual respondents to the Working Party's consultation.

7 A recent survey by the mental health charity MIND reported that over two-thirds of all key service providers who responded had encountered opposition to community mental health facilities in the past five years, although none of the residents' fears for children's safety, of violence or of falling house prices, were based on their actual experience or were backed up by research (Repper J, Sayce L, Strong S, Willmot J and Haines M (1997) **Tall Stories from the Back Yard: A Survey of 'Nimby' Opposition to Community Mental Health Facilities Experienced by Key Service Providers in England and Wales**, MIND London).

8 Fink and Tasmai (eds) (1992) Introduction to **Stigma and Mental Illness**, p18.

9 Personal communication, Harry Cayton, Alzheimer's Disease Society. The Tuberous Sclerosis Association, in their response to the Working Party's consultation, also suggested that 'the stigma associated with [tuberous sclerosis] seems to have lessened as there is more research into the condition.'

6.9 An increase in the availability of genetic information about mental illness may also affect families who suffer stigma. Genetic research findings can have a salutary influence on the way families view themselves and their role in mental illness.[10] Such information might also shift the blame to families, however, if parents were blamed for their decision to have the child in the first place.

6.10 There is evidently no simple way, no single institution and no simple piece of legislation which could eliminate the harm and injury constituted by the stigma of mental disorder. Only long-term changes in public understanding of, and support for, those with mental disorders will improve matters. The Working Party welcomes, therefore, the current Respect campaign by the mental health charity MIND to combat discrimination on mental health grounds and the forthcoming campaign against stigma by the Royal College of Psychiatrists.[11] **The Working Party recommends that campaigns to reduce stigma emphasise that it constitutes harm as well as causing it**.

Discrimination

6.11 The harms which stigma may cause are also important. If and in so far as genetic information about individuals can be used to assess their health, or future health, it might also be used to restrict their access to certain activities or services. Some restrictions may constitute acceptable forms of discrimination; others may not. We have paid particular attention to insurance, employment and education since these are areas in which discrimination on the basis of mental disorder, and potentially on the basis of genetic information about mental disorders, may be significant.

Insurance

6.12 There has been considerable debate in the UK, in other European countries and in the US about the use of genetic information for insurance purposes. In the UK, attention has so far been mainly on life insurance, but other types of insurance are now also coming under increasing consideration. In the UK there has been particular interest in the standards of consumer protection and concern that the use of genetic test results to fix levels of premiums or to refuse cover may raise issues of consumer protection that fall outside the competence of the Insurance Ombudsman.

6.13 The relation between genetic information and the actuarially significant information which insurers seek, and on which they base premiums and refusal to insure, is often complex. It is simplest in the case of single gene disorders: for example, individuals with the gene mutation for Huntington's disease have a calculable and actuarially significant reduction in life expectancy. However, even in these relatively simple cases, there is considerable and often actuarially significant variability between individuals, for example in age of onset, which may be due to other environmental or genetic factors. By contrast, information about susceptibility genes is often of quite limited actuarial use: it may provide information about slight increases (or decreases) in the risk of suffering from some multifactorial disorder in a population, but shows little, if anything, about any single individual's level of risk. Future research may be able to identify combinations of gene variations which contribute to an actuarially significant greater or lesser risk, or to a greater or lesser likelihood of benefiting from certain sorts of treatment; but at present the genetic information by which insurers could calculate the increased risk to a given individual who has certain susceptibility genes is not available.

10 Lefley H (1992) The stigmatized family, Chapter 12 in Fink and Tasmai (eds) **Stigma and Mental Illness**.
11 See also Medical Research Council (1997) **Genes and the Mind**, Medical Research Council, London.

6.14 The use of genetic information relevant to mental disorders for insurance purposes may therefore be fairly limited and specific. Even where actuarially useful information is available, it may often be useful only for certain types of insurance product. For example, knowing that an individual has the gene mutation for Huntington's disease may be relevant to life insurance; knowing that an individual has susceptibility genes for late onset Alzheimer's disease might (if the actuarial evidence were strong enough) be relevant to long-term care insurance.

6.15 In 1997 the Association of British Insurers (ABI) issued a code of practice on the use and handling of genetic test information by insurance companies.[12] The code states that applicants will not be asked to undergo genetic tests, but will be asked to reveal existing genetic test results if they are relevant to a question on the application form. Genetic test information disclosed by applicants will be used only if it shows a clearly increased risk of genetic disease and a low increase in risk will not necessarily justify an increase in the premium. For the time being a moratorium (to be reviewed in 1999) allows that existing genetic test results are not disclosed for applications for life insurance up to £100,000 linked to a mortgage on a primary place of residence.

6.16 Simultaneously, a report was published by the Human Genetics Advisory Commission which also concluded that applicants should not be required to take genetic tests for insurance purposes.[13] This report emphasised the need for insurance companies' policies to be based on sound actuarial assessments of the risks indicated by genetic information. The Commission proposed that a general moratorium on requirements to disclose the results of genetic tests should be lifted **only** as research demonstrates the actuarial relevance of **specific** sorts of genetic test results for **specific** insurance products. In its initial response to the Human Genetics Advisory Commission's report, the Association of British Insurers rejected this call for an approach based on the provision of specific actual information on the grounds that there are already eight specific genetic tests which are known to provide actuarially significant information.[14]

6.17 A central concern of the Association of British Insurers' code and the Human Genetics Advisory Commission's report is with possible misuse of genetic test results to discriminate unfairly. Both bodies accept that standard insurance practices discriminate between individuals with discriminable actuarial risk, and both hold that insurers should not apply loadings which are not actuarially justified. Neither offers a general reason for modifying standard insurance practice where genetic test results are actuarially significant. However, the Commission's report is more sceptical both about the amount of actuarially significant genetic information now available and about insurers' need for genetic test results. It notes that some insurance companies do not propose to ask for genetic test results at all, and calls on the industry to develop alternative insurance products for those unable to obtain standard ones.

6.18 The Human Genetics Advisory Commission report also noted that it is difficult at present for those who feel that they may have been unfairly discriminated against by insurers to obtain hard evidence. A recent MIND survey found that some people had been refused life or other insurance policies because of a psychiatric diagnosis.[15] It is difficult to establish whether this constitutes unfair discrimination, however, since insurers regularly refuse insurance to applicants with a variety of actuarially significant conditions and indicators without providing detailed information about the basis of their decision. The Commission's report therefore also calls for higher standards of consumer protection in the insurance industry, so that individuals can discover whether insurers have unfairly discriminated against them.

12 Association of British Insurers (1997) **Genetic Testing: ABI Code of Practice**, Association of British Insurers, London.
13 Human Genetics Advisory Commission (1997) **The Implications of Genetic Testing for Insurance**, Human Genetics Advisory Commission, London.
14 Association of British Insurers (1997) **Genetics Code of Practice Published by Insurers**, Press Release, 17 December 1997.
15 Read J and Baker S (1996) **Not Just Sticks and Stones: A Survey of the Stigma, Taboos and Discrimination Experienced by People with Mental Health Problems**, MIND UK.

6.19 It is important that insurers do not exaggerate the actuarial implications of genetic test results, and doubly important that they do not do so in the case of genetic test results relevant to mental disorders, where the risk of stigma and of its effects is high. Any exaggeration of the actuarial implications of genetic test results amounts to unfair discrimination. It is important to have systems in place that can monitor whether insurers are discriminating unfairly on the basis of genetic test results. **The Working Party recommends that the Government, in consultation with the insurance industry, makes arrangements for monitoring insurers' use of genetic tests for mental disorders, and for reporting on any tendency to load premiums excessively, any actuarially unwarranted refusal of insurance and any other forms of unfair discrimination**.

Employment

6.20 Employment is an area in which the stigma attached to mental disorders plays a large part. A survey of people with a psychiatric diagnosis, by MIND, found that "*the largest problem in people's lives was that of employment, either trying to return to work, staying in their current jobs, or even getting into work in the first place.*" Over half of respondents had had to conceal their psychiatric history for fear of losing their jobs.[16] The stress of secrecy, the fear of being found out and exclusion from work can all be very damaging, the more so since being in work is known to play an important role in maintaining mental health. Yet employers may have evident reasons for concern when employees, or prospective employees, have poor health records of any type.

6.21 Until now, the use of genetic information for employment purposes has attracted much less attention than its use for insurance. Employers' and prospective employers' use of psychometric tests has been of far greater concern than their use of genetic tests hitherto. However, in view of the employment difficulties and discrimination faced by those with mental health problems, and by those who have had such problems, it is important to consider how the use of genetic information, including genetic test results, could improve or worsen matters.

6.22 The introduction of specific genetic screening programmes for employees or potential employees was considered in the Nuffield Council's first report, **Genetic Screening: Ethical Issues**. This report, which focused on occupational risk linked to genetic make-up, did not specifically consider the issues raised by genetic tests related to mental disorders. It recommended that "*genetic screening of employees for increased occupational risks ought only to be contemplated where:-*

(i) there is strong evidence of a clear connection between the working environment and the development of the condition for which genetic screening can be conducted;

(ii) the condition in question is one which seriously endangers the health of the employee or is one in which an affected employee is likely to present a serious danger to third parties;

(iii) the condition is one for which the dangers cannot be eliminated or significantly reduced by reasonable measures taken by the employer to modify or respond to the environmental risks."[17]

6.23 That report also added that although "*it may be appropriate to introduce a genetic screening programme on these limited grounds, it should only be done if accompanied by safeguards for the employee, and after consultation with the co-ordinating body recommended*". Such bodies

16 Ibid.
17 Employment, Chapter 6 in Nuffield Council on Bioethics (1993) **Genetic Screening: Ethical Issues**, Nuffield Council on Bioethics, London, p64.

now exist. Since the publication of the report Government has established both the Advisory Committee on Genetic Testing and the Human Genetics Advisory Commission which has wider responsibilities and is charged with looking at the economic and employment implications of human genetics. Indeed, the Commission has identified the issues around genetics and employment as a priority.[18] **The Working Party recommends that the Human Genetics Advisory Commission, in its consideration of genetics and employment, determines which is the appropriate body to monitor any introduction of genetic screening programmes for increased occupational risks.**

6.24 So far as we have been able to establish there is at present only one programme for the genetic screening of employees. The Ministry of Defence tests applicants for the forces for sickle cell trait if they would be exposed to atypical atmospheric pressures; carriers as well as known sufferers are considered to be at risk of sickling on exposure to reduced atmospheric pressures or hypoxia. There are, however, other genetic tests which can identify individuals who are more sensitive than others to certain occupational hazards. For example, individuals exposed to organic solvents are at increased risk of developing Goodpasture's disease if they have a particular genotype.[19] The Royal Society, in their response to the Working Party's consultation, pointed out that the relevant genetic test has been available for many years, but has not apparently been used significantly for employment or insurance purposes. They raised the possibility that an employee who becomes ill as a result of exposure to this foreseeable risk might regard the employer as negligent for not having offered genetic testing.

6.25 We have not learnt of any genetic sensitivities to chemical or biological agents which are associated with increased risk of mental disorder. However, other features of some working environments, for example, stress, isolation or danger, might represent greater risk factors for mental disorder for individuals with susceptibility genes for mental disorders than for others. Employers are legitimately concerned to identify whether some current or prospective employees may be more vulnerable than others to such factors. Hence, it is not entirely unrealistic to think that genetic tests might be used in the future to screen for employment, and that some employers might be interested in genetic tests for susceptibility to mental disorders.

6.26 Any use of genetic tests relevant to mental disorders for employment purposes other those of controlling exposure to occupational hazards, so protecting both employees and employers, raises a number of ethical questions. While employers should act within the context of an Equal Opportunities policy, tests could be used to exclude some people from employment, to restrict the sorts of employment which they could obtain, or the sorts of promotion or benefit for which they were eligible. Employers might use this information to ensure a healthier work force with lower sickness rates; pension funds might use it to reduce the costs of early retirements. Policies of these sorts could have serious adverse implications for people whose genetic test results indicated a susceptibility to mental health difficulties.

6.27 In the UK the Disability Discrimination Act 1995 makes it unlawful for employers of twenty or more people, and for providers of goods and services, land, property and accommodation, to treat a person with a disability less favourably than other people unless they can justify their behaviour. For the purposes of the Act, disability includes physical or mental impairment which has a substantial and long-term adverse effect on abilities to carry out normal day-to-day activities. There has been concern that many people who suffer discrimination as a result of

18 Human Genetics Advisory Commission (1998) **Implications of Genetic Testing and Employment is Commission's Next Priority**, Press Release, 9 February 1998.

19 Goodpasture's disease involves inflammation of the small blood vessels of the kidneys and lungs. The genotype concerned is HLA (human leucocyte antigen) type DR2.

mental health problems will not fit into this narrow definition of disability. Moreover, while the Act covers those who have, or have had, a disability, it would not cover cases where genetic tests suggest that an individual will, or may, develop a disability in the future. Amendments to ensure that the Act would cover this category were discussed in both Houses but not incorporated into the final Act. The House of Commons Select Committee went further in its report on Human Genetics, concluding that a "*law making unauthorised release or use of genetic information an offence should give greater protection against discrimination than simply defining genetic susceptibility to a disease as a disability under the terms of the Disability Discrimination Bill.*" [20] It suggested that a Privacy Bill should make misuse of genetic information both a criminal and a civil offence. However, in its response to the report the Government indicated a reluctance to legislate on personal privacy either in general or in the area of genetics.

6.28 It is conceivable that employers might consider offering certain genetic tests to employees as a health benefit, although the financial cost would make this unlikely. In any case, the relevant ethical considerations would be those set out in Chapter 5. However, it would be particularly important to determine who would have access to test results, responsibility for undertaking any intervention indicated by those results (such as the removal of some occupational risk factor), and liability in the event of failure to so intervene.

6.29 Any wider use of genetic tests in employment may raise far-reaching issues about discrimination; but so far there is little legal or other framework for addressing these issues in the UK. We believe that this lack reflects the newness of the issues and not their lack of importance. Elsewhere there has already been legislation to address the use of genetic information by employers. Danish legislation on the use of personal health information in employment decisions established a Health Information Council and set out stringent regulation on the use of genetic information by employers; however, the enforcement of these measures is relatively weak.[21] In the US, a number of states have prohibited the acquisition and/or use of information about current or prospective employees' genetic characteristics by employers.[22]

6.30 When employment is in the UK public sector, the provisions of the European Convention on Human Rights will become relevant. In particular, any requirement for genetic testing as a condition of employment could compromise the right to respect for private and family life guaranteed by Article 8. With the imminent enactment of the European Convention into UK statue law, other aspects of the Convention may well apply.

6.31 The Working Party welcomes the forthcoming consideration of genetics and employment by the Human Genetics Advisory Commission and **recommends that, in view of the special significance of stigma in mental disorder, the Commission pays particular attention to the implications of testing for genetic factors relevant to mental disorders for employment purposes.**

20 Shaw G (Chairman) (1995) **Human Genetics: The Science and Its Consequences, House of Commons Science and Technology Committee Third Report, Session 1994-95, Volume I Report and Minutes of proceedings**, 41-I, HMSO, London, paragraph 226.

21 Presentation by Soren Holm, member of the Danish Health Information Council, at the conference **Genetic information: acquisition, access and control** held at the University of Central Lancashire, Preston, 5–6 December 1997.

22 Yesley M (1997) Genetic privacy, discrimination, and social policy: Challenges and dilemmas, **Microbial and Comparative Genomics** 2:19-35.

Education

6.32 Education is another area in which the use of genetic information might become a controversial issue. On one hand, genetic test results might be relied on, for example, to establish a case for special educational provision. On the other hand, current methods of educational assessment might prove entirely adequate for this purpose. Such dilemmas may arise both for certain single gene disorders (for example, fragile X syndrome) and for conditions such as dyslexia where little is yet known about the involvement of genetics.

6.33 Reliance on genetic tests should not, we believe, become automatic in educational assessment even for single gene disorders, since testing itself may have other, possibly adverse, implications. For example, the debate about fragile X syndrome screening and the benefits and disadvantages of testing school age children for the syndrome is by no means settled. Some argue that a specific diagnosis is helpful in tailoring an educational programme and that a diagnosis itself can be therapeutically helpful and can help parents and children get the resources they need. Others consider that there is little, if any, evidence that a genetic test for fragile X syndrome would suggest any drug treatment or educational programme that would not be recommended on the basis of conventional assessment of the child's needs, although test results might be of use to a family making further reproductive decisions.

6.34 The reasons for or against using other genetic tests of children for educational purposes may vary. In some cases a genetic test might be useful in identifying the specific educational approach of most use; in others it might be of doubtful value. In the latter case there would be *prima facie* grounds for relying on conventional tests. Even in the former case, reliance on genetic tests should not, we believe, become automatic in educational assessment since testing itself may have other, possibly adverse, implications.

6.35 In the US there have been moves to demand that education systems take more systematic account of cognitive ability, and it is conceivable that pressure will develop for genetic screening for cognitive ability. We have not found evidence to support wider use of genetic tests, and suggest only that their use for children with special needs be systematised with due regard for the child's and family's needs.

Chapter 7

Genetic research on mental disorders: ethical and legal issues

Introduction

7.1 So strong is the opposition of some people to genetic research into mental disorders that they regard it as ethically inappropriate. This viewpoint appears to be based on a reductionist interpretation of such research (paragraphs 1.4–1.7). If this was indeed the rationale for undertaking genetic research, it would be of considerable concern to the Working Party. In practice, however, this does not seem to be the case. On the contrary, we would construe it as unethical to exclude people with a mental disorder from the possibility of benefit arising from an improved understanding of mental disorders. There is, nevertheless, a need to consider in detail how best to safeguard individuals who may participate in such research.

Consent to involvement in research

7.2 A request for consent to participation in research is an expression of respect for persons and for human dignity; as with any procedure this extends to a legal requirement when body contact is involved. If harm were to follow from research not involving contact, in the absence of the participant's valid consent, this too could be an invasion of legal rights. In this chapter the aim has been to draw out the specific issues relating to research into the genetics of mental disorder.

7.3 Most people with mental disorders will be competent to consent on their own behalf to participation in research. There is, in law, a presumption that an adult has the capacity to make decisions unless there is evidence to the contrary.[1] In relation to research into the genetics of mental disorder, the competence of most other participants to consent is even less likely to be in doubt. Most relatives, for example, will not themselves have a mental disorder nor be likely to develop one and many volunteers are unlikely to be patients in any sense other than that they are registered with the National Health Service.

7.4 As noted in Chapter 5 (paragraphs 5.22–5.27), an individual's capacity to make a particular decision will depend partly on the complexity of the issues and partly on its risks and benefits. In considering the risks and benefits of participating in genetic research, a person with a mental disorder will face similar issues to those with any other kind of disorder. In most cases the personal benefits are likely to be small, at least in the short term, and advantage is most likely to be conferred on sufferers as a group. Physical procedures involved in genetics research are generally not hazardous, involving perhaps the withdrawal of a small sample of blood from a vein. It is now feasible, although less common, to take a sample from the lining of the mouth (a sample of so-called buccal mucosa), which may be obtained with a mouthwash or a gentle scrape of the inside of the cheek. For those with a mental disorder, and indeed for some with a physical disorder, the attendant structured interview and family study may, however, be psychosocially intrusive and even hold the potential for creating difficulties and tensions within the family.

7.5 Consent to participation in research as opposed to treatment may raise special difficulties because, by definition, the risks and benefits of any given procedure are unlikely to be fully known. In some therapeutic research, the likelihood of immediate benefit is at its highest. For the rest, although the research may be likely ultimately to bring benefits for the class of people to which the putative participant belongs, it is unlikely to carry any direct specific benefits for individual participants. Benefits such as a sense of contributing and increased attention should not be underestimated, but these, like placebo effects, are non-specific. Such non-therapeutic

1 For England and Wales, see the Law Commission (1995) **Mental Incapacity**, No 231, HMSO, London.

research may be most likely to attract legal problems (paragraphs 7.11–7.18). Some have argued that the capacity for consent to research in this field should be of sounder quality than the capacity to make other health care decisions. Others argue that the approaches to clinical research and clinical practice should be similar and should not be needlessly burdensome for patient or participant.[2]

7.6 Either way, the capacity of patients is usually a matter of subjective judgement on the part of, at best, someone who is primarily working in the interests of the individual. In the case of someone with a mental disorder, this is usually the consultant psychiatrist but, if the consultant is also the researcher, then capacity should be judged by someone independent of the research team. There are now tested methods of assessing such consent more objectively,[3] but they are time-consuming, and therefore also costly, and raise further questions about when and if they should be applied to research. It is more than likely that their widespread use would inhibit research by proving too costly for researchers and too burdensome for potential participants who might decline to continue. This might indirectly damage the prospects of the group of people with the disorder under study. It may be, however, that specific tests of competence could be of value in very difficult or contentious circumstances.

7.7 For many individuals with mental disorders, mental capacity varies and it is desirable, and almost always possible, to involve them in relevant genetic research at a time when they are competent to consent on their own behalf. **The Working Party recommends that individuals who are intermittently competent should only be approached about participation in research when competent**. In these circumstances, the problems in obtaining informed consent from individuals suffering from psychiatric disorders are not qualitatively different from those encountered in research on other medical disorders. Unaffected relatives or unrelated participants included as control groups also need to give informed consent to participation in research.

7.8 Informed consent may be given verbally or in writing. Commonly, ethics committee requirements in this regard depend on the nature of the research. Invasive research invariably requires written consent, while for non-invasive research, such as interview-based studies, verbal consent alone has sometimes sufficed given the consent implied if the subject continues with the interview. Although genetic research tends now to be minimally physically invasive, **the Working Party recommends that written consent for participation should be the general rule**. Some professional and scientific journals now require written confirmation of the nature of the consent to participation in the research.

7.9 The need to obtain genuine consent was discussed in Chapter 5 (paragraph 5.25). Particular circumstances may impede the process of obtaining genuine consent. There may be some grounds, for example, for believing that in the past, prisoners have been overtly or covertly coerced into taking part in research. It is particularly important in circumstances where potential participants in research may be confined in an institution, or may be detained patients, to be clear that participation cannot and will not be used for bargaining. Another concern in relation to freely given consent is the issue of personal reward. Small fixed, or individually calculated, sums of money for time spent are sometimes offered to individuals participating in projects. With respect to each funded project, it must be a matter for careful ethical consideration.

2 Tobias J and Souhami R (1993) Fully informed consent can be needlessly cruel, **British Medical Journal** 307:1199–201.

3 Appelbaum P and Grisso T (1995) The MacArthur Treatment Competence Study: I Mental illness and competence to consent to treatment; Grisso T, Appelbaum P, Mulvey E and Fletcher K (1995) The MacArthur Treatment Competence Study: II Measures of abilities related to competence to consent to treatment; Grisso T and Appelbaum P (1995) The MacArthur Treatment Competence Study: III Abilities of patients to consent to psychiatric and medical treatment, all in **Law and Human Behaviour** 19: 105–26, 127–48 and 149–74.

The assumption, for which there is no evidence, is that people with a mental disorder may be indirectly coerced into participation by the offer of payment. (It is arguable that a more pernicious practice was their attempted recruitment or retention by supplying cigarettes.) **The Working Party recommends that any proposed payment for participation in research should always be carefully considered by research ethics committees and by grant-giving bodies.** Researchers who make no explicit comment on this point should be asked to do so.

7.10 An important issue is that consent may not be for all time. Those deciding to withdraw from a research project should be able to do so without any sense of failure or disadvantage. Nevertheless, it is important that an indication of intent to withdraw is met with attention similar to that given when consent was originally sought. The researcher must fully understand the problems that have led the participant to ask to withdraw; for example, any unforeseen problems in the research design or presentation. The participant should also understand the implications of his or her withdrawal including a possible contribution to misleading research findings.[4] Although this may risk the appearance of coercion, withdrawal is a serious problem and a competent participant is unlikely to be harmed or unduly pressurised by a properly given explanation of the situation. There have been suggestions that the nature of some mental disorders makes withdrawal particularly likely as ambivalence or fluctuating commitment may be intrinsic to the disorder. It may be that if these cases exist, the contingencies should place greatest weight on safeguarding as far as possible data already gathered, since the greatest risk lies in distortion of the data collection and therefore misleading findings in relation to the condition. Another, more real, concern is that the capacity of the person to consent, and therefore the validity of that consent, may fluctuate with the course of the disorder, for example in dementia. The possibility that the potential participant's capacity to consent to the research might change during the course of that research, with proposed contingencies for dealing with that, should be presented to a research ethics committee at the outset and appropriate procedures agreed with participants.

Safeguards for individuals considered to be incompetent

7.11 Some people may, by reason of their disorder, have a profound and continuing lack of understanding. Most commonly these are people with severe mental retardation or advanced dementia. Some will be both young and of impaired mental capacity. Problems like this are particularly likely to arise for some with a rare, single gene disorder. This leads into discussion of the ethics and law relating to those unable to consent on their own behalf to involvement in research.

7.12 Provided that the research is therapeutic, that is, aimed at least in part at benefiting the individual patient, it is likely to be lawful. It is not always easy, however, to determine whether research is indeed therapeutic.[5] If the research is non-therapeutic, in other words is not of any *immediate* benefit to the individual patient, then in the current state of the law it is of doubtful legality. In relation to children, the rigour of this position may be mitigated by permitting the parent to consent on behalf of the child relying, not on the usual test of whether an intervention is in a child's best interests, but on the test of whether it is 'not against the child's best interests'.[6] This

4 Edlund M, Craig T and Richardson M (1985) Informed consent as a form of volunteer bias, **American Journal of Psychiatry** 142:624–7.

5 A similar problem has arisen in the context of HIV testing of children. See *Re HIV Tests* [1994] 2 FLR 116, in which the courts recognised that the question raised "considerations ... both of law and of social policy". There is no authority on whether such testing will be in the child's best interests and the High Court has directed that applications under the Children Act 1989 directed at the HIV testing of a child should always be heard by a High Court judge.

6 See the discussion in Dworkin G (1987) Law and Medical Experimentation **Monash University Law Review** 13:189.

test has been applied where there is an important interest served by the intervention but it is not strictly speaking in that specific child's best interests.[7] In the case of mentally incompetent adults, however, since no one may consent on behalf of another adult, it would appear that, in the current state of English law, non-therapeutic research is unlawful.[8]

7.13 This is also the case for a patient detained under the Mental Health Act 1983 who is specifically mentally incompetent to consent to treatment for his mental disorder. Such treatment is only lawful if it falls within the terms of Part IV of the Mental Health Act 1983.[9] Whereas therapeutic research and genetic treatment could be described both as treatment for a mental disorder and in the patient's best interests, non-therapeutic research and genetic testing might not be properly so described.

7.14 Several responses to the Working Party's consultation argued that research on mentally incapacitated patients should be "*explicitly restricted to therapeutic research, that is, research which is potentially beneficial for the individual research subject.*" [10] The Working Party does not consider that such a stance is tenable when individuals are suffering from a condition, or particular presentation of a condition, which would render all such people incapable of complex decisions; we would regard an automatic bar on non-therapeutic research in such circumstances as an unacceptable disadvantage to people with that condition, necessarily limiting progress into the understanding and, indeed, treatment of their disease. We think that the more restrictive view is likely to reflect a need for wider and more considered education beyond the immediate disciplines concerned. There is also a need for further inquiry, research and debate on best practice in this particularly difficult area. In the meantime, we endorse the views summarised below.

7.15 A number of bodies have concluded that non-therapeutic research involving adults unable to consent to participation on their own behalf may, in certain circumstances, be ethical, and some of the principles regarding ethical research with children may help here.[11] In particular, even though the process may not constitute legal consent, involvement of the patient's next of kin or nearest relative and, where relevant, the patient's legal adviser would be good practice. MRC guidance states that an individual unable to consent should be included in non-therapeutic research only if:

- it relates to the individual's condition and the relevant knowledge could not be gained by research involving those able to consent;
- it is approved by the appropriate Local Research Ethics Committee (LREC);

7 See, for example, *S* v. *S, W* v. *Official Solicitor* [1972] AC 24, [1970] 3 All ER (HL). These two appeals, heard together, concerned the permissibility of having a child's blood tested in order to establish paternity. The case is the English authority on the legality of medical interventions which are not, on the face of it, intended to be therapeutic. The House of Lords found that the child's interests were best served by the truth being made known.

8 See the Law Commission (1995) **Mental Incapacity**, No 231, HMSO, London, paragraph 6.29: "If, however, the participant lacks capacity to consent to his or her participation, and the procedure cannot be justified under the doctrine of necessity, then any person who touches or restrains that participant is committing an unlawful battery. The simple fact is that the researcher is making no claim to be acting in the best interests of that individual person and does not therefore come within the rules of law set out in *Re F" (Mental patient: Sterilisation)* [1990] 2 AC 1]. "In some cases relatives are asked to 'consent' to what is proposed, and do so. It appears that some funding bodies and Ethics Committees stipulate for consent by a relative where the research participant cannot consent. As a matter of law, such 'consent' is meaningless. It appears that the question of the legality of non-therapeutic research procedures is regularly misunderstood or ignored by those who design, fund and approve the projects." In paragraph 6.25, the Law Commission suggests that the genetic testing of a person without capacity to consent would be unlawful, unless connected to a specific treatment for that person.

9 See, in particular, section 63 which provides that the consent of the patient shall not be required for any medical treatment given to him or her for the mental disorder from which he or she is suffering (save for certain treatments described in sections 57 and 58) if the treatment is given by, or under the direction of, the responsible medical officer. There is some suggestion in the reported cases that such treatment must also be in the patient's best interests (see, for example, *B.* v. *Croydon District Health Authority* [1995] 1 All ER 683).

10 Response from the Centre for Bioethics and Public Policy to the Working Party's consultation and others.

11 Nicholson R (ed) (1986) **Medical Research With Children: Ethics, Law and Practice**, Oxford University Press, Oxford.

- the individual does not object or appear to object in either words or action;
- an informed, independent person acceptable to the LREC agrees that the individual's welfare and interests have been properly safeguarded; and
- participation would place the individual at no more than negligible risk of harm and is not against that individual's interests.[12]

7.16 A similar approach has also been recommended by the Law Commission for England and Wales[13] and the Council of Europe.[14] The options are summarised in a Consultation Paper issued by the Lord Chancellor's Department.[15] It has been suggested that the options differ somewhat in the degree of risk or harm to the research participant considered ethically acceptable. The language differs, but in the absence of legally tested definitions of terms we remain convinced by the principle rather than by any particular variant of its expression. Thus, the Council of Europe refers to "*risks … not disproportionate to the potential benefits of that research*", and entailing "*only minimal risk and minimal burden for the individual concerned*" (Articles 16 and 17). The Law Commission refers to "*minimal risk and minimal invasiveness*", and, in its Draft Mental Incapacity Bill "*that the research will not expose a participant to more than negligible risk, will not be unduly invasive or restrictive … and will not unduly interfere with a participant's freedom of action or privacy*". The MRC guidance (quoted in paragraph 7.15) seems to differ only in terms of adopting the general concept of 'interests' rather than in the detail. A medical position on degrees of risk in this context is that 'negligible' is 'risk less than that run in everyday life'; 'minimal' is 'risk questionably greater than negligible'; any greater risk is referred to as 'more than minimal'.[16]

7.17 **The Working Party recommends, therefore, that non-therapeutic research involving people lacking the capacity to consent to participation on their own behalf should be considered ethically acceptable, subject to strict safeguards**. Whether or not some additional, statutory body is created (paragraph 7.18), the expertise of existing Research Ethics Committees (RECs) to consider such research may need to be broadened, and a mechanism established by the Department of Health, which provides guidance in such matters, by which consistency can be ensured. The Working Party welcomes the first annual report of the Advisory Committee on Genetic Testing[17] which notes that RECs have been raising questions about genetic testing and that it proposes to produce information for RECs setting out 'points to consider' and 'questions to ask' when presented with research proposals which involve genetic testing. **The Working Party recommends that every research ethics committee should include at least one member who has experience in the area of competence in decision making about research participation**. Where necessary, committees should seek to co-opt such a person on occasions when such research is to be considered.

7.18 The question of legislation exercised the Working Party considerably. It would appear to be an important protection for the interests of such people as a group, for researchers in this field, and, especially, for individual participants, that there should be legislative backing for, and controls

12 MRC Ethics Series (1991) **The Ethical Conduct of Research on the Mentally Incapacitated**, London, Medical Research Council. Presumably, the same guidance would now be expected to apply to the recently established Multicentre Research Ethics Committees.

13 The Law Commission (1995) **Mental Incapacity**, No 231, HMSO, London.

14 Council of Europe (1996) **Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine**, Council of Europe, Strasbourg, Articles 16 and 17.

15 Lord Chancellor's Department (1997) **Who Decides? Making Decisions on Behalf of Mentally Incapacitated Adults**, Cm 3803, Lord Chancellor's Department, London.

16 British Paediatric Association (1980) Guideline to aid Ethical Committees considering research involving children. **Archives of Diseases of Childhood** 55:75–7.

17 Advisory Committee on Genetic Testing (1998) **First Annual Report July 1996–December 1997**, Health Departments of the United Kingdom, London.

over, non-therapeutic research, as outlined above (paragraphs 7.15–7.17). The Law Commission has called for a new statutory 'Mental Incapacity Research Committee' on the grounds that RECs (and multi-centre RECs) have no statutory power to make a researcher's actions lawful. While recognising the need both for new legislation on non-therapeutic research, and for regulation of all research on people with mental incapacity, we are not persuaded that an additional Ethics Committee would be appropriate. An alternative might take the form of review of the work of LRECs and MRECs in these matters. **The Working Party recommends that further consideration be given to the details of legislation and regulation to safeguard the interests of people with mental incapacity with respect to participation in research**. The necessary legislative framework could be found in the present review of mental capacity under the auspices of the Lord Chancellor, or form a part of the promised wider review of mental health legislation. Alternatively, it could be free-standing.

Boundaries between research and clinical work

7.19 In a rapidly evolving field such as human genetics, it is probably inevitable that research and clinical work will be closely entwined. Research aimed at identifying genes related to particular disorders may depend on assembling the largest possible collection of families with the disorder. Contact with family members develops as they may be asked to contribute DNA samples and information about themselves and other family members. Many will have questions about the disorder which runs in their family and researchers at the forefront of their field may be better placed than other clinicians to answer these (but see paragraph 7.24 below). In some areas of genetics (for example, cancer genetics) researchers have set up special clinics to which family members at risk may be referred for genetic counselling.

7.20 Provided that appropriate guidelines are followed and patients are not pressurised to be involved in research, such arrangements should not raise any particular ethical problems. Indeed, such clinics may be a very effective way of providing well-informed genetic counselling and other clinical support to members of families that carry some of the rarer genetic disorders. Difficulties over financing may arise, however, as such clinics are often initially financed by research funding but research bodies may be reluctant to continue to support clinics that provide a routine clinical service. As the discovery rate of rare disease genes is accelerating rapidly, this difficulty is likely to increase.

7.21 More complicated ethically are situations where DNA samples have been collected for research purposes and researchers later discover information which is of clinical significance to the donor of the sample. This is quite a common situation in research aimed at identifying disease-related genes. When such a gene is identified and its location and sequence published, most research groups working in the area will screen DNA samples in their possession for relevant mutations. Correlating the presence or absence of particular mutations with information about the development of the disease in individuals can provide important insights into the disease process. Such research should be covered by the general consent that individuals will have given when they provided DNA samples and information about themselves and other family members.

7.22 When such a disease-linked gene has been identified and significant mutations found, the question arises as to how to deal with any clinical implications for individuals who have contributed DNA and information to a research project. For those who have been found to have the condition and a relevant mutation, there could be implications for relatives (who may or may

not have consented to take part in the research), in terms of their risk and also possibilities of direct testing. For those in the research sample who do not have the condition, the presence of a mutation may indicate a risk of developing it in the future while its absence may suggest that the individual will be free of the condition that runs in their family.

7.23 The ethical difficulty arises because the process of obtaining the informed consent required for research does not usually include consent for disclosure of identifiable data to clinics outside the strict environs of the research. Nor is the kind of genetic counselling included that would be required for an individual seeking a genetic test for clinical purposes. To provide an individual with information from a research study about gene mutations which they might or might not carry and which, at the time samples and information were collected, could not have been foreseen, could be to give them information they would choose not to have, and/or information for which they or other members of the family are not prepared or cannot understand in terms of its implications.

7.24 A further difficulty is that quality controls and procedures used for clinical testing may be different and sometimes more rigorous than those used in research studies. For example, in some protocols for direct predictive testing in Huntington's disease, DNA samples are collected on two separate occasions from an individual who chooses to undergo testing. These are tested independently and only if these yield identical results is the result regarded as valid. Such checking procedures are unlikely to be used in a research study. **For these reasons the Working Party recommends that, as a general rule, those who consent to take part in research should be told that individual information derived from analysis of their DNA will not be given to them**. This principle should certainly apply in all situations where the genetic loci under study would, at best, identify only weak susceptibility to a disorder. A summary of the overall findings of the research can be provided if the participant wishes.

7.25 **The Working Party further recommends that, in any research study that could yield genetic information which is clinically relevant to a research participant and/or their relatives, consent to that research should make it clear whether or not such information will be made available**. If it is to be made available then, before consenting to the research an individual should receive genetic counselling, and give written consent to make it clear whether or not they wish their designated medical adviser to receive information of clinical relevance derived from analysis of his or her own DNA, and/or to receive such information personally. Where information is to be given to research participants (or, with their consent, to their medical adviser), the procedures used for collecting and processing samples should be of the same standard as those used in clinical services, and accompanied by further appropriate advice.

Consent for further research use of samples and data

7.26 Many, if not most, studies into the genetics of mental disorder are likely to depend on longitudinal accumulation of data for their maximum value. This may be so for at least two reasons: first, the outcome depends on being able to follow the individual and any changes in their state, during a lifetime; and, second, over the years, more sophisticated possibilities in testing may arise. Another issue that may arise in relation to research where there is a large, established and reliable data bank is that, for reasons of efficiency, other researchers may seek to have access to some of the material. They may, however, only require aggregate data which will be anonymised, which raise few problems and are often obtainable in published tables.

7.27 Researchers may also seek named data or seek to use registers or cohorts as a source for identifying groups of individuals with rare conditions. Once again, there is a need to consider the special needs of those who are not competent to make their own decisions. **The Working Party recommends that, when a person is considered to be incompetent to make his or her own decision about participation in research, data collected for non-therapeutic research purposes should not be used for any other purpose**. For individuals deemed competent, discussion about the possibility of further research should be included in the original process of seeking consent. In some cases, much of the additional data may be collected without further reference to the person. In this case it would be expected that the initial consent process would take account of how further research might be conducted. For some further research it will be necessary to meet the individual again to collect additional information or to take further samples, so that consent for data sharing can be sought in the usual way. At the very least, either approach must include the principle that any new research requires referral to a research ethics committee, together with an indication of what constitutes new research: for example, to include new data collection, the application of previously unavailable tests to material already collected, and the supplying of any part of the data to others, explicitly for research. Research ethics committees have a responsibility to check the progress of any research and to ask what the data has been used for. **When an individual participant is regarded as competent, the Working Party recommends that any possible further use of data in the longer term should be discussed with him or her as part of the consent procedure; new research should, as a minimum, be submitted for approval to a research ethics committee before proceeding**.

Use of research data by outside agencies

7.28 An often cited concern is whether agencies for which data were never intended may be able to get access to research information. These agencies may include health or social services (the latter may still have an open records policy which can extend to other local authority departments), but also to the police or sectors of the criminal justice system, and, sometimes of most concern, insurance and other finance agencies. As with clinical information (Chapter 5), access to research data, without permission, needs strong justification. The European Human Rights Convention and recent EU initiatives on data protection address the protection of privacy. If anything, research data are likely to be safer because they are kept under entirely separate records systems and because, by their nature as research databases, they tend to be seen as likely to be less meaningful than routinely collected clinical data. Potential problems around confidentiality should not be exaggerated. We know of no instance in which raw research data have been used for non-research purposes without the knowledge or consent of the researchers, nor of any where the latter may have been forthcoming inappropriately. Researchers do have a responsibility to take all reasonable steps to ensure that their raw, individualised data will not be used for any other purpose. In one case where this seemed more possible because research was with pre-trial prisoners, express guidance was sought from the Director of Public Prosecutions (DPP) before proceeding with the research. While, in line with the law, the DPP was not able to offer guarantees nor rule out the possibility of subpoena, the advice was that withholding of research data was likely to prove defensible in all but the cases of greatest public interest and that perhaps these alone should be avoided. In practice, this proved to be good advice and, even in these circumstances, notwithstanding a few inquiries about the data, none was demanded or given for non-research purposes.

7.29 Participation in research also raises a question about how a participant should respond if they were ever to have to complete an insurance or mortgage questionnaire which requires them to state if they have ever been tested for a genetically transmitted condition. The process of giving consent for the research should include this as part of the counselling. As discussed, the results would not, in any event, be available for the company, and probably not to the individual completing the questionnaire. Further, with respect to mental disorder, in almost all cases genetic information would in reality add nothing to a clinical risk assessment (paragraphs 4.18–4.20). In the very few cases where it may, for example Huntington's disease, then the issue would emerge anyway in a good clinical history. **The Working Party recommends that genetic information obtained during participation in research should not be made available to organisations such as insurers or employers**.

Chapter 8

Conclusions and recommendations

Introduction

8.1 Genetics is just one approach to tackling the burden of mental disorder but, since both genetics and mental health are areas which raise significant and sometimes distinctive ethical, social and legal concerns, this report has examined the ethical issues that may arise in the course of genetic research into mental disorders and in the application of that research in clinical and other settings (paragraph 1.2).

8.2 The Working Party adopted a broad ethical and humanistic perspective which considered two ethical requirements as basic: the limitation of harm and suffering to all humans and respect for human beings and human dignity. The genetics of mental disorders raises distinctive ethical issues both for the limitation of human suffering and for maintaining respect for persons (paragraphs 1.8–1.13).

8.3 Some of these issues arise because the concern is with genetic conditions; for certain mental disorders the concern is with inherited predispositions rather than with gene mutations that have a more predictable effect. This led the Working Party to adopt two broad categories for discussion; the rare single gene disorders for which Huntington's disease and early onset Alzheimer's disease have provided the main examples, and the common mental disorders influenced both by susceptibility genes and by environmental factors, for example schizophrenia and the more common late onset form of Alzheimer's disease (paragraph 1.3). Finally, some ethical issues arise because the concern is with mental disorders. These cluster around the notion of personal well-being, of how people view themselves and are viewed by others, the implications for reproductive decisions, the stigma associated with mental disorders and the fact that some mental disorders may impair the capacity to make decisions (paragraphs 1.19–1.25). Some of the recommendations which follow are narrowly drawn and concern mental disorders alone. Others are naturally relevant to different kinds of disorder and therefore apply more generally.

Definition and study of mental disorders

8.4 The Working Party noted philosophical arguments that psychological phenomena are not reducible to physical ones, that human behaviour only develops fully within a social context and that there are society-specific expectations about what constitutes normal behaviour (paragraphs 2.7–2.10). The Working Party concluded that there was a need to be mindful that conditions at one time regarded as pathological might come to be regarded as legitimate lifestyles (paragraph 2.10). The notions of personal distress or dysfunction integral to the definition of mental disorder aim to minimise the impact of society-specific expectations in clinical practice. Even so, while the precision and consistency of diagnosis has much improved, little is known about the underlying causes of mental disorders.

What do genetic studies of mental disorder tell us?

8.5 Given that our understanding of normal brain function is still quite limited, it is not surprising that it has been very difficult to study the abnormal function of the brain in mental disorders. The attraction of genetics, which is attested by many precedents from other fields of medicine, is that it enables functionally important components to be identified without any pre-existing knowledge of how the brain works.

8.6 By studying affected families, the gene mutations causing rare single gene disorders, such as Huntington's disease and early onset Alzheimer's disease, have been isolated and this is contributing to our understanding of those conditions. Many common mental disorders, however, such as schizophrenia, manic depression and depression are more complex, their development being affected by a number of factors which may include variation in several genes; in other words, they are multifactorial and polygenic. Heritability studies are used to estimate, using various simplifying assumptions, how much of the variation within a population for a characteristic can be attributed to genetic rather than environmental factors. Considerable energy has been expended on trying to demonstrate that either biological or environmental factors are of prime importance in the development of mental disorders (paragraphs 3.16–3.20). But recent and more constructive work is revealing the complex interactions between genetic and environmental factors for the common mental disorders. Because such disorders do not have a simple Mendelian pattern of inheritance, however, linkage studies in large families are difficult. The search for susceptibility genes associated with complex conditions is characterised by many claims, few of which have been confirmed.

8.7 The Working Party noted, but did not accept, the concerns of some that genetic research into mental disorders is methodologically flawed (paragraph 3.22). We would emphasise, however, that genetic research has so far yielded little practical help in limiting the suffering of those with mental disorder. Almost every susceptibility locus identified for the complex disorders discussed in Chapter 3 is still the subject of scientific controversy (paragraph 3.26). The difficulty of identifying reproducible gene localisations in common mental disorders represents a key scientific discovery in its own right. It indicates that they are rarely, if ever, caused by simple dominant or recessive mutations analogous to Huntington's disease or phenylketonuria. This has crucial implications for clinical practice, as set out below.

8.8 Methodology for genetic research is progressing rapidly and there seems little doubt that over the next ten years, susceptibility genes will be identified and some of these will hold up to robust scientific scrutiny. These discoveries will certainly improve understanding of the causes of mental disorder though probably by small incremental steps rather than through major revolutions (paragraph 3.27). The full potential of these discoveries will only be realised, however, if accompanied by a well-integrated and rigorous research programme covering all approaches to the understanding of mental health including the complex interactions of susceptibility genes, both with each other and with environmental influences.

Clinical applications

Classification and diagnosis

8.9 With respect to the classification of mental disorders it has been suggested that developments in genetics may allow psychiatrists to define subtypes of mental disorders with different causes. The Working Party concluded, however, that such developments are more likely to result in modification rather than complete revision of classification systems (paragraph 4.4).

8.10 The discovery of gene mutations associated with single gene disorders has had profound implications for their diagnosis. But the Working Party concluded that genetic tests will not be particularly useful in diagnosing mental disorders with more complex causes (paragraphs

4.6–4.10). Similarly, it is unlikely that genetic tests will be useful in prenatal diagnosis or for general population screening for susceptibility to common mental disorders. It is more probable that identifying genes involved in susceptibility to common mental disorders will improve our understanding of abnormal processes and hence lead to the development of useful biochemical diagnostic tests.

Genetic counselling

8.11 It has been claimed that the identification of susceptibility genes will be very valuable in personalising risks and that the increase in precision provided by the ability to calculate risks on an individual basis will be of huge clinical benefit (paragraph 4.16). Evidence to support such claims, however, is lacking. Even if a number of susceptibility genes were identified, without understanding the interactions between them it would be difficult to predict individual risk. The Working Party concluded that only a small proportion of variance in risk is likely to be predictable even when multiple susceptibility genes can be tested (paragraph 4.20). In these circumstances, further research will be required before it can be known whether genetic testing for susceptibility to common mental disorders will be useful in genetic counselling of individuals known to be at high risk because of a family history of mental disorder.

Development of new and better drug treatments

8.12 While the Working Party concluded that genetic research will be of limited benefit for the classification, diagnosis and genetic counselling of common mental disorders there may be other long-term gains. Genetic research will contribute to an improved understanding of the causes of mental disorder and hence to the development of drug treatments which are either more effective or better tailored to individual requirements with fewer side effects (paragraphs 4.22–4.24).

Improved preventive measures

8.13 Genetic research into mental disorders may also enable more sophisticated study of the environmental factors that contribute to mental disorders. It is sometimes claimed that, once genes conferring susceptibility to common mental disorders have been identified, there will be potential for preventive measures. The Working Party concluded, however, that this potential will be limited for the common mental disorders for which predictive certainty is also limited (paragraphs 4.25–4.26). Moreover, it is not always possible to avoid the environmental triggers of mental illness and sophisticated concepts of targeted environmental modification must also be viewed realistically within the perspective of a health care and social welfare system in which simple basic inequalities of service delivery themselves contribute substantially to morbidity (paragraph 4.27).

Gene therapy

8.14 The usefulness of gene therapy in single gene disorders has so far been disappointing. Although the application of gene therapy to common mental disorders at some point in the future cannot be discounted, the Working Party concluded that it would not be appropriate to formulate an approach until general principles have been validated in the technically more straightforward single gene disorders (paragraphs 4.28).

Clinical applications of genetic information about mental disorders: ethical and legal issues

Genetic counselling

8.15 As noted above, the contribution to risk of any one susceptibility gene will be small and is unlikely to lead to clinically useful estimates of individual risk. Genetic counsellors will only be able to offer very precise figures about the risk of recurrence for a few single gene disorders such as Huntington's disease (paragraph 5.4). The Working Party concluded that it is essential that counsellors make clear to individuals the current limitations of scientific knowledge about the majority of mental disorders and, in particular, our limited understanding of the interaction of different environmental and genetic factors.

8.16 An exaggerated perception of the degree to which genetic influences determine an individual's current and future health appears widespread. Accuracy in genetic counselling is profoundly important where mental disorders are concerned, because individuals may suffer additional assaults on their personal integrity and increased fear of stigma. The Working Party concluded that, where risk is slight, it is particularly important that genetic counselling is not urged on individuals who do not wish to have it (paragraph 5.5).

8.17 Where mental illness is concerned, genetic counselling has the potential to affect family dynamics adversely and to trigger anxiety and even illness. Stress may arise when counselling cannot predict a precise level of risk. There is as yet little evidence about the effects of counselling for mental disorders and caution should therefore be exercised (paragraph 5.7). **The Working Party recommends that research is undertaken to clarify the appropriate aims and outcomes of genetic counselling for mental disorders and to assess the response of individuals and families to counselling. Such research should investigate the expertise and training needed by those undertaking counselling for various conditions and purposes.**

8.18 The future demand and need for genetic information and counselling is difficult to predict but, as more knowledge about genetics becomes available, demand may well increase. For the common mental disorders, however, susceptibility genes are unlikely to increase an individual's risk to a degree which would merit specialist counselling. The challenge is to identify the few who genuinely need specialist genetic counselling and to provide adequate information to those who do not. Psychiatric nurses trained in genetic counselling would be well placed to provide a link between primary care teams and genetic clinics offering specialist counselling (paragraphs 5.11–5.12). **The Working Party recommends that the British Society for Human Genetics and the Royal Colleges of General Practitioners, Nursing, Psychiatrists and Physicians consider arrangements for the education, training and support both of primary health care teams providing genetic information about mental disorders and of those providing specialist genetic counselling.**

Genetic testing

8.19 One outcome of initial clinical consultation or of genetic counselling may be that a patient is advised, and chooses, to seek genetic testing. What little evidence there is suggests that the uptake of genetic tests varies depending on the condition. This suggests that caution should be

exercised in drawing general conclusions about genetic testing for different conditions, particularly in drawing conclusions about common mental disorders from experience with single gene disorders (paragraph 5.18).

8.20 At present, the number of conditions for which tests are available is small, as is the number of people taking tests. The stigma associated with mental disorders, however, may lead to exaggerated demands for, or fear of, genetic testing. For most mental disorders, genetic tests are likely to have limited value for the diagnosis or prediction of individual risk. In the case of late onset Alzheimer's disease, one or two copies of the apoE4 allele will only result in a small alteration in risk which cannot take into account the other genetic and environmental variation between individuals (paragraph 5.19). Given the very low predictive power of apoE4 tests, the Working Party endorses the position that testing for apoE4 alleles to provide predictive or diagnostic input for Alzheimer's disease is currently inappropriate. **It recommends that genetic testing for susceptibility genes providing predictive or diagnostic input of certainty comparable to, or lower than, that offered by apoE tests for Alzheimer's disease should be discouraged unless and until the information can be put to effective preventive or therapeutic use.**

8.21 Genetic testing may reveal additional medical information about the patient. This will become more likely as increasing numbers of genes are identified which confer susceptibility to more than one condition. The possibility that additional information will be revealed should be discussed with the patient before the test is undertaken (paragraph 5.20). **The Working Party recommends that the duty of physicians to discuss and disclose any possible increase in risk revealed by genetic tests for conditions other than that under investigation be considered equivalent to the duty to do so for other, non-genetic, types of information.**

8.22 The potentially large numbers of people carrying susceptibility genes for common disorders may lead to commercial pressure for the promotion of testing for susceptibility genes even where this would not be advisable or appropriate. The Advisory Committee on Genetic Testing discourages directly marketed tests other than for carrier status for inherited recessive diseases. The Working Party endorsed this position but concluded that the present voluntary system of approval is likely to prove insufficient (paragraph 5.21). **The Working Party recommends that the Advisory Committee on Genetic Testing monitors the uptake of directly marketed tests and the consequences of their use. If, in the light of such monitoring, adverse consequences become apparent, it recommends that the UK government seeks national or international regulation of directly marketed tests.**

Consent and impaired capacity

8.23 Most people with mental disorders will be competent to consent on their own behalf to genetic counselling and any further procedures, including genetic tests. Obtaining genuine consent requires health care professionals to do their best to communicate accurately, and in an understandable and appropriate way, the purposes and implications of the procedure as well as its risks. They should respect the limits of individuals' understanding and capacity to deal with difficult information, and allow time for them to ask questions (paragraphs 5.22–5.24). For a person deemed mentally incompetent to make his or her own treatment decisions, a doctor must act in that patient's best interests even though there are difficulties in translating from the general principle to the specific case. Often best interests can only be determined after prolonged consultation with the person concerned and other appropriate people (paragraph 5.26).

The genetic testing of children

8.24 For children deemed able to give consent to medical treatment, the issues raised by genetic testing are comparable to those for adults (paragraph 5.28). For genetic testing that cannot be considered as medical treatment, it is unclear whether children below 16 would be regarded as able to give valid consent on their own behalf. For the child unable to give valid consent, the consent must be given by the child's parent (or, rarely, the Court). The guiding criterion is the best interests of the child. Once again, it should be borne in mind that, for the common mental disorders, the identification of susceptibility genes is unlikely to allow the diagnosis or prediction of the condition in children, and the use of genetic testing is likely to be limited (paragraph 5.29).

8.25 **Diagnostic testing:** When a condition begins during childhood, deciding whether genetic testing for diagnostic purposes is in the best interests of the child is not in principle any different to a decision about any other medical treatment (paragraphs 5.30–5.31).

8.26 **Predictive testing:** For genetic tests which offer some degree of predictive certainty, professional opinion amongst clinical geneticists has been against the testing of children for adult onset conditions on the grounds that this has no benefit for the individual during childhood and denies him or her the chance of making their own choice as an adult, and could lead to discrimination within the family. Some parents and patient groups have argued, to the contrary, that parents have a right to know about their children's genetic make-up. Whatever the ethical arguments, such testing, if not carried out explicitly to serve the best interests of the child, would not be permissible in law (paragraph 5.32). **The Working Party recommends that, for children unable to give consent, predictive genetic testing should be strongly discouraged unless there are implications for clinical intervention in childhood.**

8.27 **Carrier testing:** The use of genetic tests to determine the carrier status of young children denies them the possibility of making their own decisions about being tested at a later stage. For the law these ethical arguments translate into the question posed earlier: whether it would be in the child's best interests to carry out the test? It is not immediately obvious that it would be (paragraph 5.33). **The Working Party recommends that children should not be tested for carrier status for mental, or indeed other, disorders until they are competent to make their own decisions.**

8.28 **Directly marketed tests:** Despite guidance to the contrary from the Advisory Committee on Genetic Testing, the direct marketing of tests to the public may result in the inappropriate testing of children since it is not clear how a company would determine whether a sample had in fact come from a child under 16 (paragraph 5.34). This emphasises the importance of monitoring the uptake of directly marketed tests (paragraph 8.22).

8.29 **Adoption:** Genetic testing of children might also be considered during adoption. Placing children born to parents with mental disorders for adoption is not uncommon since severe mental disorders may be a reason for a parent to give up a child for adoption voluntarily or as a result of a Court Order. The law would once again insist that a test may only be carried out on a child incapable of giving consent if it can be shown to be in the child's best interests to do so. But it is not in a child's best interests to be adopted if there is a risk that he or she will later be rejected because the adoptive parents had an incomplete understanding of the child they were adopting. Most good adoption agencies would probably want to address the issue of mental illness in the birth family (paragraphs 5.35–5.36). **The Working Party recommends that, given the**

importance and complexity of the issues, the Health Departments, in consultation with the appropriate professional bodies, provide guidance on the pre-adoption use of genetic testing.

8.30 At 18 years of age, adopted children may ask to know the identity of their birth parents and this might be an appropriate time at which to provide other information about possible family histories of disease so that, from early adulthood, they may make informed decisions about seeking genetic counselling or testing or other forms of investigation or treatment (paragraph 5.37).

Genetic information and reproductive decisions

8.31 Where the common mental disorders are concerned, genetic information will not be particularly helpful in making reproductive decisions. The predictive certainty of genetic tests will be slight in the majority of cases making prenatal testing and termination less relevant and acceptable to parents. It will also be less likely to meet the criteria of S.1.(1)(d) of the Abortion Act. Even within this framework, what one woman or couple will see as a sufficient reason for abortion, another will see as quite insufficient (paragraphs 5.38–5.41). **The Working Party recommends that people making reproductive decisions in the light of a family history of a mental disorder should have access to genetic counselling.**

8.32 The ideal of non-directiveness in genetic counselling is widely endorsed. There is accumulating evidence, however, that non-directiveness is rarely achieved. The Working Party questioned the appropriateness of non-directiveness as a universal aim in genetic counselling and felt that, in some circumstances, it would be inappropriate and unhelpful. It has emphasised, however, how important it is that genetic counselling and testing are undertaken voluntarily, and that individuals are enabled to make their own decisions at each stage of the process (paragraphs 5.42–5.44). **The Working Party notes the need for further debate about the appropriateness of non-directiveness in genetic counselling and recommends that further research to establish appropriate aims and outcomes for genetic counselling is undertaken.**

Eugenic programmes

8.33 Historically, eugenic programmes have been characterised by compulsion, a degree of coercion or the restriction of individual choice. The Working Party considers that the present use of genetic testing for reproductive choice in the UK cannot be considered to be eugenic. It recognises, nevertheless, that there are concerns that the growing use of new genetic technologies will lead to a 'new eugenics' (paragraph 5.45).

8.34 As our knowledge of psychiatric and behavioural genetics is enhanced through the identification of new genes, the past abuse of genetics through eugenic programmes targeted at the mentally ill must not be forgotten (paragraphs 5.46–5.48). With rare exceptions, it is very unlikely that there will be population screening programmes based on genetic tests for mental disorders in the near future. Of more concern is the potential misuse of genetic testing and genetic information in families known to be at risk for certain disorders. The Working Party considers that the best safeguard against new eugenic pressures is properly informed, freely given consent to genetic testing. There must be vigilance therefore that informed consent is always sought for any genetic test or other procedure.

8.35 Particular concern has been expressed about the confidentiality of the information contained in

genetic registers (paragraph 5.49).The Working Party concluded that clear guidelines are needed. **The Working Party recommends that the British Society for Human Genetics explores mechanisms for the development of guidelines for the establishment and maintenance of genetic registers in the new NHS.**

Confidentiality and disclosure

8.36 The duty of medical confidentiality is not absolute. When genetic screening reveals information which may have serious implications for relatives, "*health professionals should seek to persuade individuals, if persuasion be necessary, to allow disclosure of relevant information to other family members*".[1] For the common mental disorders, problems of non-disclosure are likely to be rare since genetic information is unlikely to lead to such significant modification of risk that non-disclosure would have serious consequences. It is, nevertheless, necessary to be wary of breaking confidentiality in those cases where an individual opposes disclosure of information about his or her condition (paragraphs 5.55–5.60). **The Working Party recommends that the confidential nature of genetic information should be maintained. It can conceive of exceptional circumstances in which, in the absence of the consent of the individual, disclosure to close family members might be justified, if there are serious implications for them. Such decisions should be judged on a case by case basis.**

8.37 There is some doubt as to whether doctors owe an obligation of confidence to those who lack the mental competence to form a relationship with them. The unsatisfactory outcome could be that the confidentiality of such patients is not subject to any legal protection. Where the lack of mental competence is temporary, the decision about whether to disclose information must be deferred until the individual has regained sufficient competence for the matter to be discussed. Where the lack of mental competence is likely to be permanent, we assume that the requirement to act in an individual's best interests would extend to disclosure of information to others (paragraph 5.61).

8.38 The fact that some family members may not wish to be presented with genetic information raises dilemmas which cannot be resolved by simple guidelines. The Working Party accepts that, if an effective intervention is known, disclosure may be justified when a person is not aware of their risk (paragraph 5.60).

Wider uses of genetic information about mental disorders: ethical and legal issues

Stigma

8.39 The issues raised by genetic information about mental disorders go beyond the clinical context. The Working Party considered the implications of genetic information for the stigma that mental disorders evoke. It noted that much stigma stems from ignorance and misconceptions about mental disorders and the behaviour of people suffering from them. This stigma frequently causes unfairness in areas such as employment and housing. But, even in the absence of such injury or harm, stigma injures those with mental disorders, because they are regarded or represented in a disrespectful and debasing way. The Working Party concluded that proper treatment of those with mental disorder must include efforts to eliminate both the injury which stigma constitutes and the harm which it causes and it noted that the former may be deeper and less easy to rectify (paragraphs 6.2–6.6).

1 Nuffield Council on Bioethics (1993). **Genetic Screening: Ethical issues,** London, Nuffield Council on Bioethics..

8.40 Genetic information could, in principle, decrease stigma by increasing the understanding of mental disorders, putting them on a par with conditions thought of as physical and countering notions that some mental disorders reflect weakness of character. Similarly the stigma suffered by families may decrease if genetic information provides evidence for a biological component to some mental disorders. Genetic information could, however, be interpreted in different ways; as indicating that people with mental disorders are fundamentally different from others or that parents are to blame for having affected children in the first place. Genetic information may also serve, therefore, to increase stigma (paragraphs 6.8–6.9).

8.41 This emphasises the importance of combating stigma and ensuring that additional genetic information decreases, rather than increases stigma. There is no simple way, no single institution and no simple piece of legislation which can eliminate the stigma of mental disorder; only long-term changes in public understanding of, and support for, those with mental disorders will improve matters (paragraph 6.10). The Working Party welcomes, therefore, the current Respect campaign by MIND to oppose discrimination on mental health grounds and the newly launched campaign against stigma by the Royal College of Psychiatrists. **The Working Party recommends that campaigns to reduce stigma emphasise that it constitutes harm as well as causing it.**

8.42 Genetic information about any condition raises the prospect of discrimination and for mental disorders this is compounded by stigmatisation. The Working Party paid particular attention to discrimination in relation to insurance, employment and education.

Insurance

8.43 The Working Party noted that the use of genetic information relevant to mental disorders for insurance purposes is likely to be fairly limited and specific. Even for single gene disorders such as Huntington's disease, for which individuals with the gene mutation have a calculable and significant reduction in life expectancy, there is considerable variability between individuals, for example in age of onset. In addition, information may be useful only for certain types of insurance products. By contrast, information about susceptibility genes is currently of very limited actuarial use: it may provide information about slight increases in the risk of suffering from some multifactorial disorder in a population, but reveal little about any single individual's level of risk (paragraphs 6.12–6.14)

8.44 The Working Party concluded that it is doubly important that insurers do not exaggerate the actuarial implications of genetic test results relevant to mental disorders, where the risk of stigma and its effects is high. It is important to have systems in place that can monitor whether insurers are discriminating unfairly on the basis of genetic test results (paragraph 6.19). **The Working Party recommends that the Government, in consultation with the insurance industry, makes arrangements for monitoring insurers' use of genetic tests for mental disorders, and for reporting on any tendency to load premiums excessively, any actuarially unwarranted refusal of insurance and any other forms of unfair discrimination.**

Employment

8.45 In view of the employment difficulties and discrimination faced by those with mental disorders, the Working Party considered it important to consider how the use of genetic information might improve or worsen matters. With respect to genetic screening of employees for increased

occupational risks, although the Working Party has not learnt of any genetic sensitivities to chemical or biological agents which are associated with an increased risk of mental disorder, other features of some working environments might represent greater risk factors for mental disorder for individuals with relevant susceptibility genes (paragraph 6.25). This adds force to the recommendation in the Council's previous report, **Genetic Screening: Ethical Issues**, that genetic screening of employees for increased occupational risks should occur subject to strict safeguards and only after consultation with a co-ordinating body (paragraph 6.23). **The Working Party recommends that the Human Genetics Advisory Commission, in its consideration of genetics and employment, determines which is the appropriate body to monitor any introduction of genetic screening programmes for increased occupational risks.**

8.46 It is possible to envisage the use of genetic tests for mental disorders for reasons other than identifying occupational risks; possibly even to exclude some people from employment on health grounds. The Working Party notes that, in the UK, the Disability Discrimination Act 1995 offers some protection from discrimination, but it does not cover those for whom genetic information has revealed that they may develop a disability in the future (paragraph 6.27). There has also been concern that the definition of disability is too narrow for some people with mental disorders. Any wider use of genetic tests in employment may raise far reaching issues about discrimination; but so far there is little legal or other framework for addressing these issues in the UK (paragraph 6.29). The Working Party welcomes the forthcoming consideration of genetics and employment by the Human Genetics Advisory Commission and **recommends that, in view of the special significance of stigma in mental disorder, the Commission pays particular attention to the implications of testing for genetic factors relevant to mental disorders for employment purposes** (paragraph 6.31).

Education

8.47 The Working Party noted that in some cases a genetic test might be useful in identifying a specific educational approach; in others it might be of doubtful value. In the latter case there would be *prima facie* grounds for relying on conventional tests. Even in the former case, reliance on genetic tests should not, we believe, become automatic in educational assessment since testing itself may have other, possibly adverse, implications. The Working Party does not endorse any wider use of genetic tests to assess individual or group potential of any sort (paragraphs 6.32–6.35).

Genetic research into mental disorders: ethical and legal issues

8.48 For most people with a mental disorder, arrangements about consent for research need not and should not be any different from those required for other people. While the mental capacity of many individuals with mental disorders varies, it is desirable, and almost always possible, to involve them in relevant genetic research at a time when they are competent to consent on their own behalf (paragraphs 7.2–7.7). **The Working Party recommends that individuals who are intermittently competent should only be approached about participation in research when competent**. Although genetic research tends to be of minimal physical invasiveness, **the Working Party recommends that written consent for participation should be the general rule** (paragraph 7.8).

8.49 The intermittent nature of some mental disorders and the confinement of some patients to institutions are two aspects of mental disorders which suggest that special safeguards are needed when obtaining informed consent to research participation. The Working Party concluded that where potential participants in research are confined in an institution, special care is needed to ensure that no form of coercion is used to secure participation. In particular, the use of payment must be carefully considered (paragraph 7.9). **The Working Party recommends that any proposed payment for participation in research should always be carefully considered by research ethics committees and by grant-giving bodies**. The Working Party also noted that the validity of consent should not be assumed when the potential participant's capacity to consent changes during the course of the research. Proposed contingencies to deal with such a situation should be presented to a research ethics committee and discussed with the patient at the outset (paragraph 7.10).

8.50 An important subgroup of people for whom genetics research is likely to hold particular relevance, those with severe mental retardation, will never have had and never will have the capacity to make complex decisions, and that will include decisions about participation in research (paragraphs 7.11–7.13). For another important subgroup, those with dementing disorders, earlier competence may have been exercised in this regard, and an individual's views about research participation may be on record. Where this is the case, these views should be honoured; more usually, they are not a matter of record, so here too, with competence unlikely to be recovered, special safeguards are needed.

8.51 Most genetic research into mental disorders is unlikely to lead to any immediate benefit to patients lacking the capacity to consent to participation and is therefore of doubtful legality. In the case of children, provided that there is an important interest served by the intervention, a parent may consent on the child's behalf. It is unlikely, however, that progress can be made in the treatment of mentally incapacitated patients without research and most relevant research is probably only possible if it involves individual patients (paragraph 7.14). The Working Party considers that genetic research holds out important prospects of advances in understanding and treatment of mental disorders and that restrictions on participation are not in the patient's best interests. **The Working Party recommends therefore that non-therapeutic research involving people lacking the capacity to consent to participation on their own behalf should be considered ethically acceptable, subject to strict safeguards** (paragraph 7.17). The Working Party recognises that there should be legislative backing for and controls over non-therapeutic research involving mentally incapacitated patients. **It recommends that further consideration be given to the details of legislation and regulation to safeguard the interests of people with mental incapacity with respect to participation in research** (paragraph 7.18).

8.52 The Working Party concluded that additional specialist ethics committees to consider research involving those unable to give consent on their own behalf were not necessary or desirable. It considered that such committees might increase the stigma suffered by potential participants and diminish the skills of regular ethics committees (paragraph 7.17). Rather, **the Working Party recommends that every research ethics committee should include at least one member who has experience in the area of competence in decision making about research participation.**

8.53 It is not uncommon for researchers to discover, using DNA samples collected for research purposes, information of clinical significance to the individual donor of the sample. An ethical difficulty arises because the process of obtaining the informed consent required for research does not usually include consent for disclosure of identifiable data to clinics outside the strict environs of the research, nor the kind of genetic counselling that would be required for an individual seeking a genetic test for clinical purposes (paragraphs 7.19–7.22). To provide an individual with information from a research study about gene mutations they might or might not carry, could be to give them information they would choose not to have, and/or information for which they or other members of the family are not prepared or cannot understand in terms of its implications. A further difficulty is that quality controls and procedures used for clinical testing may be different and sometimes more rigorous than those used in research studies (paragraph 7.24). **For these reasons the Working Party recommends that, as a general rule, those who consent to take part in research should be told that individual information derived from analysis of their DNA will not be given to them**. A summary of the overall findings of the research can be provided if the participant wishes. **The Working Party further recommends that, in any research study that could yield genetic information which is clinically relevant to a research participant and/or their relatives, consent to that research should make it clear whether or not such information would be made available** (paragraph 7.25).

8.54 In relation to the additional use of research samples or data, **the Working Party recommends that, when an individual participant is regarded as competent, any further use of data in the longer term should be discussed with him or her as part of the consent procedure; new research should, as a minimum, be submitted for approval to a research ethics committee before proceeding. When a person is considered to be incompetent to make his or her own decision about participation in research, data collected for non-therapeutic research purposes should not be used for any other research purpose** (paragraph 7.27).

8.55 While debate about the use of clinical genetic information by outside agencies continues (Chapter 6), information that is obtained within a research context and is not being used for clinical purposes is clearly distinct. **The Working Party recommends that genetic information obtained during participation in research should not be made available to organisations such as insurers or employers** (paragraphs 7.28–7.29).

Appendix

Genetic techniques for studying mental disorders

Introduction

1 This Appendix describes the main techniques used in genetic research (Box 1).[1] There are two main approaches:

- **quantitative genetic research,** which examines whether, and to what extent, conditions or characteristics are subject to genetic influences;
- **molecular genetic research;** which attempts to identify specific genes associated with a condition or characteristic and to understand their effects.

Box 1

Techniques used in genetic research

1 Studies involving families, twins and adopted children.

2 Examination of the chromosomes (cytogenetics). This may reveal a non-random association between a particular chromosomal abnormality and mental disorder.

3 Linkage studies of inheritance, using families. This method involves identifying regions of DNA inherited by family members with the disorder, which might, therefore, influence the development of the disease or condition.

4 Linkage studies using pairs of affected siblings rather than whole families. This reduces problems with data analysis and eliminates the need to specify the mode of inheritance of the disorder.

5 Association studies, which examine samples of affected and unaffected individuals to identify whether a particular gene variant is associated with a disorder.

6 Candidate gene studies, which examine genes with functions of potential interest, for example, neurotransmitters.

7 Studies of individual gene structure and function that contribute to knowledge of basic neurobiology.

8 Animal studies are potentially useful because controlled breeding is possible. Studying animals with abnormal behaviour, however, raises the question of how far it is possible to draw conclusions from these studies about mental disorders in human beings.

9 Quantitative trait locus (QTL) analysis is a set of techniques, originally developed in plant and animal breeding, for identifying genes which influence a continuous (or quantitative) characteristic.

10 New scientific techniques (for example, semi-automated, high through-put genotyping and analysis of gene expression using improved DNA markers) have the potential to improve the efficiency and power of genetic studies.

Quantitative genetic studies

2 Many illnesses run in families. Studying families prone to such illnesses has, in many cases, allowed the identification of genes that influence the development of the condition. Not surprisingly, considerable efforts have been made to determine whether certain families are

1 This review has drawn on the following: Quantitative genetics, Chapter 2 and Linkage and association, Chapter 3 in McGuffin P, Owen M, O'Donovan M, Thapar A and Gottesman I (1994) **Seminars in Psychiatric Genetics**, Gaskell, London, and Plomin R, Owen M and McGuffin P (1994) The genetic basis of complex human behaviours, **Science**, 264:1734–9.

prone to mental disorders and, if so, whether this is due to genetic influences.

3 The fact that a mental disorder, or indeed any other illness or characteristic, runs in a family does not demonstrate that it is genetically inherited. This is because, in addition to having similar genetic material passed down from parent to child, family members share, to a greater or lesser extent, a common environment, often called the family or shared environment. Key questions, then are:

- To what extent does a condition run in families?
- To what extent is this due to genetic similarities and/or to environmental similarities within families?

The next sections describe the three classic quantitative genetic techniques: family, twin and adoption studies.

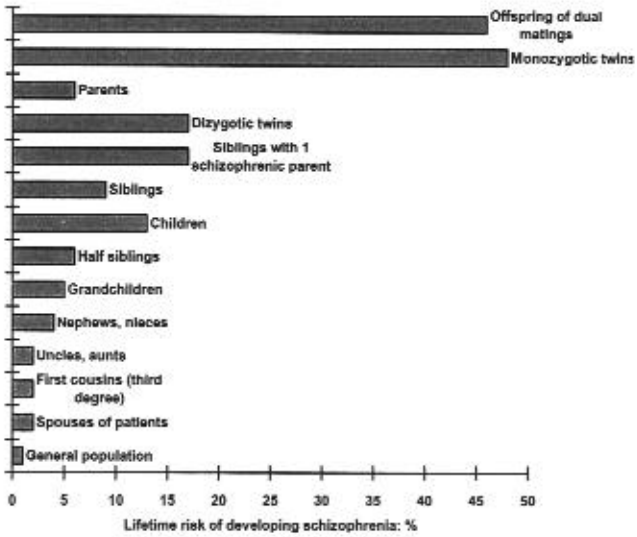
Family studies

4 Family studies involve investigation of the relatives of people suffering from a mental disorder and assessing the risk that they too will develop the disorder. This risk is then compared with the risk that someone in the general population will develop the disorder. For example, the lifetime risk that someone in the general population will develop schizophrenia, as defined using modern diagnostic criteria, is about 0.6%. But the risk that the sibling of a person with schizophrenia will develop the same condition is about 10% or about sixteen times greater. The risk increases 50–70 fold for the co-twin of an affected twin of an identical pair.

5 Thus, such studies can be used to assess whether conditions run in families. It is a common finding that the increase in risk increases with the degree of genetic relatedness to the affected person (Figure 1). But for people of increased genetic relatedness, the shared environment may become more similar too. This issue is discussed further in the sections below, on twin and adoption studies.

Figure 1:

Average risks of developing schizophrenia, compiled from European studies 1920–87[2]



2 Source: An adaptation of Gottesman (1991) **Schizophrenia Genesis**, New York, W H Freeman, reproduced in Schizophrenia, Chapter 5 in McGuffin P, Owen M, O'Donovan M, Thapar A and Gottesman I (1994) **Seminars in Psychiatric Genetics**, Gaskell, London, p88. The 'offspring of dual matings' means the children of two parents affected by schizophrenia. Monozygotic twins are identical, dizygotic twins are non-identical.

Twin studies

6 Identical (or monozygotic) twins develop from a single embryo which then splits. Thus, their genetic material is essentially identical – all their genes are the same. Non-identical (or dizygotic) twins result when two eggs are fertilised, each by a different sperm. Thus, non-identical twins are no more closely related genetically than any brother or sister, having only about half their genes in common.

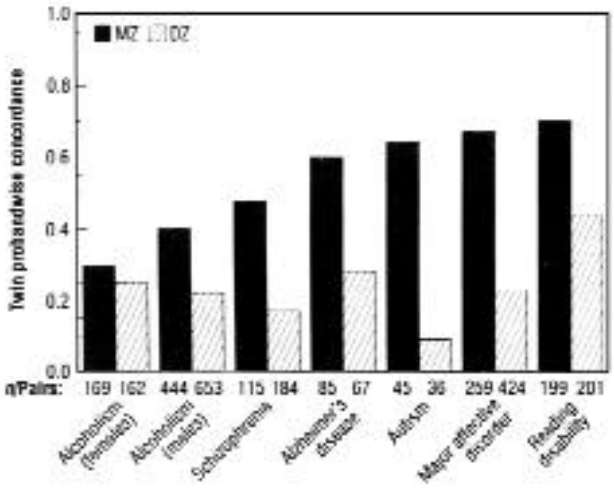
7 A common type of study is to compare identical and non-identical twins. For example, if one of a pair of identical twins has schizophrenia, the likelihood that the second twin will develop schizophrenia is consistently higher than for non-identical twins. It is common to find that the **concordance** (the chance of both being affected) is greater for identical twins. This could be because they share identical genetic material, suggesting a genetic influence, but it could also be because identical twins are treated more similarly than non-identical twins, suggesting an environmental effect. There are a number of ways to distinguish between these possibilities:

- Measure whether identical twins are indeed treated more similarly than non-identical twins. Such studies show that there are differences in the way that twins are treated but such differences tend not to predict the degree of concordance for conditions of interest.
- Examine the concordance of wrongly designated twins: identical twins who have been reared on the assumption that they are non-identical or vice versa. This should compensate for systematic differences in the way identical and non-identical twins are treated. What is normally found is that, for a given disorder, the concordance for mis-specified twins is similar to that for correctly specified twins, supporting the assumption that differences in family environment are not having a major effect on concordance rates.
- Examine the concordance of twins who have been reared apart. Although this is fairly rare, and the circumstances may be unusual, such studies tend to show that the concordance rate for identical twins remains higher than for non-identical twins, even when they are reared apart.
- Studies of adopted children, described below, can also help to distinguish genetic and environmental influences.

8 These studies suggest that it is reasonable to assume that the family environment is similar for identical and non-identical twins. This means that an increase in concordance for identical twins can be taken to indicate a genetic contribution to the condition. Figure 2 gives some examples. The higher concordance for autism in identical twins compared to non-identical twins suggests that autism is highly heritable. Twin studies provide similarly high figures for heritability of many aspects of human behaviours. Twin studies, however, can be equally useful for identifying important environmental factors. This is the case for alcoholism in women. The concordances are fairly low and similar for both types of twin suggesting that alcoholism in women is influenced little by either genes or family environment. The remaining factor that can influence the development of any condition is non-shared environment to which each family member will be exposed. This will include influences like peers, school or work and, in the case of alcoholism in women, non-shared environment would appear to be the most important influence. Conversely, if the concordance is high for both identical and non-identical twins, it suggests that the condition runs in families but that shared environment, rather than inheritance, is important.

Figure 2:

Concordances for identical twins (solid bars) and non-identical twins (shaded bars) for different disorders[3]



9 It is striking that there is no mental disorder for which identical twins show 100% concordance, in other words, if one of a pair develops the disorder, the other invariably does. Even for highly heritable disorders such as autism, the concordance in identical twins is only about 65%, indicating that for about 35% of pairs of identical twins, only one will develop the condition. This suggests that environmental factors almost always have a major influence in the development of mental disorders. Environmental factors may contribute to similarities within families but, equally important, they may serve to make family members different rather than similar.

Adoption studies

10 Adoption studies assess the likelihood that adopted children will develop a condition. If the risk that adopted children will develop a disorder correlates best with the incidence of the disorder in their biological parents this would suggest that genetic influences are important. If the risk correlates best with the incidence in their adoptive parents then family environment would seem to be more important. Adoption studies have had their difficulties: adoption itself is an unusual event that may be associated with increased rates of mental disorder or antisocial behaviour. Moreover, placement of adopted children in families is not random. Nevertheless, adoption studies can help to distinguish the influence of genetics and shared environment. For example, studies indicate that if children are born of mothers with schizophrenia and then adopted by parents without schizophrenia their risk of developing schizophrenia remains high, indicating the importance of a genetic influence.

What do quantitative genetic studies reveal about mental disorders?

11 Applying the methods described above confirms that certain mental disorders, such as schizophrenia and manic depression, run in families. The studies provide evidence that this is explained, at least in part, by genetic influences.

3 Reprinted with permission from Plomin R, Owen M and McGuffin P (1994) The genetic basis of complex human behaviours, **Science** 264:1734–9, copyright 1994 American Association for the Advancement of Science.

Heritability

12 Statistical models have been developed which allow numerical estimates to be made of the relative contributions of genetics and environment to any condition. For example, data from twin studies can be used to estimate heritability. Heritability estimates how much of the total variation in a population can be explained by genetic differences. The same model can also be used to estimate how much of the variation is due to environmental differences. Estimates of environmental differences can be divided further into estimates of the difference in shared environment and differences in the non-shared environment. Twin data can be used to estimate what proportion of the variation in a condition can be explained by genes, shared environment and non-shared environment. Table 1 gives some examples of heritability estimates for different mental disorders.

Table 1:

Examples of heritability estimates for different disorders

	Percentage of variance explained by differences in:		
	Genetic factors(heritability)	Shared environment	Non-shared environment
Schizophrenia[4]	66–80	0	20–34
Major depression[5]	47–70	0–46	11–30
Bulimic symptoms[6]	4	24	72

13 There are strengths, and also limitations to heritability estimates. Heritability estimates apply to the population studied, at that time and under those circumstances. If any of these conditions changed, the heritability estimate would also change. This means that the estimates are not fixed or absolute. Strictly, therefore, it is not accurate to talk about heritability estimates 'for schizophrenia' for example. In particular, estimates of heritability depend on the environmental variability of the population. When the environment is very uniform, heritability estimates are greater. Heritability estimates also reveal that the relative contributions of genetic and environmental influences to a condition may change during a person's lifetime. For example, the genetic contribution to antisocial behaviour is estimated to be stronger in adulthood than adolescence. This is thought to be because adolescents are more susceptible to environmental influences such as peer pressure.

14 Heritability estimates apply to populations and cannot be applied to individuals. This is nicely illustrated by the following example. "*If we say that height has a heritability of 0.80, that means that 80 percent of the variation in height observed in this population at this time is due to genetic differences. It obviously does not mean that an individual who is 5 feet tall grew to the height of*

4 McGuffin P, Owen M and Farmer A (1995) The genetic basis of schizophrenia, **The Lancet** 346:678–82.
5 McGuffin P, Katz R, Rutherford J and Watkins S (1996) The heritability of DSMIV unipolar depression: A hospital based twin register study, **Archives of General Psychiatry** 53:129–36.
6 Rutherford J, McGuffin P, Katz R, and Murray R (1993) Genetic influences on eating attitudes in a normal female twin population, **Psychological Medicine** 23: 425–36.

4 feet as the result of genes and that the other 12 inches were added by the environment."[7] The situation is different for the findings of molecular genetic studies which, as discussed below, may apply to individuals. But much confusion arises if the concept of heritability is mistakenly applied to the individual process of development.

15 Heritability estimates apply to the differences within a particular population. They do not provide any information about the reasons for the differences between groups. Hence it is not valid to make assumptions about the differences between groups based on the findings about one population. For example, heritability estimates indicate that there is a genetic component to IQ and also that IQ differs between races. It is not valid, however, to conclude that the IQ difference is due to genetic differences between races. The reasons for the differences between groups could be the same as the reasons for the differences within one of the groups, but equally, they could be different.

16 Heritability studies reveal information about the environmental contribution to the variance in a condition as well as the genetic contribution. This is because the same data, and the same statistical model can be used to obtain estimates of the contributions of shared and non-shared environment to the variance in a condition. This information indicates that heritability estimates never explain all of the variation in a population. Thus environmental influences account for at least some of the variation in every condition that has been studied. For some conditions, such as schizophrenia, the heritability is high, and environmental influences explain less of the variation. Conversely, the heritability of mild depression is low and environmental influences are thought to be more important.

17 Finally, heritability estimates assume that genetic differences, shared environment and non-shared environment act independently of each other in explaining the variation in a condition. In fact, this is not the case. Some genetic effects operate through rendering individuals more vulnerable than others to risky environments (gene-environment interactions). There is evidence for these influences in antisocial behaviour and depression.[8]

Searching for specific genes

18 If there is evidence that a mental disorder is affected by genetic factors, an important step is to try and identify the specific gene, or genes, that are involved. This involves molecular genetic techniques. Several methods are available and these are summarised briefly below. Such techniques are now very successful in identifying the genes involved in single gene disorders. Identifying the genes involved in multifactorial conditions, where the contribution of any one gene is relatively small, is more difficult.

Linkage studies using family trees

19 This method involves analysing the DNA of both affected and unaffected members of families in which the particular disorder runs. The aim is to identify a region, or **locus**, of DNA for which a particular sequence is found only in family members with the disorder. This locus might, therefore, contain a gene which contributes to the development of the disorder. Linkage studies

7 Plomin R, DeFries J and McClearn G (1990) **Behavioral Genetics: A Primer**, Second Edition, Freeman, New York, p232.
8 Rutter M and Plomin P (1997) Opportunities for psychiatry from genetic findings, **British Journal of Psychiatry** 171:209–19.

depend on having small, well-defined pieces of DNA, called **markers**, corresponding to particular regions of DNA and which can be used to analyse those regions. An advantage of linkage studies is that they might succeed in identifying sub-types of mental disorders running in individual families. There are, however, several problems with linkage studies:

- It is difficult to find families that are large enough to provide statistically significant data and not all family members may want to participate in the study.
- All family members must be diagnosed as either affected or unaffected. This may not be easy for a disorder that shows considerable variation, from mildly affected to severely affected. Moreover, family members thought to be unaffected may subsequently develop the disorder and change the linkage data. The most notorious example of this problem occurred in a US study of manic depression in an Amish family. Evidence suggesting that there was a locus influencing the disorder on chromosome 11 collapsed when two family members thought to be unaffected subsequently developed the disorder.[9]
- Family linkage studies require information about the mode of inheritance. The inheritance of mental disorders is complicated, however, and the mode of inheritance is often not clear. This leads to problems where assumptions must be made about the mode of inheritance.
- Family linkage studies can only identify genes if they have a fairly major effect. If a disorder is caused by several different genes, each of which has a small influence on the development of a condition, identifying any one gene using a linkage study will be difficult.

20 Large genetic linkage studies are under way to try to identify genes conferring susceptibility to disorders such as schizophrenia and manic depression. However, the statistical problems are formidable when dealing with disorders where the mode of transmission is not known.

Sib-pair studies

21 An adaptation of the linkage method is to include only pairs of siblings, rather than whole families, in the study.[10] This reduces problems with diagnosis since it is not necessary to make a diagnosis for each member of the family. Only sib-pairs with clear diagnoses need be included. Studies may involve sib-pairs in which both are affected or those in which only one sibling is affected. Studies of affected pairs have the added advantage that they eliminate the possibility that someone diagnosed as unaffected may develop the disorder subsequently. Unlike linkage studies, sib-pair studies do not require knowledge of the mode of inheritance, thus avoiding the need to make assumptions about it. A disadvantage of sib-pair studies is that large sample sizes are needed, involving many participants. Another drawback is that, if the disorder is heterogeneous, the inclusion of siblings with different sub-types of the disorder in one study may confuse the results.

22 Using these new approaches, there have been recent advances in the understanding of the genetic basis of diabetes: the involvement of two previously identified loci in insulin-dependent diabetes mellitus has been confirmed and several new loci look promising. All the loci appear to be having a relatively small effect, indicating that such studies may be useful for analysing polygenic diseases. However, extremely large sample sizes (>1000) are required to identify loci accounting for 10% or less of the variance of a disease.

9 Reviewed by Risch N and Botstein D (1996) A manic depressive history, **Nature Genetics** 12:351–3.
10 Lander E and Schork N (1994) Genetic dissection of complex traits, **Science** 265:2037–48.

Association studies

23 Association studies involve populations of unrelated individuals, both affected and unaffected. Researchers use DNA markers to examine a small region of the genetic material. If there is a higher frequency of a particular form of the DNA in affected individuals it suggests that it is, or is close to, a locus associated with the disease. An advantage of association studies is that, in contrast to linkage studies, they can detect genes having a smaller effect (5% or less of the total variation),[11] and they can be used to study both gene–gene and gene–environment interaction.

24 By using DNA markers that cover the whole genome, it is theoretically possible, and becoming practically feasible, to perform a complete search for genes that influence a particular condition. This approach is painstaking, time-consuming and expensive but, nevertheless, several research collaborations have been established to search for genes associated with the major mental disorders.

Candidate gene studies

25 Candidate gene studies are a particular form of association study. Based on what is already known about a disorder, researchers focus on genes which might plausibly influence its development, asking whether there is evidence that those genes are associated with the disorder. For example, drugs used to treat various mental disorders are known to affect the receptors in the brain which bind to the neurotransmitters dopamine and serotonin. This has led to the study of possible associations between natural variants of receptors and transporters of these molecules, and the frequency of different mental disorders. Some of the positive associations that have been identified are listed in Chapter 3, Table 3.1.

Animal studies

26 Animal studies can be useful in genetic research because controlled breeding experiments can be performed which are not possible in human studies. It is also helpful that rats and mice, commonly used species, breed rapidly. However, rats and mice have brains that are developed differently to our own species and they cannot describe their subjective experiences. Thus there are limits to how much animal studies can reveal about human behaviour and mental disorders. Nevertheless, one approach that is attracting a lot of attention is quantitative trait locus (QTL) analysis.

Quantitative trait locus (QTL) analysis

27 The fact that many mental disorders show variation from mild to severe is one reason for thinking that some of them may be influenced by several genes (polygenic). Continuously varying characteristics such as these are sometimes referred to as **quantitative traits** and the genes that influence them are called **quantitative trait loci**. As described above, it is difficult to identify such genes, each of which has a fairly small effect, using linkage and association studies. Quantitative trait loci analysis, or QTL analysis, is a technique for identifying these genes.

11 Risch N and Merikangas K (1996) The future of genetic studies of complex human diseases, Science 273:1516–17.

28 Two strains of an animal, for example a mouse, are bred which show different characteristics such as high emotionality and low emotionality. Emotionality refers to behaviour such as defecation and level of activity in a new environment. It has been argued that emotionality might be related to anxiety in human beings. The two different mouse strains are then mated together. The hybrid offspring are tested and individuals chosen which show either high or low emotionality. The DNA of these individuals is then examined in an approach similar to an association study: markers are used to find regions of the genome that are similar in one group but not in the other. The effect of the mating is that all the other regions of the DNA should be randomly mixed up in the hybrid offspring thus reducing the chance of falsely positive results. In the study described here, six loci were identified that may influence emotionality.[12]

Animal models for human disease

29 Another advantage of animal studies is that it is possible to produce genetically modified animals in which a gene of interest has been inactivated in the animal's genetic material. This may provide information about the function of that gene. For example, mice have been produced which lack the gene that enables them to produce nitric oxide in the brain, where it acts as a neurotransmitter. Male mice of this strain are violent and sexually overactive.[13] Disruption of a different gene appears to disrupt nurturing behaviour since female mice lacking the gene fail to keep their offspring in the litter. The gene is a transcription factor which controls the expression of other genes.[14] These experiments raise the question of how far it is possible to draw conclusions about mental disorders and human behaviour from animal studies. Can studies of violence in fighting male mice, for example, really be related to violence in men? Even for physical conditions, such as retinoblastoma, an animal in which a gene is knocked out may have rather different symptoms to those seen in the human disease.[15] Clearly, it is necessary to be very careful when interpreting such experiments.

New techniques

30 Several new developments are facilitating rapid and thorough analysis of the genome and improving the efficiency with which linkage and association studies can be carried out. These include:

- the development of extensive DNA markers, covering the genome more densely and in more detail;
- semi-automated, high throughput genotyping;
- improved statistical analysis and computer models;
- under development are microchips which can contain up to a million DNA fragments. In the future, such DNA chips will make genotyping and analysis of gene expression much faster and cheaper.[16]

12 Flint J, Corley R, DeFries J, Fulker D, Gray J, Miller S and Collins A (1995) A simple genetic basis for a complex psychological trait in laboratory mice, **Science** 269:1432–5.
13 Nelson R, Demas G, Huang P, Fishman M, Dawson V, Dawson T and Snyder S (1995) Behavioural abnormalities in male mice lacking neuronal nitric oxide synthase, **Nature** 378:383–6.
14 Cohen J (1996) Does nature drive nurture? **Science** 273:577–8.
15 Wynshaw-Boris A (1996) Model mice and human disease, **Nature Genetics** 13:259–60.
16 Anonymous editorial (1996) To affinity...and beyond! **Nature Genetics** 14:367–70.

Appendix

The use of genetic information in legal proceedings

Duty of care

1 Those professionals who are involved in the care and treatment of mentally disordered patients owe a duty to take care, a duty not to expose the patient to harm, and (where appropriate) a duty to ensure that a patient is fully informed as to any proposed treatment. This is not the place to set out the details of those various duties. However, the Working Party considers that the discussion of genetics and mental disorder may be assisted by identifying some particular areas of concern where practitioners may be exposed to claims for negligence, on the assumption that there is an increase in the availability of genetic testing and a marked improvement in the reliability of the information obtained.

2 For example, failure to detect genetic predisposition may expose the responsible doctor to claims by parents, children and family members. If there is a family history of a particular disorder, it may be suggested that a doctor should offer genetic testing, or at least inform the patient about the possibility of testing even if it is only available in the private sector. However, if the cause of action is formulated in terms of the breach of a duty of care, there may be some difficulty in identifying what damage has been caused solely by the failure to carry out testing – without identifiable harm (quantifiable as damages) the cause of action will be incomplete.

3 If there is a known means of preventing the mental disorder developing, and action could or should have been taken, damages could be recovered for the onset of the disorder itself. If there is no known means of preventing the disorder, damages may be claimed for any harm which was caused by the disorder being left untreated until it was properly diagnosed. This might include damages for distress (although there is some doubt whether damages are allowed for distress which is not consequent upon some personal injury caused by the defendant). If the individual develops the mental disorder, an action may be brought to recover damages for additional harm which it is claimed would not have been suffered had he or she known in advance of the genetic predisposition to mental illness. For example, a woman might argue that she would not have had a child if she had known that she herself had the genetic predisposition. She might therefore claim for the additional injury to herself, either in the form of additional psychiatric injury caused by pregnancy and childbirth, or of the hardship of raising a child while suffering from a mental condition.[1]

4 A similar claim could be made by parents claiming that had they known of the genetic predisposition they would not have had a child, irrespective of whether or not this caused them any physical injury. In the UK, damages have been awarded for the birth of a healthy but 'unwanted' child where the parents did not want to conceive at all.[2] The claim is in essence for the cost of raising the child. In theory, a claim should succeed notwithstanding that the child is born *without* the defective gene. In practice, however, such a claim is unlikely unless it can be shown that the parents would not have had a child at all if they had known of their genetic predisposition.

5 A claim may be brought for damages for harm to other non-medical interests, such as financial interests. This has not been tested in the UK. Such a claim was ultimately rejected by the Supreme Court of California, but successful before the Californian Court of Appeal, where the plaintiff claimed that if he had been informed of the statistical mortality rates with his form of

1 In *R.* v. *Croydon Health Authority* (Court of Appeal) **The Times**, 13 December 1997, the plaintiff, who had a heart condition which the defendant's radiologist negligently failed to diagnose, attempted to claim (unsuccessfully) for the expenses of pregnancy and the costs of bringing up her daughter. The Court of Appeal decided that there was no sufficient connection between that damage and the breach of duty.

2 See, for example, *Allen* v. *Bloomsbury Health Authority* [1993] 1 All ER 651.

cancer he would have spent his last days at peace with his family and would have taken time to organise his business affairs.[3]

6 If testing is carried out, negligent breach of duty may be alleged in the failure to provide sufficient information to the patient to enable him to make an informed decision about whether or not to undergo the testing. The standard of sufficiency of information would be that recognised by a responsible body of professional opinion as acceptable and appropriate (the *Sidaway* test).[4]

7 If it is discovered that an individual has a genotype conferring high risk of a particular mental disorder, there would be a *prima facie* obligation on the treating doctor to provide the individual with appropriate information about the available options for preventing the disorder from developing (assuming that prevention was a real possibility).

8 Another novel action in negligence which may arise out of the developing technology, is a claim for the distress and or psychiatric consequences of a *false* positive report following genetic testing for mental disorder. It is highly likely that such a claim would succeed if it could be shown that the deficiencies in the report were caused by some negligent act or omission on the part of those who carried out the test or who analysed the results.

Use of genetic information in legal proceedings[5]

9 Genetic information relating to an individual's mental disorder may be relevant in legal proceedings against a doctor or hospital. This might arise, for example, where the individual is seeking to establish that he or she should have been informed of a genetic predisposition. It might also be relevant where a third party is seeking to establish that the doctor ought to have provided information that he or she was also either at risk of carrying the defective gene, or was at risk of injury at the hands of the patient with the mental disorder. Disclosure of this information can be ordered by the court, even before an action has commenced, provided that it is not shown to be contrary to the public interest for it to be disclosed (for an example from the United States see s.33 Supreme Court Act 1981).[6]

10 More difficult questions arise where the genetic information is sought in order to characterise the individual as having a mental disorder for the purposes of proceedings which are entirely unrelated to the doctor–patient relationship.[7] An example can be taken from criminal proceedings where genetic information might be sought as part of the defence either as evidence of unfitness to be tried, or to exonerate the defendant, or as mitigating circumstances.[8] Although genetic information could affect defendants positively, increasing their chances of obtaining treatment rather than punishment, the same genetic information might, perversely, produce a negative reaction raising a presumption that the person is untreatable. Although it is far from the case that genetic disorders are necessarily untreatable, the court is in these terms a lay body and there may be a tendency to view the effects of a defective gene as less mutable than, say, social conditions

3 See *Arato* v. *Avedon* [1993] 858 P 2d 598 (S. C. Cal).

4 See *Sidaway* v. *Governors of Bethlem Royal Hospital* [1985] AC 871, as considered and applied in, for example, *Smith* v. *Tunbridge Wells Health Authority* [1994] 5 Med LR 334, and *Bolitho* v. *City and Hackney Health Authority* [1997] 4 All ER 771.

5 For the use of genetic information generally, see also Chapter 6.

6 Once litigation has been commenced, the High Court has the power to order the disclosure of such information under section 34 of the Supreme Court Act 1981, but will do so only where it is shown that it is not against the public interest and is necessary to dispose of the case fairly or to save costs.

7 The Working Party acknowledges the views expressed by some respondents to the consultation that the use of genetic information in the legal system (and in education and healthcare) is 'too wide an area to discuss at this stage'. However, there is room, and a need, for introductory comments and an understanding of particular areas of concern.

8 Such an attempt, eventually unsuccessful, was made in the US murder trial of Stephen Mobley, where it was argued that genetic information revealed that the defendant was 'programmed' to be violent and, therefore, he should not be blamed for the murder which he had committed.

or disease due to infection or other causes of `external' origin since the origin of his condition is genetic rather than social or environmental. A person with a genetic disorder might be seen by the sentencing court as 'unlikely to respond to treatment', 'likely to be a serious continuing danger', or 'likely to be a continuing nuisance'. As pointed out in a submission to the Working Party, if the genetic information (and the conclusions which are said to follow from that information) is capable of being established in a criminal trial to show, for example, that a particular defendant is unfit to plead, then it may be unjust for that material to be excluded.[9]

11 Genetic information might also be sought to be admitted in family proceedings, as evidence of a person's unfitness to be a parent or guardian – for example, in fostering, adoption, care or custody proceedings.

12 Such information could also be used to attempt to limit liability in civil cases. There is evidence that this is starting to happen in the United States – for example, where a company, which had been sued by an employee alleging that her exposure to chemicals had caused damage to her mentally handicapped child, obtained a court order requiring the child to be genetically tested for fragile X syndrome on the grounds that this might be the cause of the mental retardation.

13 There is also the possibility that the science will develop to such a degree that a court might want to order that an individual undergoes genetic testing in order to establish whether or not he is suffering from a particular mental disorder. This is less likely in the case of an adult, but, where a child is involved and it could be shown to be in the interests of justice and not against the interests of the child, the court may well consider that further investigation is appropriate.

14 The law is inevitably concerned with evidence which can be examined and tested, at some point, in court proceedings. Legal procedures are not ideally suited to grappling with a moving and developing body of knowledge. Further, the standards of proof which apply in litigation (proof beyond reasonable doubt in criminal proceedings, and proof on a balance of probabilities in civil proceedings, and in relation to some aspects of criminal proceedings) may be inapt to deal with the resolution of scientific uncertainties. There is, at present, an underlying factual uncertainty in relation to many aspects of the scientific investigation into the relationship between genetic factors and mental disorder. That uncertainty covers the degree to which scientists are able to confirm their suspicions and identify the 'relevant' genes, the causal connection between identification of the gene and development of the disorder,[10] and the use which might be made of the knowledge acquired from that process of identification.

9 Lady Kennet's response to the Working Party's consultation.
10 See, for example, Chapter 3.

Appendix

Method of working and consultation

Method of working and consultation

1 The Working Party met thirteen times between October 1996 and July 1998. The inquiry was announced in the press in February 1997 and interested organisations and individuals were invited to obtain a consultation pack (also placed on the Web) and comment on the issues. Over one hundred responses were received from a wide variety of organisations and individuals, including some who currently or previously had had mental health problems or a psychiatric diagnosis or who came from a family with a history of mental health problems (10), carers (5), mental health user groups, charities and other organisations (18), learned and professional organisations and regulatory bodies (13), individual clinicians and scientists (20), ethicists or centres of ethics (8), lawyers or centres of law (4) other academics and individuals (18), religious groups (8), health care providers (4), research ethics committees (4) and women's organisations (4). Those who responded are listed in Appendix 4 and the Working Party is grateful to all of them. Some of the main themes to emerge from the consultation responses are set out below.

General comments

2 Several respondents pointed out that many of the ethical concerns raised by genetic research into mental disorders also applied to other diseases and that it was important not to give the impression that such concerns were unique either to mental disorders or to genetics. It was suggested that the ethical concerns might be about either the treatment of research participants, the acceptability of the research itself, or the consequences of such research. Some considered that only potential applications, and not the research itself, required examination. Many thought that the ethical implications would depend on the predictive strength of genetic information about mental disorders and that there would be a need to cope with a period during which diagnostics were more advanced than therapeutics. Others felt that there was a need to look at the implications of medically oriented research for normal behavioural and cognitive processes. The importance of distinguishing ethical questions from empirical questions that could be answered by further research was stressed.

3 The importance of mental health service users' views, and of accommodating different views, was emphasised. It was argued that, while the regulation of science was dominated by professionals, lay people had the capacity to contribute and should have the right to do so.

Definition and classification of mental disorders

4 The range of mental disorders from Huntington's disease to mild depression and the distinction between mental disorders and learning difficulties were given emphasis by many respondents. The importance of not making inappropriate generalisations was noted.

5 Several respondents questioned the conventional definition of mental disorder and reminded the Working Party that concepts of madness changed over time and were sometimes used for political purposes. Others challenged the very existence of conditions such as schizophrenia and argued that scientific research represented a fundamental non-acceptance of people with mental health problems. Some argued that, if disability was treated as a medical concern, then more important social, economic, political and environmental factors might be overlooked. Others highlighted the importance of environmental factors including solidarity within the family and institutionalisation in relation to mental health problems. Several respondents commented that, while the suffering caused by mental disorder should not be underestimated, the contributions of people with mental disorders should also be acknowledged. Mental disorders were described by

some as the extreme end of an otherwise normal dimension, a feature of the human condition that could affect anyone.

What do genetic studies of mental disorders tell us?

6 Some questioned the assumptions implicit in studying mental disorders and criticised what they saw as ideologically motivated research and reliance on the medical model. Others asked whether such research reflected the concerns of those with mental disorders. The danger that research might select for extreme phenotypes and hence give rise to results that were not generally applicable was noted. The complexity and history of genetic research on mental disorders suggested that researchers needed to be cautious when presenting claims. Some were concerned that undue emphasis on genetic explanations of behaviour and difference might affect preventive behaviour, social policy, and research funding. Tuberous sclerosis was cited as an example of how research into the biological basis of a condition could improve educational and psychological care.

Clinical applications

7 One view was that families can have difficulty in getting the early signs of schizophrenia taken seriously so that it would be welcome if genetic information helped with diagnosis. Others considered that, while needs-based assessments were ideal, firm diagnoses might suggest the range of problems to anticipate. More precise diagnosis would be helpful if linked to treatment or prevention, but some were pessimistic about the possibility of effective interventions in families disrupted by mental disorder.

8 One view was that genetic advances would allow better understanding of disease, development of drugs for cure rather than relief of symptoms, and better targeting of treatment and prevention. It would be important to develop diagnostics and therapeutics together. Therapeutics might include low molecular weight drugs, antisense technology and therapeutic vaccines but gene therapy was a remote prospect for polygenic diseases. Research should become more effective because it would become possible to identify non-responders and those likely to suffer side effects.

Ethical issues arising from clinical applications

9 **Counselling:** it was pointed out that for **individuals** it is important they decide for themselves if they want information and, if they do, that they understand its implications before making a choice, whereas for **institutions** regulation is necessary. But many respondents reflected on the difficulty of making such decisions, with the uncertainty of predictive information being described as a 'sword of Damocles'. The value of user support groups was noted.

10 Some felt that the emphasis on genetic causes was disempowering, especially given the arcane nature of the science involved. This might undermine the efforts of people with mental disorders to take part in managing their condition. Others were concerned that children might also blame their parents, and parents worry about their children, or that genetics might increase the degree of intervention in people's lives. Conversely, others felt that genetic information about the cause of a condition would be helpful.

11 Some considered that genetic information might worry people who were not already ill and even influence the course of a disease. It might be important to think especially hard about the risks and benefits of giving information if people were already anxious. The importance of post-test

counselling was noted. Others felt that healthy people should be able to cope with predictive information especially since, if the condition ran in the family, it would not be entirely unexpected. Some felt that 'forewarned was forearmed'. Some pointed out that beliefs about the causes of misfortune determined how they were addressed. Genetics tended to be seen as an influence that a person could not control and this might decrease the blame associated with certain conditions. The need for resources to monitor the impact of genetic counselling, testing and information giving was emphasised. It was argued that shared susceptibility might increase the sympathy within a family for affected members, but others cited evidence that families shied away from knowledge of members' diagnoses of Alzheimer's disease. In the specific case of tuberous sclerosis it was argued that a diagnosis decreased the blame for badly behaved children, though many clinicians still focused on family dynamics as an explanation for the condition.

12 The need for informed consent was seen as implying the provision of counselling. The same principles and standards should apply as in all counselling: gauging competence, judging risks and benefits, assessing the broader ramifications and tailoring advice to the individual. How communication needs should be met in practice should be based on empirical investigation. Counselling might be especially difficult if those counselled lacked insight into their condition. This would suggest that counsellors should have experience of the disability in question or special training.

13 **Genetic testing:** one view was that clinical tests should only be offered when the knowledge base allowed a judgement about the significance of the data. If the effect of a gene was very small this should be emphasised – but would testing be of any value in these cases? It was argued that predictive testing expanded the category of people perceiving themselves as, seen as, or treated as, disabled.

14 **Screening:** the importance of distinguishing between individual and population benefits of genetic testing was noted. The Working Party was reminded of the consensus that, for population genetic screening to be offered, there should be a health benefit. It was suggested that for susceptibility testing, the harms would outweigh the benefits, with many false positives and a heavy burden on the NHS. It was argued that general measures to improve the health of population would be more cost-effective. The importance of anonymous testing to study the population frequency of different genotypes was noted.

15 **Consent and impaired capacity:** in relation to testing incapacitated adults it was argued that extreme disability should not preclude the ability to determine life outcomes. In a dominant disorder such as tuberous sclerosis, these might be the only people who could provide samples which were informative about other family members.

16 **Confidentiality:** it was pointed out that confidentiality was threatened by large multidisciplinary teams and direct pressure to justify social benefits or legal defences with clinical information.

17 **Genetic information and reproductive decisions:** one view was that the role of the parent was changing with increasing reproductive choice and decision making. Some felt that the possibility of abortion made parental acceptance conditional on a child's state of health. Evidence of a more positive attitude to terminating pregnancy for mental rather than physical disorder was mentioned. Many expressed concern about, or opposition to, any possibility of selective abortion of fetuses thought to be predisposed to mental disorder. It was argued that over-reliance on the single gene model would lead people to think that abortion was feasible and cause environmental factors to be overlooked. Many considered that the predictive certainty of genetic information would, in fact, be very limited. Some felt that counselling for conditions such

as Down's syndrome was currently inadequate. It was suggested that obstetricians would welcome guidelines on which prenatal tests should be offered.

18 It was argued that prenatal testing had direct consequences for aborted fetuses and indirect consequences for those born with handicaps. Each individual, it was argued, should be valued as part of the human family. By contrast, some expressed the view that people with genetic diseases should not pass them on and pointed to the fact that people with one affected child often take steps to avoid the birth of another affected child. Others questioned whether concern about abortion for abnormality was logical in a country in which healthy babies were sometimes aborted.

19 **Eugenic programmes:** many respondents, in expressing concern about the possibility of selective abortion drew parallels with past eugenic practices in Nazi Germany and elsewhere. Others described personal experiences in which they had not been expected, or allowed, to make independent reproductive choices.

Wider ethical issues

20 It was pointed out that the social context played a major role in the response to any phenomenon and that attitudes to mental disorders were already negative. The recent history of care in the community also suggested the need for caution before using new genetic information.

21 **Stigma:** it was asked whether the stigma associated with mental disorders could get any worse than it was already. The difference in attitudes towards cancer and mental disorders was pointed out. It was suggested that, if many people were found to possess susceptibility genes but did not develop the condition, the stigma associated with mental disorders might lessen. Moreover, it might emphasise the fact that people's characteristics are, at least to some degree, theirs by good (or bad) fortune. The need to educate people and combat media misrepresentation was emphasised. It was noted that claims for the identification of a gene associated with homosexuality had been made use of by both gay and homophobic groups.

22 **Discrimination:** many respondents affirmed the principles of justice and non-discrimination. Some felt that this stemmed from the creation of all human beings in the image of God. It was argued that those who were not perfect should not be penalised and that access to employment and other opportunities should be based on a person's merits at the time and not on what might happen in future. The role of clinicians in determining access to resources and opportunities was noted.

23 Many expressed concern about discrimination and the potential exploitation of genetic data about mental and physical differences which, it was felt, could be a special danger for mental disorders. It was argued that standard methods for presenting information clearly should be developed to minimise the risk of discrimination. Some argued for statutory legislation for the regulation of genetic data along the lines of the Data Protection Act and Equal Opportunities legislation, but others questioned whether genetic information differed from other medical information to such an extent that this would be justified.

24 **Insurance:** the potential for discrimination in insurance (especially chronic care, long-term care and critical events insurance) was pointed out by many respondents. There was a view that those most needing cover would be least able to afford it. Some considered that, given the uncertainties around diagnosis of mental disorders, genetic information should not be available to outside agencies.

25 **Employment:** it was felt that employers would find it difficult to interpret genetic information. While there was some potential for positive discrimination, the likelihood was negative discrimination. One view was that trends such as high unemployment and short-term contracts might increase the use of genetic testing. Some had the view that the Disability Discrimination Act should be amended to cover predispositions including those that might be detected with genetic information.

26 **Healthcare:** concern was expressed that healthcare purchasers might exclude patients with genetic conditions on grounds of cost. The fact that, currently, some people with genetic conditions were not offered fertility treatment, other forms of treatment or compensation for vaccine damage was noted.

The ethics of genetic research on mental disorders

27 Some argued that it was not justifiable to put constraints on the scope of research but others felt that there was an ethical obligation to focus on prevention, alleviation and cure and not just causation. Some thought that genetic research into mental disorders would receive more support if such benefits were demonstrated. Others had the view that a case could be made for deferring such research until there was more promise of benefit. Yet others expressed concern that over-regulation would stifle research. It was argued that a review of any possible consequences, including access to any benefits, should take place when research was being planned and that debate about ethics, and contribution to public discussion, should be an essential component of research. It was suggested that participants should be involved in planning research.

28 It was argued that the cost effectiveness of genetic research should be judged in relation to other medical research, and the research budget itself in relation to the care budget. There was a view that genetic research should not exclude research into social and environmental influences and some respondents were concerned that basic research was funded at the expense of other initiatives such as giving information and advice to affected people. The fact that the NHS document the **Health of the Nation** had made mental health a priority area for the NHS was noted.

29 **Consent:** it was suggested that, while much importance was attached to individual consent in Western society, in other cultures, and in situations involving carers, it might be appropriate to involve family or group members. It was argued that capacity should be assessed on a case by case basis rather than assumed on the basis of a diagnosis of mental disorder. In the case of individuals lacking capacity it was noted that relatives did not always have the independence to consider a person's best interests. An increased use of advocates was suggested.

30 **Disclosure of information:** in considering the benefits and disadvantages of passing research information to participants, it was useful to distinguish between basic research on the condition and the provision of clinical information for individuals. It was suggested that withholding identifiable clinically significant information was probably unlawful. It was argued that the question of disclosure should be dealt with during the consent procedure at which point a person might be identified who would make a decision about whether disclosure is in an individual's best interests.

31 It was considered important not to rush from research into practice too soon and to analyse the risks and benefits before doing so. Equally, it was important to audit genetic research to see that effective transfer into practice occurred.

Appendix

Consultation responses

Organisations

Association of Directors of Social Services, Mental Health Strategy Group
Baptist Union of Great Britain: Revd Anne Wilkinson-Hayes
Bethlem and Maudsley NHS Trust and Institute of Psychiatry, Ethical Committee (Research)
British Medical Association
BUPA, DNA Medicine Group
Cardiff Bipolar Disorder Genetics Group
Central Oxford Research Ethics Committee
Centre for Bioethics and Public Policy
Christian Medical Fellowship
Charlie Reid Centre
Church of England Board for Social Responsibility
Dalriada School, Co Antrim, Northern Ireland: VI form students
Department of Health: Advisory Committee on Genetic Testing
Depression Alliance
Duke University Medical Center, North Carolina
European Bioethical Research
Euroscreen Core Group
Faculty of Public Health Medicine
General Medical Council
Genetic Interest Group
Highland Community Care Forum
Highland Health Board Ethics Committee
Institute of Biology
Institute of Psychiatry
Joint Ethico-Medical Committee of the Catholic Union of Great Britain and the Guild of Catholic Doctors
Kent Law Clinic (Mental Health and Learning Disability): Kate Diesfeld, JD
League of Jewish Women
Linacre Centre for health care ethics
Lord Chancellor's Department, Family Policy Division
Lothian Research Ethics Committee
Medical Research Council
Mencap
Mental Health Foundation
MIND: London E15
MIND: Colchester
MIND: Leeds
National Council of Women of Great Britain
National Schizophrenia Fellowship (Scotland)
National Spiritual Assembly of the Baha'is of the United Kingdom
NHS Executive, Department of Health
North Yorks East Federation of Women's Institutes

Official Solicitor to the Supreme Court
Open University, Brain and Behaviour Research Group: Professor Steven Rose
Oxford Hearing Voices Group
Oxfordshire Psychiatric Research Ethics Committee
Quaker Ethics and Genetic Engineering Network members Joy Bell, Amber Carroll, John Crookall-Greening, Robert Ward and Ioan Thomas
Royal College of Nursing
Royal College of Pathologists
Royal College of Physicians, College Committee on Ethical Issues in Medicine
Royal College of Physicians, Faculty of Occupational Medicine, Ethics Committee
Royal College of Psychiatrists
Scottish Association of Health Councils
SmithKline Beecham Pharmaceuticals
Soroptimist International, UK Programme Action Committee
South Thames Regional Genetics Centre (East)
Survivors Speak Out
The Royal Society
The Wellcome Trust
Trades Union Congress
Tuberous Sclerosis Association
UK Central Council for Nursing, Midwifery and Health Visiting
UMDS, Guy's & St Thomas's, Psychology & Genetics Research Group: Professor Theresa Marteau
University College London, Dept of Science & Technology: Jon Turney/Jill Turner
University of Bradford: Professor Hilary Rose
University of Cambridge, Dept of Social Anthropology: Prof Marilyn Strathern
University of Central Lancs, Centre for Professional Ethics: Prof Ruth Chadwick
University of Edinburgh, Dept of Psychiatry: Dr Douglas Blackwood
University of Oxford, Dept of Experimental Psychology: Dr Gordon Claridge
University of Oxford, Dept of Psychiatry: Dr T J Crow
University of Oxford, Dept of Psychiatry: Prof Guy Goodwin
University of Oxford, Dept of Psychiatry: Dr Katharine Rimes/Dr Paul Salkovskis
University of Sussex, Dept of Experimental Psychology: Prof Stuart Sutherland
University of Virginia, Institute of Law, Psychiatry & Public Policy
University of Virginia, School of Law
University of Wales, Institute of Medical Genetics: Dr Angus Clarke
University of Wales, Institute of Medical Genetics: Prof Peter S Harper
University of Warwick, Dept of Philosophy: Professor Bill Fulford
Western Health & Social Services Council, Co Tyrone
Women's National Commission

Individuals

Andrew, Christine: NSF Voices Forum
Anim, Mrs Cecilia
Anonymous student
Antoniou, Ms Janey
Balsom, Elizabeth
Barrett, James
Crampton, Dr Diana
Cresswell, Janet
Evans, Chris: member of Highland Users Group
Gardner, Dr E Gwen
Gearie, Andrew Dalziel
Hands, Mr Brian
Hart, Ms Dyana
Hoffenberg, Raymond
Hope, Dr Anthony
Jones, Mrs EM
Jones, Sandra
Kennet, Lady
Kohler, Anne
Hyams, Mrs Jack
Lefever, Dr Robert MH
Members of Women in MIND
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Glossary

Glossary

Affective disorders

These are mood disorders such as depression and manic depression.

Allele

The particular sequence of a gene can vary and an allele is the term given to any one sequence.

Alzheimer's disease

This is a form of dementia which results in progressive decline in memory, initiative and intellect, leading to generalised dementia and death, usually within 5 years (Box 3.3).

Anticipation

The phenomenon of an earlier age of onset or more severe manifestation of an inherited disorder in successive generations.

Anxiety disorders

The group of disorders including panic, phobic and obsessive-compulsive disorders.

ApoE

A gene which occurs in different variants (alleles). A person's likelihood of developing Alzheimer's disease depends in part on which ApoE allele they possess (E2, E3 or E4). The ApoE gene encodes a protein called apolipoprotein E which is found in the blood and the brain (Box 3.3).

Autosome

Any chromosome which is not a sex chromosome.

Calculated risk figures

Calculated risk figures are based on objective criteria, usually the results of blood tests, X rays or genetic tests. In some cases, they will modify the results of empirical risks, resulting in an increased or decreased figure (paragraph 4.14).

Chromosome

The thread-like DNA in a cell is divided into several separate lengths. Each length forms a structure called a chromosome. There are two copies of each chromosome in every cell. Human cells contain 23 pairs of chromosomes.

Complex disorder

A disorder with complex causes, affected by a number of factors both genetic and environmental (multifactorial). The genetic contribution to the disorder may include several genes (oligogenic) or many genes (polygenic).

Dementia

Deterioration of intellectual function associated with pathological changes in the brain.

DNA

DNA (deoxyribonucleic acid) is the biochemical substance that genetic material is made of. DNA has a thread-like structure. A gene is a short length of DNA containing the information needed to make one protein. The DNA in a cell is in several long lengths, each of which contains many genes. Each length of DNA forms a structure called a chromosome.

DNA repeat

An expansion of a small region of a gene. In Huntington's disease, the repeat is the disease mutation, the size of the repeat correlating with the age of onset of the disorder (Box 3.2).

Dominant

The form of inheritance in which a genetic disorder or characteristic is manifest when only one copy of the gene is faulty.

Empiric risk figures

These are based on data on the frequency of a disorder in a population. The empiric risk of schizophrenia in the UK is about 1% (paragraph 4.13).

Enzyme

A protein that catalyses (speeds up) a biochemical reaction.

Eugenics

The use of measures to change the genetic characteristics of a population either by preventing or discouraging those with the (inherited) characteristics held to be undesirable from having children or by encouraging those with characteristics held to be desirable to have more children.

Familial hypercholesterolaemia

An single gene disorder in which affected individuals have high levels of blood cholesterol from birth and have an increased risk of heart disease

Fragile X syndrome

A disorder for which severe learning difficulty is the main characteristic, although this varies markedly in severity between individuals. It is caused by a visible change near the tip of the X sex chromosome. Boys, and to a lesser extent, girls are affected.

Gene

A length of DNA that contains information needed to make one protein. For example, the haemoglobin gene contains the information needed to make a haemoglobin protein found in red blood cells.

Gene variant

A less technical term for allele.

Genetic counselling

This can be broadly defined as "*the process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it and of the ways in which this may be prevented, avoided or ameliorated.*" [11] (paragraph 4.11).

Genetic material

Genetic material refers to the material made of DNA in each cell of any organism. The DNA is divided into genes. Each gene contains the information required to produce one protein needed by the cell.

Genetic predisposition

The situation in which an individual may have susceptibility genes that confer an increased risk to a disease but there is no certainty that the disease will develop.

Genetic test

A test to detect the presence or absence of, or change in, a particular gene or chromosome.

Genome

The full complement of genetic material of an organism.

Genotype

The particular pair of alleles at a specified gene locus. One of these alleles is inherited from the father, the other from the mother.

11 Risch N and Merikangas K (1996) The future of genetic studies of complex human diseases, **Science** 273:1516–17.

Heritability

An estimate of how much of the total variation in a population can be explained by genetic differences (Appendix 1, paragraphs 12–17).

Human Genome Project

An international scientific collaboration to clone, map and sequence the entire human genome. It is expected that the complete sequence will be known by about 2005.

Huntington's disease

A dominantly inherited single gene disorder resulting in progressive degeneration of the central nervous system leading to involuntary movements, loss of motor control and dementia. Symptoms usually begin to appear when people are between 40 to 50, with death occurring 15–20 years later (Box 3.2).

Late onset disorders

Disorders where the symptoms are not present from birth, but occur later in life. For example, symptoms of Huntington's disease most commonly first appear in individuals of between 40 and 50 years of age.

Linkage studies

A technique for identifying regions of DNA inherited by family members with the disorder and which might, therefore, influence the development of the disease or condition (Appendix 1, paragraphs 19–20).

Manic Depression

A condition which is characterised by both manic and severely depressed episodes.

Mendelian disorders

Those which follow the patterns of inheritance originally identified by Gregor Mendel.

Mental disorders

According to a major current international system of classification, mental disorder "is not an exact term, but it is used to imply the existence of a clinically recognizable set of symptoms or behaviour associated in most cases with distress and with interference with personal functions. Social deviance or conflict alone, without personal dysfunction, should not be included in mental disorder as defined here" [12] (paragraph 2.1).

Multifactorial disorders

Disorders that result from abnormalities in more than one gene and may be affected by other factors such as the environment, for example, coronary heart disease and some cancers. May also be called 'polygenic'.

Mutation

A process during which the DNA of an organism changes or mutates. In humans, this can lead to conditions such as phenylketonuria in which a mutation has occurred in a gene required for metabolism of the substance phenylalanine found in many foods. The mutant gene is passed down from parent to offspring and so the condition can be inherited.

Neurotic disorders

Another term for anxiety disorders.

Obsessive-compulsive disorders

This is characterised by obsessions causing anxiety or distress and/or by compulsions which serve to neutralise anxiety.

12 World Health Organisation (1992) **The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines**, World Health Organisation, Geneva, p5.

Oligogenic

An oligogenic disorder is one that is affected by several genes.

Penetrance

The proportion of carriers of a genetic alteration who will manifest the effects of it. A highly penetrant mutation, for example, is one for which perhaps >80% of carriers will develop the disease at some point in their lifetime. Penetrance will depend upon an individual's age and possibly other factors, including gender and environmental factors.

Personality disorders

A personality disorder is an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time and leads to distress of impairment.

Phenylketonuria

A recessively inherited single gene disorder that results in an inability to metabolise the substance phenylalanine, found in many foods. If affected people eat food containing phenylalanine, a component of most proteins, severe mental handicap results. With rigorous dietary control, development can be normal (Box 3.1).

Phenotype

The physical characteristics, including disease manifestations, of an individual.

Polygenic

A polygenic disorder is one that is affected by many genes.

Polymorphism

The manner in which, in a particular site in DNA, variations occur in the nucleotide sequence between individuals in the population, producing multiple different detectable forms on DNA analysis. Usually these are located outside the coding regions of genes, or do not alter the amino acid sequence of coded polypeptides. Useful in gene mapping and DNA fingerprinting.

Protein

A protein is a particular kind of molecule, made up of amino-acids. Every protein in the human body must be assembled from its constituent amino-acids. The information controlling this process is contained in the gene corresponding to that protein.

Recessive

The form of inheritance where a genetic disorder or characteristic is manifest only when both copies of the gene are faulty.

Schizophrenia

A disturbance that lasts at least six months and includes at least one month of symptoms such as delusions, hallucinations, disorganised speech, disorganised or catatonic behaviour, or negative symptoms (for example, flattening of mood).

Sex-linked disorder

A disorder caused by a mutation on the sex chromosomes which is inherited in a gender-specific way.

Single gene disorder

A disorder that results from a mutation in a single gene, for example, phenylketonuria, Huntington's disease.

Susceptibility gene

A gene for which a variant (or allele) is associated with a relatively slight predisposition to a disorder, rather than a near certainty of suffering from a disorder. For example, a variant of the apoE gene (called the apoE4 allele) is associated with a predisposition to Alzheimer's disease, but a genetic test result can indicate no more than a somewhat increased susceptibility (paragraph 4. 7).

Trinucleotide repeat

An expansion of a small region of a gene, consisting of three base pairs or nucleotides. In Huntington's disease, the repeat is the disease mutation, the size of the repeat correlating with the age of onset of the disorder (Box 3.2).

Nuffield Council on Bioethics

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