Personal paper

Risk of diabetic nephropathy in potential living related kidney donors

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Diabetic nephropathy is the leading cause of end stage renal failure in New Zealand.[1] Cadaveric organs are in short supply here, as elsewhere, and we need to consider living related donation. Kidneys from living related donors also provide a better graft and improved survival of transplant patients. However, donors from ethnic groups who have a high incidence of end stage renal failure because of diabetes and glomerulonephritis are also at increased risk of developing diabetes.[2] This risk is compounded by environmental factors such as obesity. In New Zealand the ethics of living related donation within the diabetic family are being questioned.

Renal transplantation is preferred to dialysis in diabetic patients who are fit enough for surgery. It is associated with an improved quality of life, lower morbidity and mortality, reduced long term costs, and greater incremental benefit in diabetic patients compared with patients without diabetes.[3] The main reason for not transplanting kidneys into suitable candidates is the low availability of compatible organs for transplantation. Some ethnic groups object to donating body parts after death for cultural and spiritual reasons. The resulting underrepresentation of these ethnic groups in the donor pool further reduces the likelihood that patients with end stage renal failure from these ethnic groups will receive an organ. Organ donation from living relatives is therefore particularly encouraged in these groups.

Diabetes and the development of nephropathy once diabetes has occurred are familial and cluster in families.[4,5] It is therefore important to be able to advise a potential donor of his or her personal risk of developing end stage renal failure.

Summary points

- Living related kidney donors may have a pre-existing increased risk of diabetes and diabetic nephropathy
- Undiagnosed diabetes and impaired glucose tolerance in potential living related kidney donors need to be excluded by a glucose tolerance test
- Clinical risk factors for diabetes and diabetic nephropathy need to be considered before kidney donation
- The underlying prevalence of diabetes in a given ethnic group is particularly important
- Balancing the immediate benefit of kidney transplantation to the recipient with the possible long term harm to the donor may be difficult

Risk factors for diabetes

Apart from a few rare cases in patients with impaired glucose tolerance, development of clinical diabetes precedes the onset of diabetic nephropathy. Undiagnosed diabetes may already be present, but if it is not there are four major predictors of future diabetes—ethnic group, previous gestational diabetes, a high titre of islet cell antibody (for insulin dependent diabetes mellitus), and impaired glucose tolerance (table). The underlying prevalence of diabetes is a major determinant of risk for both impaired glucose tolerance and gestational diabetes. In those aged 30-64 years, the prevalence of non-insulin dependent diabetes varies from 1% to 50% between ethnic groups.[6] The prevalence also varies within the same ethnic group in different geographical locations.[6] The risk of diabetes in terms of familial relationship and type of diabetes in different ethnic groups is shown in the table.

Prospective studies have shown that other components of the metabolic syndrome are risk factors for developing diabetes. In the eight year follow up of the middle aged cohort of the San Antonio heart study, 34% of hypertensive people and 30% of overweight subjects went on to develop non-insulin dependent diabetes mellitus or impaired glucose tolerance (compared with 15% of people without hypertension and 10% of those with a normal weight).[7] Other risk factors for the development of non-insulin dependent diabetes include the degree of fasting hyperglycaemia and hyperinsulinaemia after an oral glucose load.[8,9]

Among Pima Indians, a family history of diabetic nephropathy is itself a risk factor for the development of diabetes.[10] The risk of developing non-insulin dependent diabetes mellitus is three times greater where both parents have diabetes and one has renal disease than where both parents are diabetic but

neither has kidney disease. If this applies to other ethnic groups, the people who are most likely to be asked to give kidneys may be those with the highest chance of developing diabetes (and possibly nephropathy).

Risk factors for development of nephropathy

Only a proportion of people with diabetes progress to nephropathy and then to end stage renal failure. Many of the modifiable risk factors for diabetic nephropathy depend upon the quality of health care and self care (for example, blood pressure, glycaemia, smoking, and obesity).[11] Ethnic and familial factors are also important for determining those with diabetes who will probably develop nephropathy. While few (around 0.4%) Europeans with non-insulin dependent diabetes mellitus develop end stage renal failure,[12] overt nephropathy occurs in up to 50% of Pima Indians who have had non-insulin dependent diabetes mellitus for more than 20 years.[13] Ethnic groups at high risk of diabetes related to end stage renal failure often have a relatively high prevalence of microalbuminuria but are not overtly diabetic, and this should be considered by any potential donor. A parental history of hypertension is associated with an increased the risk of microalbuminuria.[14]

The findings of the study by Seaquist et al are of particular concern.[5] The development of nephropathy and end stage renal failure was compared in the diabetic siblings of insulin dependent diabetics with and without end stage renal failure.[5] Although 17% of siblings of subjects without nephropathy developed albuminuria, most of the siblings of patients with diabetic nephropathy developed either albuminuria (41%) or end stage renal failure (41%).

Does having only one kidney increase the risk of nephropathy?

The final and most relevant question is whether having only one kidney increases the risk of nephropathy should diabetes develop. The few animal studies undertaken suggest that the resulting hyperfiltration is associated with increased renal morbidity.[15,16] Clinical studies are few. Two follow up studies of patients with either unilateral agenesis or uninephrectomy included eight patients with diabetes, two of whom experienced progression of renal disease.[17,18] In two studies, one of 363 patients with non-insulin dependent diabetes mellitus[19] and the other of over 5000 patients with both non-insulin dependent and insulin dependent diabetes mellitus,[20] the proportions of albuminuric patients with reduced renal mass were 8% and 3% respectively. None of the patients without albuminuria was known to have a reduced renal mass (although these subjects were not as extensively investigated as the patients with albuminuria). Unilateral renal agenesis occurs in approximately 1/1000 births.[21] Studies are urgently needed to investigate this issue further.

Assessment of the potential living related donor

The clinical information that needs to be collected for assessment of the potential living related donor is shown in the box. Clearly, the risk of developing diabetic nephropathy in relatives of those with insulin dependent diabetes mellitus complicated by end stage renal failure incorporates a low risk of developing diabetes with a high risk of developing nephropathy should diabetes occur. The risk of diabetic nephropathy in relatives of people with end stage renal failure caused by non-insulin dependent diabetes mellitus is especially high in those with impaired glucose tolerance and previous gestational diabetes. Some ethnic groups have a very high risk of developing non-insulin dependent diabetes mellitus, but a variable risk of developing end stage renal failure, depending on ethnic group. Other risk factors, such as obesity and hypertension, may be cumulative. The final calculation will be an assessment of clinical risk rather than of a true actuarial risk.

Risk factors for developing diabetes in various ethnic groups

Risk factor	Ethnic group (risk)	Rate of progression	Trial (reference no)
Non-insulin dependent diabetes (NIDDM)			
Ethnic group	Pima Indians (very high)	64% by age 94 years	22
	UK South Asians (high)	30% by age 70 years	23
	US whites (medium)	21% by age 89 years	22
Gestational diabetes	South Asians (high)	62% after 6 years	24
	Europeans (low)	76% after 27 years	25
Impaired glucose tolerance	Europeans	1.5% a year	26
	Mexican Americans	7.3% a year	26
Monozygous twin with NIDDM	Finns	34% over 30 years	27
Dizygous twin with NIDDM	Finns	16% over 30 years	27
Offspring with NIDDM	US whites	16% over 20 years	28
Insulin dependent diabetes (IDDM)			
Relative of patient with IDDM	US whites	47% after 7 years	29
Monozygous twin with IDDM	Finns	23% over 30 years	27
Dizygous twin with IDDM	Finns	5% over 30 years	27
Sibling with IDDM	Danes	10% over 60 years	30
Offspring with IDDM	Danes	6% over 34 years	30

Conclusion

There may be an increased risk of developing nephropathy after nephrectomy, but this has not been quantified. The issues need to be carefully discussed

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Benefit to the recipient must be balanced against possible long term harm to the living related donor

Assessment of the risk of diabetes and subsequent nephropathy in potential living related donors

Risk of diabetes
- Age
- Ethnic group
- History of gestational diabetes mellitus
- Impaired glucose tolerance
- Family history of diabetes
- Body mass index
- Two hour oral glucose test to exclude diabetes and impaired glucose tolerance
- Fasting and two hour insulin measurements
- Islet cell antibody status
- Risk of nephropathy should diabetes develop

Risk of nephropathy should diabetes develop
- History of renal disease or hypertension
- Family history of diabetic nephropathy or hypertension
- Smoking history
- Blood pressure
- Microalbuminuria

with potential living donors, and clinicians need to balance the immediate benefit to the intended recipient with the possible harm, some time in the future, to the potential donor.

1 Disney APS, ed. *ANZDATA report 1994.* Adelaide: Australia and New Zealand Dialysis and Transplant Registry, 1994.
2 Simmons D. Epidemiology of diabetes and its complications in New Zealand. *Diabetic Med* 1996;13:371-5.
3 Disney APS. *ANZDATA report 1993.* Adelaide: Australia and New Zealand Dialysis and Transplant Registry, 1993.
4 Simmons D, Gatland BA, Leakehe L, Fleming C. Frequency of diabetes in family members of diabetic probands. *J Intern Med* 1995;237:315-21.
5 Seaquist ER, Goek FC, Rich S. Barbosa J. Familial clustering of diabetic kidney disease: evidence for genetic susceptibility to diabetic nephropathy. *N Engl J Med* 1989;320:1161-5.
6 McCarty D, Zimmet P. Diabetes 1994 to 2010: global estimates and projections. Melbourne: International Diabetes Institute, 1994:46.
7 Morales PA, Mitchell BD, Valdez RA, Hazuda HP, Stern MP, Haffner SM. Incidence of NIDDM and impaired glucose tolerance in hypertensive subjects: the San Antonio heart study. *Diabetes* 1993;42:154-61.
8 Nagi DK, Knowler WC, Charles MA, Liu QZ, Hanson RL, McCance DR, et al. Early and late insulin response as predictors of NIDDM in Pima Indians with impaired glucose tolerance. *Diabetologia* 1995;38:187-92.
9 Zimmet PZ, Collins VR, Dowse GK, Knight LT. Hyperinsulinaemia in youth is a predictor of type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1992;35:534-41.
10 McCance DR, Hanson RL, Pettitt DJ, Jacobsson LTH, Bennett PH, Bishop DT, et al. Diabetic nephropathy: a risk factor for diabetes mellitus in the offspring. *Diabetologia* 1995;38:221-6.
11 Klein R, Klein B, Moss SE. Incidence of gross proteinuria in older onset diabetes: A population perspective. *Diabetes* 1993;42:381-9.
12 Fabre J, Balant LP, Dayer PG, Fox HM, Vernet AT. The kidney in maturity-onset diabetes mellitus: a clinical study of 510 patients. *Kidney Int* 1982;21:730-8.
13 Kunzelman CL, Knowler WC, Pettitt DJ, Bennett PH. Incidence of proteinuria in type 2 diabetes mellitus in Pima Indians. *Kidney Int* 1989;35:681-7.
14 Krolewski AS, Canessa M, Warram JH, Laffel LMB, Christlieb AR, Knowler WC, et al. Predisposition to hypertension and susceptibility to renal disease in insulin dependent diabetes mellitus. *N Engl J Med* 1988;318:140-5.
15 Hostetter TH, Rennke HG, Brenner BM. The case for intrarenal hypertension in the initiation and progression of diabetic and other nephropathies. *Am J Med* 1982;72:375-80.
16 Steffes MW, Brown SM, Mauer SM. Diabetic glomerulopathy following unilateral nephrectomy in the rat. *Diabetes* 1978;27:35-41.
17 Grossman HB, Sommerfield D, Konnak JW, Bromberg J. Long term assessment of renal function following nephrectomy for stage I renal carcinoma. *Br J Urol* 1994;74:279-82.
18 Schmitz A, Christensen CK, Christensen T, Solling K. No microalbuminuria or other adverse effects of long standing hyperfiltration in humans with one kidney. *Am J Kidney Dis* 1989;13:131-6.
19 Nielson FS, Gall M, Parving HH. Acquired oligonephropathy and diabetic nephropathy. *Am J Kidney Dis* 1995;26:893-903.
20 Sampson MJ, Drury PL. Development of nephropathy in diabetic patients with a single kidney. *Diabetic Med* 1990;7:258-60.
21 Bernstein J. The morphogenesis of renal parenchymal maldevelopment (renal dysplasia). *Pediatr Clin North Am* 1971;18:395-400.
22 Meneilly GS, Tessier D. Diabetes in the elderly. *Diabetic Med* 1995;12: 949-60.
23 Simmons D, Williams DRR. Diabetes in the elderly: an under-diagnosed condition. *Diabetic Med* 1993;10:264-6.
24 Ali Z, Alexis SD. Occurrence of diabetes mellitus after gestational diabetes mellitus in Trinidad. *Diabetes Care* 1990;13:527-9.
25 O'Sullivan JB. Subsequent morbidity among gestational diabetic women. In: Sutherland HW, Stowers JM, eds. *Carbohydrate metabolism in pregnancy and the newborn.* Edinburgh: Churchill Livingstone, 1984:174-80.
26 Harris MI. Impaired glucose tolerance-prevalence and conversion to NIDDM. *Diabetic Med* 1996;13(suppl 2):S9-11.
27 Kaprio J, Tuomilehto J, Koskenvuo M, Romanov K, Reunanen A, Eriksson J, et al. Concordance for type 1 (insulin dependent) and type 2 (non-insulin dependent) diabetes mellitus in a population based cohort of twins in Finland. *Diabetologia* 1992;36:1060-7.
28 Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinaemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern Med* 1990;113:909-15.
29 Riley WJ, MacLaren NK, Krischer J, Spillar RP, Silverstein JH, Schak DA, et al. A prospective study of the development of diabetes in relatives of patients with insulin dependent diabetes. *N Engl J Med* 1990;323:1167-72.
30 Lorenzon T, Pociot F, Hougaard P, Nerup J. Long term risk of IDDM in first-degree relatives of patients with IDDM. *Diabetologia* 1994;37:321-7.

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A difficult case

Management of metastatic melanoma during pregnancy

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About 35% of women with melanoma are of child bearing age, and the coexistence of melanoma and pregnancy is increasing.[1] Many doctors recommend that women wait two to three years after successful treatment for melanoma before becoming pregnant as most recurrences occur during this time. This advice is inadequate. Doctors need to inform these women about the considerable problems that may arise if relapse occurs while they are pregnant. We present our recent experience of this difficult situation: malignant melanoma within the maternal intervillous space, invading into the core of the villus. Immunostaining for S100 protein and HMB45 was positive, and staining for human chorionic gonadotropin was negative in the tumour cells.

Case report

A 41 year old woman presented with left axillary lymphadenopathy. A superficial spreading melanoma had been removed from her back two years previously. Radical lymph node dissection was performed. All nodes contained metastatic melanoma that stained positive for S100 and HMB45. There was evidence of extranodal tumour towards the deep resection margin, but her chest radiograph and liver ultrasonography

were both normal. The woman had a professional career and had never been pregnant.

The patient presented four months later with a short history of low back pain. Clinical examination showed no abnormalities and her neurological signs were normal. However, plain radiographs of the lumbar spine and computed tomography showed that the 8th thoracic vertebra had collapsed, associated with a soft tissue mass consistent with metastatic melanoma. The spinal cord was not affected.

The patient reported that she was 12 weeks pregnant. Termination was discussed and the patient was counselled, but she and her partner were determined to continue with the pregnancy. Since she had no neurological signs of cord compression and her pain was intense, she was given a single palliative dose of radiotherapy to the affected vertebra (8 Gy to a depth of 5 cm). The scatter dose of radiation received by the uterine fundus was calculated to be 0.0005 Gy, which represents a small increased risk of fetal malformation and leukaemia. The use of analgesic drugs in pregnancy was discussed, but she was reluctant to take these.

The patient's pain improved initially, but eight weeks later she developed bilateral leg weakness and difficulty in walking. Neurological examination showed that she had grade 3-4 weakness in her legs and loss of both ankle jerk reflexes. Magnetic resonance imaging confirmed that her spinal cord was being compressed by tumour at D8/9, and that there were several tumour deposits at other levels. She underwent a decompressive laminectomy and pediculotomy. Histological examination of the tumour confirmed metastatic melanoma. During her recovery several skin nodules developed and splenic metastases were noted on ultrasonography. Fetal growth and development seemed normal at 25 weeks' gestation. The clinical problem was how to manage progressive systemic metastases in a woman expecting her first child.

1 Reintgen OS, McCarthy K, Vollmer R. Malignant melanoma and pregnancy. *Cancer* 1985;55:1340-4.

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Commentary: Pregnancy should not have affected treatment for melanoma

Robert Hammond

The occurrence of malignant disease in pregnancy turns what is usually a happy experience into a potential nightmare. In no situation in medical practice is the concept of informed choice more important when considering management options. As in all problems related to pregnancy, there are two individuals to consider and it is imperative that the woman and her partner are helped to prioritise their objectives on the basis of information given in a caring and sympathetic manner.

The issues

Maternal survival is usually of paramount importance, and doctors would normally wish to offer the same treatment they would give to a woman who is not pregnant. However, other factors must be considered, such as the effect of pregnancy on the disease process and vice versa. The impact of treatment on the fetus must also be borne in mind as this may result in fetal demise, congenital abnormalities, or failure of development in utero. In addition, there may be long term risk to the fetus after birth if it is affected by metastatic tumour.

The gestational age at which the problem arises is important, not just from the point of view of risks of treatment but because the doctor may wish to delay treatment until fetal viability is reached—so long as this does not compromise maternal survival. There may be circumstances in which the couple would wish to place fetal survival above maternal outcome—particularly if they have moral objections to termination or if the prognosis for the mother is so poor that further treatment is unlikely to influence the course of the disease.

Fortunately, malignant disease in pregnancy is uncommon, but this rarity may cause problems when it does arise because doctors may not have reliable information about some of the issues. In this case, the mother presented with metastatic malignant melanoma at 12 weeks of pregnancy. Sutherland et al reported that malignant melanoma was affected by hormones, and was stimulated by increasing oestrogen and progesterone concentrations in pregnancy.[1] However, MacKie et al did not find any adverse effect of pregnancy on the disease.[2] On balance, there does not seem to be sufficient evidence to recommend termination of pregnancy in these cases.

The mother's median survival with treatment was about six months, and the time until fetal viability would be reached was between four and five months.

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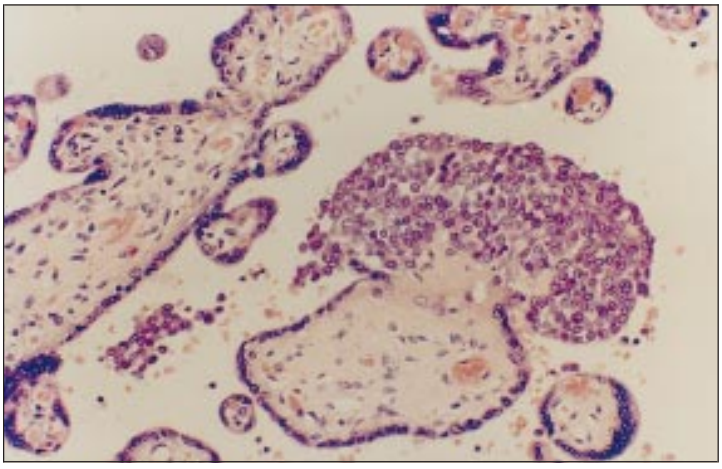

Haematoxylin and eosin stained section of placenta showing deposit of malignant melanoma within the maternal intervillous space, invading into core of the villus. Immunostaining for S100 protein and HMB45 was positive, and human chhorionic gonadotropin negative in the tumour cells

The risks to the fetus of thoracic radiotherapy and general anaesthesia for surgical treatment were small, and data suggested that it would not be affected adversely by the preferred drug. Indeed, it is possible that this treatment would reduce the risk of the fetus being affected by metastatic disease.

Recommendation

In this case information on both parents' views on termination of pregnancy, as well as the father's feelings about the probability that he would be a single parent from early in the child's life, is not reported. Assuming that the parents found this scenario acceptable, and they were prepared to take the small but statistically significant risk that the fetus might develop metastatic disease after birth, I would not have recommended termination of pregnancy to them. I would have treated the patient as I would a woman who was not pregnant in the hope that she would survive for long enough to experience some joy from her baby.

1 Sutherland CM, Wittliff J, Mabie WC. The effect of pregnancy on hormone levels and receptors in malignant melanoma. *J Surg Oncol* 1983;22:191-2.
2 MacKie RM, Bufalino R, Morabito A, Sutherland C, Cascinelli N. Lack of effect of pregnancy on outcome of melanoma. *Lancet* 1991;337:653-5.

Commentary: Self interest is not the sole legitimate basis for making decisions

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Treating cancer in pregnancy presents the patient and doctor with difficult medical, ethical, and, at times, even legal questions. Should the pregnancy be terminated? How best should the cancer be treated? How should potential benefits of treatment to the mother be balanced against risks to the fetus?

Texts on bioethics help little

Little guidance is found in publications on bioethics. Discussion to date has focused on cases in which a mother has refused a potentially life saving treatment for the fetus, for example, caesarian section.[1] The best known case is that of Angela Carter, a terminally ill cancer patient who was 26.5 weeks pregnant.[2] Close to death, Carter refused a caesarian section and demanded that comfort measures be continued, even if the delay in surgery resulted in the death of her fetus. The hospital consulted the court, which ordered that a caesarian section be performed and, unfortunately, neither Carter nor her child survived. Review by a higher court found that the court erred in its decision: "We hold that in virtually all cases the question of what is to be done is to be decided by the patient—the pregnant woman—on behalf of herself and the fetus. If the patient is incompetent … her decision must be ascertained through … substituted judgement.[3]"

The case at hand is the mirror image of the Carter case. We are told that the patient determined to continue with the pregnancy. Her actions bespeak a willingness to sacrifice her own comfort, and perhaps her chances of survival, to protect her unborn child. Even when she developed bone metastases she was reluctant to use analgesics. Continuing the pregnancy precluded treatment options such as high dose or multiagent chemotherapy, which is associated with higher response rates than chemotherapy with a single agent.[4]

Selfless decisions in others make us uncomfortable

Decisions in which one person sacrifices her own well-being for the sake of a loved one, a fetus in this case, make us uncomfortable. The temptation is to regard these decisions as not voluntary, as the result of "internal coercion."[5] This temptation ought to be resisted. The problem is not with the decision as such but rather with the prevalent view of human agency in bioethics that proceeds as if self interest is the only legitimate basis for decision making. The fact is that people make sacrifices for loved ones all the time: parents get by with less so their children may go to a better school, and spouses turn down lucrative job offers to remain with their mate. Our interests, and those of the patient in this case, therefore comprise both self interest and interest with regard to others. The patient's decision to proceed with the pregnancy is thus voluntary and valid.

A muted victory

Whatever moral discomfort we might feel in such cases in general is alleviated by the particular circumstances of this case. There is no convincing evidence that therapeutic abortion improves the cure rate of melanoma in pregnancy.[6] Dacarbazine is the most effective single agent regimen, and can be safely given in the second and third trimesters. Furthermore, while high dose and multiagent regimens are promising, none have yet been proved better than dacarbazine alone in a prospective randomised controlled trial.[4] Finally, no currently available regimen is likely to provide cure or even long term survival. In this context, salvaging a healthy child seems like a victory, albeit a muted one, for the mother and her doctors.

1 Mahowald MB. *Women and children in health care: an unequal majority.* New York: Oxford University Press, 1993:131-47.
2 Annas GJ. Foreclosing the use of force: AC reversed. *Hastings Center Report* 1990;20:27-9.
3 *In re: AC.* District of Columbia Court of Appeal, April 26, 1990.
4 Houghton AN, Meyers ML, Chapman PB. Medical treatment of metastatic melanoma. *Surg Clin N Am* 1996;76:1343-4.
5 Siegler M, Lantos JD. Commentary: ethical justification for living donor transplantation. *Cambridge Q Healthcare Ethics* 1992;1:320-5.
6 Kjems E, Krag C. Melanoma and pregnancy. *Acta Oncologica* 1993;32:371-8.

Commentary: Management of the patient

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Because of the progressive metastases, systemic chemotherapy was started with single agent dacarbazine (250 mg/m^2 given intravenously for three days every 21 days). After two courses, which were tolerated well, metastatic spread halted. However, at 31 weeks' gestation the patient's back pain increased and was not relieved by opioid analgesics. She became confused and was hypercalcaemic (calcium 3.04 mmol/l). An elective caesarian section was performed and a live girl (1.22 kg) was delivered. Unfortunately, the mother's condition deteriorated and she died four days later. Histological examination of the placenta showed evidence of melanoma deposits, which again stained positive for S100 and HMB45. Metastases seemed to breach the single layer of syncytial cells and extend into the chorionic villous space in places. One year later the infant remains well and has no signs of metastatic melanoma.

In retrospect—ethical and clinical issues

Whether pregnancy influences the natural history of malignant melanoma has been debated. Primary melanomas in pregnant women were thicker than melanomas in matched control women who were not pregnant, but whether this was because of late diagnosis or hormonal or growth factor stimulation during pregnancy is unclear.[1] When corrected for tumour thickness, no adverse effect of pregnancy on overall survival in women of childbearing age treated for stage I primary cutaneous disease has been shown.[1] However, patients with metastatic melanoma confined to the regional lymph nodes (stage II) who have disease recurrence or who need treatment during pregnancy may have a shorter survival than either nulliparous or parous women with no disease recurrence during pregnancy.[2]

Difficult ethical and clinical issues arise. Firstly, the question of terminating the pregnancy may be raised in light of a median survival of only six months in these patients. The expectant mother may become seriously ill before term, putting the life of the fetus at risk, or she may die soon after delivery, leaving a child without a mother. Secondly, cancer treatment may affect the fetus. In our patient the risk of radiotherapy was considered low. In addition, dacarbazine is the most active chemotherapeutic agent in melanoma and can be given safely during the second and third trimesters. In Hodgkin's disease, where dacarbazine was used as part of the regimen, no long term effects were seen in children followed for up to 19 years.[3] Finally, the risk of transplacental spread of melanoma to the fetus has been perceived to be low up to now.[4] In a recent report of 16 cases of placental metastases, however, 25% of the infants developed metastatic melanoma (mainly skin and liver) at 1-8 months of age, with a mortality of 100%.[5] Maternal factors associated with an unfavourable outcome for the infant were: age less than 30 years, nodal metastases before pregnancy, primiparity, onset of disease more than three years before pregnancy, more than three sites of metastases before the third trimester, and maternal death within one month of birth.

All these issues need to be considered when counselling women who develop regional (stage III) or metastatic (stage IV) recurrence of malignant melanoma during the early stages of pregnancy, especially in view of the difficult clinical and ethical decisions which may need to be taken if they develop progressive disease.

1 MacKie RM, Bufalino R, Morabito A, Sutherland C, Cascinelli N. Lack of effect of pregnancy on outcome of melanoma. *Lancet* 1991;337:653-5.
2 Shiu MH, Schottenfeld D, Maclean B, Fortner JG. Adverse effect of pregnancy on melanoma. *Cancer* 1976;37:181-7.
3 Aviles A, Diaz-Maqueo JC, Talavera A, Guzman R, Garcia EL. Longterm follow-up of 43 children exposed to chemotherapy in utero. *Am J Hematol* 1991;36:243-8.
4 Ross MI. Melanoma and pregnancy: prognostic and therapeutic considerations. *Cancer Bull* 1994;46:412-7.
5 Anderson JF, Kent S, Machin GA. Maternal malignant melanoma with placental metastases: a case report with literature review. *Pediatric Pathol* 1989;9:35-42.

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Fifty years ago

The new NHS: Statement by the B.M.A. Council to every member of the medical profession

We are now on the eve of a decision of the profoundest importance to the public and to the medical profession. For years the British Medical Association has been working for the extension, improvement, and consolidation of the country's health services, publishing its constructive proposals in a series of reports. It is now confronted with an Act of Parliament directed to the establishment of a comprehensive health service but embodying forms of organisation which are in conflict with the principles of the profession. The conflict is based on the profession's conviction that the Act leads unmistakably towards a whole-time State medical service, and that such a service would be harmful to medicine. This conviction is strengthened by the knowledge that the Act of 1946 is in the hands of those who profess as their objective a whole-time salaried State medical service.

We have sought a number of changes, some of principle, some of detail. The answer has been a refusal to modify one word of the Act. The Council recognises that some points of the profession's case make a stronger appeal to some members of the profession than to others. But it firmly believes that, viewed as a whole, the Act in its present form is in conflict with the best interests of the community and the profession.

After years of discussion the time has come for the profession to translate words into actions. The issue is one not of money or compensation but of the intellectual freedom and integrity of a great profession. The Council of the Association will abide by the result of the plebiscite, as defined on the plebiscite form. It would be lacking in its duty, however, if it did not make abundantly clear to every member of the profession its carefully considered and determined view that the profession should not take service under the Act in its present form. (*BMA statement*, 31 January 1948, p 207. See also editorial by Gordon Macpherson, 3 January 1998, p 6.)

The new genetics

Genetic testing and public policy

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This is the last of four articles discussing the broader implications of advances in genetics

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The increasing rate of discovery of genes related to disease and the development of tests for them has fostered the idea that healthy people will be able to prevent future disease by undergoing genetic testing. The genetics of many diseases are such that tests have only a limited ability to predict the clinical outcome accurately. Nevertheless, the benefits of some predictive genetic tests can be substantial, such as screening newborns for phenylketonuria and sickle cell anemia and testing of older children at risk of familial medullary thyroid carcinoma and multiple endocrine neoplasia type 2a.[1] The fact remains that relatively few interventions have yet been devised to improve the outcome of most mendelian disorders.[2] When no treatments are available, genetic testing can be used to avoid the conception or birth of affected offspring. Carrier screening in Sardinia, Cyprus, and elsewhere in the Mediterranean has led to an appreciable reduction in the birth of infants with thalassaemia through the use of prenatal diagnosis in couples at high risk and their selective termination of affected fetuses.[3]

Genetic testing (box), including prenatal testing, also carries the risks of inducing psychological sequelae[4] and of making individuals vulnerable to discrimination and diminishing their privacy. Additional benefits of testing in refining clinical diagnosis and tailoring treatent may be in the offing,[5] but these remain to be shown.

Summary points

- The genetic components of many diseases are responsible for the predictive limitations of genetic tests
- The validity and benefits of predictive genetic tests need to be established before these tests enter clinical use
- Adverse social consequences of genetic tests, including discrimination and possible breaches of confidentiality, are barriers to testing; policies to minimise them need to be developed before testing will be widely accepted
- Laboratories performing genetic tests require special quality assurance procedures. Further assurance of the quality of pretest and post-test education and counselling is also needed
- Government policies are needed to assure the safe and effective use of genetic tests

Government involvement

Both the American and British governments have recognised at least some of these problems, but solutions have been slow in coming. The United States started earlier to create a structure to consider the problems, but at present no federal committee is dedicated to addressing issues of genetic testing (box). In its final report, the Task Force on Genetic Testing reviewed many of the problems of genetic testing and laid out specific recommendations[6]; the Secretary of Health and Human Services is considering how they should be implemented. The major stakeholders in genetic testing were represented on the task force.

In Britain, in response to the House of Commons Select Committee on Science and Technology,[7–9] the Conservative government set up two committees (box). Both committees contain clinical geneticists, other professionals concerned with genetic applications, media representatives, and consumers. Each committee has now addressed one issue in genetic testing.

Predicting genetic risks

Without sufficient data, there is no assurance that genetic tests will predict disease accurately. Although the quality of test performance is a factor, the genetics of the disorder often explains most of the difficulty. Variable expressivity, incomplete penetrance, and genetic heterogeneity all reduce the ability of genetic tests to predict future disease accurately, even when single genes have a prominent role (box). For many common disorders, including insulin dependent diabetes, hypertension, and schizophrenia, it seems likely that in the vast majority of cases, no single gene will be prominent but multiple genes will be implicated. However, different combinations of alleles at multiple loci and environmental factors will each be capable of increasing the risk of disease. Testing for any one of the possible combinations, which is not yet possible, will account for only a small proportion of patients. Unless a test detects most of the necessary alleles, it will have low predictive value.

Despite these limitations, exaggerated claims are made for genetic testing,[21] and providers and the public are given incomplete and sometimes misleading information about tests (B Wilfond, unpublished data).[6 22]

In the United States, the Task Force on Genetic Testing recommends requiring organisations developing new genetic tests to submit protocols for establishing the clinical validity (including sensitivity and positive predictive value) and utility of the tests to institutional review boards,[6] equivalent to local research ethics committees in the United Kingdom. Once data are collected, the task force calls for review of the data by an independent body including consumer representatives. The task force recommends using the results of review to consider whether the test should be introduced into practice and become the "standard of care." The Food and Drug Administration will perform the review for genetic tests marketed as tangible products, such as kits. For genetic tests marketed as services, as many genetic tests are, the Food and Drug Administra-

AKG PHOTOS

A person's genetic test results may have bearing on relatives' risks of future disease

tion has elected not to perform the review, although it has the legal authority to do so.[6] The Task Force on Genetic Testing indicated it was "concerned about the quality of information made available to providers and consumers" and emphasised the role of the provider in ensuring that potential test users receive accurate information.[6]

In the United Kingdom, the terms of reference of the Advisory Committee on Genetic Testing include: "to establish requirements, especially in respect of efficacy and product information to be met by manufacturers and suppliers of genetic tests."[12] This could lead the committee to examine the need for review of genetic testing protocols by research ethics committees. It has published a policy for genetic testing without the involvement of a doctor; this was prompted by a company that offers cystic fibrosis carrier screening directly to the public for a fee of £95 per couple. The policy states that carrier testing for inherited recessive disorders with childhood onset, like cystic fibrosis, can be obtained directly by individuals without the intervention of a healthcare provider unless there is a family history of the disorder.[12] (On the matter of direct testing, the United States's Task Force on Genetic Testing proceeds more cautiously: "The Task Force discourages advertising or marketing of predictive tests to the public."[6])

Improving laboratory quality

In both the United States and the United Kingdom it is generally agreed that laboratories performing clinical tests should be subject to external quality control. In the United States, the Clinical Laboratory Improvement Amendments passed by Congress in 1988 provide some control but none specifically for genetic tests. Laboratories can voluntarily participate in proficiency testing and inspection programmes for genetic tests offered by professional associations. A few laboratories do not participate in any proficiency testing programmes.[23] The Task Force on Genetic Testing recommends the creation of a genetics specialty under the amendments. Once it is established, every laboratory performing genetic tests will have to comply with the specialty requirements.

In the United States, most clinical laboratories are private and many are run for profit, but most of those in the United Kingdom are associated with health authorities and are subject to Department of Health rules. The Clinical Molecular Genetics Society established a quality assurance scheme, now operated by an independent body. By 1995 it was assessing the quality of testing for eight specific genetic disorders.[24] Assessment has now been considerably extended to more diseases. A proposed European Union directive on in vitro diagnostic medical devices provides greater assurance of the quality of tests marketed as kits and reagents.[25] As is the case in the United States, this Directive does not extend to tests provided as services.

The therapeutic gap

It has proved far easier for scientists to develop tests for genetic diseases than to devise effective interventions to prevent manifestations in people who are born affected. This therapeutic gap has already lasted over 10 years for Huntington's disease, Duchenne muscular dystrophy, and cystic fibrosis. For all three of these disorders, prenatal diagnosis and termination of pregnancy can be used to avoid the birth of an affected child. This option is not acceptable to people who oppose abortion on religious or moral grounds. Among those who do not oppose abortion entirely, questions still arise about pregnancy termination for adult onset disorders, like Huntingdon's disease, or for disorders whose prognosis is improving, like cystic fibrosis, and for which gene therapy is already being

Definition of genetic tests

"The analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect inherited disease-related genotypes, mutations, phenotypes, or karyotypes, for clinical purposes. Such purposes include predicting risk of disease, identifying carriers, establishing prenatal and clinical diagnosis or prognosis. Prenatal, newborn, and carrier screening, as well as testing in high risk families, are included. Tests for metabolites are covered only when they are undertaken with high probability that an excess or deficiency of the metabolite indicates the presence of inherited mutations in single genes" (Task Force on Genetic Testing[6]).

This definition excludes tests conducted purely for research, tests for somatic (as opposed to inherited) mutations, and testing for forensic purposes; it also excludes eliciting genetic information from a family history.

Government responses to the implications of genetic testing

In the United States, a joint working group of the National Institutes of Health and the Department of Energy on ethical, legal, and social implications of human genome research was created in 1990.[10] It has now been disbanded. This group created two task forces to make policy recommendations on the implications of genetic testing.[6 11] In the United Kingdom, a non-statutory Advisory Committee on Genetic Testing was created in 1996. It has issued a report on offering genetic tests direct to the public.[12] The government established the Human Genetics Advisory Commission in 1996 to review scientific progress, report on issues that have "social, ethical, and/or economic consequences, for example in relation to public health, insurance, patents and employment" and to "advise on ways to build public confidence in, and understanding of, the new genetics."[13] It has recently published a report on the implications of genetic testing for insurance.[14]

Genetic limitations of genetic testing

For single gene (mendelian) diseases, the finding that a healthy person possesses a disease causing genotype will be highly predictive that future disease will occur, but:

- Expression cannot be forecast with great accuracy (variable expressivity). For instance, the severity of the lung disease in cystic fibrosis cannot be predicted very well by the genotype[15]
- Not all disease causing genotypes will be detected because many mendelian diseases can each result from several different inherited mutations at one gene locus (allelic diversity) or several loci (genetic or locus heterogeneity). Often, current technology cannot detect all of them. Over 600 mutations cause cystic fibrosis,[15] but the best technology available for clinical testing can detect no more than 90% of white carriers; the percentage is smaller in other racial groups

In contrast with the mendelian diseases, in common disorders, usually of adult onset, in which a genetic role has been identified:

- Inheritance of a relatively rare mutation may increase risk but does not always result in the disease (incomplete penetrance). For instance, the lifetime risk of breast cancer among a relatively unselected group of Ashkenazi Jewish women with the susceptibility conferring BRCA1 or BRCA2 alleles is less than 60%.[16] The risk is higher when multiple cases occur in families, suggesting that other gene loci as well as environmental factors influence the appearance of disease
- Genetic polymorphisms, which occur in 1% or more of the population, may contribute to the appearance of disease, but most people with the risk-increasing form of the polymorphism will never develop the diseases. For instance, fewer than 30% of people with the apolipoprotein E4 polymorphism develop Alzheimer's disease[17]
- Alleles of single genes play a significant role in only a small proportion (usually less than 5%) of all people with common diseases. This is the case for breast[18] and colon cancer[19] and Alzheimer's disease[20]

attempted. Marteau and Croyle have discussed issues related to the therapeutic gap.[5]

Although treatments are available for some of the common, complex disorders, such as breast and colon cancer, their safety and effectiveness in asymptomatic people found to have genetic susceptibilities to these disorders have not been established.[26 27] In families in which disease is known to be associated with a specific inherited susceptibility mutation, a negative test result greatly lowers the chance of future disease and could help dispel concerns about the need for special surveillance or prophylactic surgery.[28] In the absence of a known inherited susceptibility mutation in the family, a negative test result for genetic susceptibility to a common disorder affects risk estimates negligibly.

Interest in some predictive genetic tests wanes as people are told of their limitations,[29 30] but people are not always fully informed. The American task force emphasises that information on the risks and benefits of tests must be presented "fully and objectively" and that informed consent should be obtained.[6] Genetic testing could be inflicted on ethnic minorities when they are not informed of the implications of testing.[31] In the United Kingdom, there is evidence that patients with haemoglobinopathies, many of whom come from minority groups, are not always looked after in the best possible way.[32]

Discrimination and breaches of confidentiality

In the United States, some people cannot afford health insurance and others are denied coverage (or covered only if they can pay very high premiums) because of past illness. Asymptomatic people have been denied insurance (or charged higher premiums) because they were at risk of genetic conditions,[33–35] although it is difficult to gauge the extent of the problem. The ability of genetic tests to predict future risks could also be used to deny insurance. The solution to this problem has taken two forms, both involving legislation. The first is to deny health insurers the opportunity to use genetic test results, or knowledge that a person has had a genetic test, to deny insurance to healthy people. In some cases, the denial extends to genetic information as embodied in a family history. The second is to deny health insurers access to genetic test results or information without the explicit consent of the person being tested even though insurers will often pay for these tests. Both approaches would help reduce people's apprehension that having genetic tests would cause them to lose their insurance.[36] Over the opposition of the insurance industry, 26 states in the United States have passed laws barring health insurance discrimination on the basis of genetic testing or information.[37 38] At the federal level, the Health Insurance Portability Act and Accountability of 1996 specifically prohibits the use of genetic information to deny group health insurance coverage when workers switch from one job to another.[37] The second approach, which is part of the bigger picture of assuring the privacy of medical records in general, is currently being explored at the federal level.

With the NHS assuring everyone some care in the United Kingdom, more attention has been focused on discrimination in life insurance. The recently published Association of British Insurers Code of Practice addresses these issues for all types of insurance (box).[39] Refusal to hire workers because testing shows they are at increased risk of disease is also a concern. American employers can no longer decline to hire someone on the basis of genetic information as long as the person can perform the essential functions of the job without threat to himself or herself or to others. After workers are employed, employers can exclude from their health insurance disorders whose future occurrences are predicted by genetic testing, as long as there is an actuarial basis for doing so.[41] Thus far in the United Kingdom terms of employment seem not to have been a constraint on health care, nor has health care constrained people to refrain from moving jobs. Only one employer's genetic screening programme could be identified in 1993 and it seemed to meet the very stringent conditions that had been suggested by the Nuffield Council on Bioethics.[42]

A person's genetic test results may have a bearing on relatives' risks of future disease. Until recently, there seemed to be a strong consensus in both the United States and Britain that health providers had a duty to protect the confidentiality of genetic information obtained from patients and not to convey it to relatives

except when, in the most dire circumstances, the tested relative refused to do so.[42 43] In a recent case in New Jersey, an appeals court seemed to take a more permissive view: when a woman with familial adenomatous polyposis brought suit against the estate of her deceased father's deceased doctor for not warning relatives of their risk 20 years earlier, the court remanded the case for trial to determine whether the duty to warn relatives was breached.[44] Meanwhile, the House of Commons Select Committee veered in the other direction, maintaining that if counselling cannot persuade someone to share genetic risk information with his or her relatives, then the individual's decision to withhold information should be respected.[7] The law on this matter in the United States is far from settled. The Task Force on Genetic Testing emphasised that in offering genetic tests "providers must make clear that they will not communicate results to relatives, except in extreme circumstances," which the provider should define.[6]

Conclusions

Both the British and American governments have been slow to respond to issues raised by the potential spread of genetic testing. Current policies do not assure that sufficient data on the predictability of genetic tests will be collected before they enter clinical practice, that laboratory quality will be high once tests are used clinically, and that test results will be useful to those who are tested. Confidentiality of test results and specimens, psychological problems, and discrimination based on test results are likely to be problems. Once these problems are satisfactorily addressed, the public will be assured that the genetic tests available will truly be to their benefit.

In both countries, the efforts to address the problems of genetic testing have started with non-statutory advisory committees. The United Kingdom is now further advanced than the United States in establishing a governmental framework; two 1997 reports[12 14] marked the first use of that framework. The United States has considered many of the substantive issues in greater depth, as evidenced by the report of the Task Force on Genetic Testing,[6] recent analyses and policy statements regarding genetic discrimination in health insurance[45] and employment,[46] and the passage of laws at the state and federal level to reduce the danger of genetic discrimination. These issues cut across government agency and departmental lines, making action difficult. New legislation may be needed. Each country could benefit from examining the course taken by the other.

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Genetic testing and life insurance

Early in 1997, the Association of British Insurers adopted a two year moratorium on asking people to take genetic tests when applying for life insurance. The association also said that genetic test results will not be used in providing life insurance of up to £100 000 that is directly linked to new applications for home mortgages; family history and other medical information will continue to be used. Decisions about use of genetic tests for other policies are up to individual companies. The association will continue to expect people to report the results of reliable and relevant genetic tests, and these results can affect the premium if the result indicates an increased risk.[39] Some major life insurance companies, however, have announced they will not require such reporting.[40]

The Human Genetics Advisory Commission has concluded that "it is unlikely that actuarially important genetic predictions of common causes of adult death will be available and validated for some time to come. . . . On balance . . . the life insurance industry could currently stand limited adverse selection. . . . Concern about the perceived threat of discrimination by insurers . . . remains an important issue and . . . the Advisory Committee on Genetic Testing should keep the situation under review. . . . We recommend that for the time being the insurance industry should respect a moratorium on requiring disclosure of results of genetic tests."[14]

1 Holtzman NA, Murphy PD, Watson MS, Barr PA. Predictive genetic testing: from basic research to clinical practice. *Science* 1997;278:602-5.
2 Treacy E, Childs B, Scriver CR. Response to treatment in hereditary metabolic disease: 1993 survey and 10-year comparison. *Am J Hum Genet* 1995;56:359-67.
3 Cao A, Saba L, Galanello R, Rosatelli MC. Molecular diagnosis and carrier screening for β thalassemia. *JAMA* 1997;278:1273-7.
4 Marteau TM, Croyle RT. Psychological responses to genetic testing. *BMJ* 1998;316:693-6.
5 Bell J. The new genetics in clinical practice. *BMJ* 1998;316:618-20.
6 Task Force on Genetic Testing. *Promoting safe and effective genetic testing in the United States. Final report.* Baltimore: Johns Hopkins University Press (in press).
7 House of Commons Select Committee on Science and Technology. *Third report. Human genetics: the science and its consequences.* London: HMSO, 1995. (HC41.)
8 Dickson D. MPs challenge rejection of genetics panel. *Nature* 1996;379:195.
9 *Government response to the Third Report, Science and Technology Committee, House of Commons.* London: HMSO, 1996. (Cm 3061.)
10 Juengst ET. Self-critical federal science? The ethics experiment within the U.S. Human Genome Project. *Social Philosophy and Policy* 1996;13:63-95.
11 Task Force on Genetic Information and Insurance. *Genetic Information and Health Insurance.* Rockville, MD: National Institutes of Health, 1993. (Publication 93-3686.)
12 Advisory Committee on Genetic Testing. *Code of practice and guidance on human genetic testing services supplied direct to the public.* London: HMSO, 1997.
13 *Human Genetics Advisory Commission.* London: Office of Science and Technology, 1997.
14 Human Genetics Advisory Commission. *The implications of genetic testing for insurance.* London: Office of Science and Technology, 1997.
15 Cutting G. Cystic fibrosis. In: Rimoin DL, Connor JM, Pyeritz RE, eds. *Principles and practice of medical genetics.* London: Churchill Livingstone, 1996.
16 Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997;336:1401-8.
17 Seshadri S, Drachman DA, Lippa CF. Apolipoprotein E e4 allele and the lifetime risk of Alzheimer's disease. What physicians know, and what they should know. *Arch Neurol* 1995;52:1074-9.
18 Healy B. BRCA genes—bookmaking, fortune telling, and medical care. *N Engl J Med* 1997;336:1448-9.
19 Toribara NW, Sleisenger MH. Screening for colorectal cancer. Current concepts. *N Engl J Med* 1995;332:861-7.
20 Morrison-Bogorad M, Phelps C, Buckholtz N. Alzheimer disease research comes of age. The pace accelerates. *JAMA* 1997;277:837-40.
21 Holtzman NA. Testing for genetic susceptibility: what you see is not what you get. *Accountability in Research* 1996;5:95-101.
22 Cho MK, Arruda M, Holtzman NA. Informational materials about genetic tests. In: Holtzman NA, Watson MS, eds. *Task force on genetic testing: promoting safe and effective genetic testing in the United States.* 1997:125-35.
23 Holtzman NA, Hilgartner S. State of the art of genetic testing in the United States: survey of biotechnology companies and nonprofit clinical laboratories and interviews of selected organizations. In: Holtzman NA, Watson MS, eds. *Promoting safe and effective genetic testing in the United States. Final report of the Task Force on Genetic Testing.* Bethesda: National Institutes of Health, 1997:99-124.
24 Mountford R. *Molecular genetics quality assurance. 1995 report of the Molecular Genetics Quality Assurance Committee.* Liverpool: Liverpool Women's Hospital, 1996.
25 Commission of the European Communities. *Proposal for a European Parliament and Council Directive on in vitro diagnostic medical devices.* Brussels: CEC, 1995..
26 Burke W, Petersen G, Lynch P, Botkin J, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. *JAMA* 1997;277:915-9.
27 Burke W, Daly M, Garber J, Botkin J, Kahn MJE, Lynch P, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. *JAMA* 1997;277:997-1003.
28 Holtzman NA. Testing for genetic susceptibility to common cancers: clinical and ethical issues. *Adv Oncol* 1997;13:9-15.
29 Lerman C, Biesecker B, Benkendorf JL, Kerner J, Gomez-Caminero A, Hughes C, et al. controlled trial of pretest education approaches to enhance informed decision-making for BRCA1. *J Natl Cancer Inst* 1997;89:148-57.
30 Holtzman NA, Bernhardt BA, Doksum T, Helzlsouer KA, Geller G. Education about BRCA1 testing decreases women's interest in being tested. *Am J Hum Genet* 1996;59:A56.

31 Press NA, Browner CH. Collective silences, collective fictions: how prenatal diagnostic testing became part of routine prenatal care. In: Rothenberg KH, Thomson EJ, eds. *Women and prenatal testing. Facing the challenges of genetic technology.* Columbus: Ohio State University Press, 1994:201-18.
32 Department of Health. *Sickle cell, thalassemia and other hemoglobinopathies. Report of a Working Party of the Standing Medical Advisory Committee.* London: Department of Health, 1993.
33 Billings PR, Kohn MA, de Cuevas M, Beckwith J, Alper JS, Natowicz MR. Discrimination as a consequence of genetic testing. *Am J Hum Genet* 1992;50:476-82.
34 Geller LN, Alper JS, Billings PR, Barash CI, Beckwith J, Natowicz MR. Individual, family, and societal dimensions of genetic discrimination: a case study analysis. *Sci Eng Ethics* 1996;2:71-88.
35 Lapham EV, Kozma C, Weiss JO. Genetic discrimination: perspectives of consumers. *Science* 1996;274:621-4.
36 Lerman C, Narod S, Schulman K, Hughes C, Gomez-Caminero A, Bonney G, et al. BRCA1 testing in families with hereditary breast-ovarian cancer. A prospective study of patient decision making and outcomes. *JAMA* 1996;275:1885-92.
37 Rothenberg KH. Genetic information and health insurance: state legislative approaches. *J Law Med Ethics* 1995;23:312-9.
38 Pear R. States pass laws to regulate use of genetic testing. *New York Times* 1997 October 18:A1-9.
39 Association of British Insurers. *Genetic testing: ABI code of practice.* London: ABI, 1997.
40 Genetic testing splits insurers. *Financial Times* 1997 March 19:22.
41 Holtzman NA. Medical and ethical issues in genetic screening—an academic view. *Environ Health Perspect* 1996;104:987-90.
42 Nuffield Council on Bioethics. *Genetic screening: ethical issues.* London: The Council, 1993.
43 Andrews L, Fullarton JE, Holtzman NA, Motulsky AG, eds. *Assessing genetic risks: implications for health and social policy.* Washington, DC: National Academy Press, 1994.
44 Safer v Pack. 1996;677 2D 1188 NJ.
45 Hudson KL, Rothenburg KH, Andrews LB, Kahn MJE, Collins FS. Genetic discrimination and health insurance: an urgent need for reform. *Science* 1995;270:391-3.
46 Rothenberg KH, Fuller B, Rothstein M, Duster T, Kahn MJE, Cummingham R, et al. Genetic information and the workplace: legislative approaches and policy challenges. *Science* 1997;275:1755-7.

Coping with loss

Bereavement in adult life

Colin Murray Parkes

This is the first in a series of 10 articles dealing with the different types of loss that doctors will meet in their practice

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Doctors are well acquainted with loss and grief. Of 200 consultations with general practitioners, a third were thought to be psychological in origin; of these, 55—a quarter of consultations overall—were identified as resulting from types of loss.[1] In order of frequency the types of loss included separations from loved others, incapacitation, bereavement, migration, relocation, job losses, birth of a baby, retirement, and professional loss. After a major loss, such as the death of a spouse or child, up to a third of the people most directly affected will suffer detrimental effects on their physical or mental health, or both.[2] Such bereavements increase the risk of death from heart disease and suicide as well as causing or contributing to a variety of psychosomatic and psychiatric disorders. About a quarter of widows and widowers will experience clinical depression and anxiety during the first year of bereavement; the risk drops to about 17% by the end of the first year and continues to decline thereafter.[2] Clegg found that 31% of 71 patients admitted to a psychiatric unit for the elderly had recently been bereaved.[3]

Despite this there is also evidence that losses can foster maturity and personal growth. Losses are not necessarily harmful.

Yet the consequences of loss are so far reaching that the topic should occupy a large place in the training of health care providers—but this is not the case. One explanation for this omission is the assumption that loss is irreversible and untreatable: there is nothing we can do about it, and the best way of dealing with it is to ignore it. This attitude may help us to live with the fact that, despite modern science, 100% of our patients still die and that before they die many will suffer lasting losses in their lives. Sadly, it means that, just when they need us most, our patients and their grieving relatives find that we back away.

Summary points

- Losses are a common cause of illness; they often go unrecognised
- Conflicting urges lead to a variety of expressions of grief; even so there is a pattern to the process of grieving
- A knowledge of the factors that predict problems in bereavement enables these to be anticipated and prevented
- Grief may be avoided or it may be exaggerated and prolonged
- Doctors can help to prepare people for the losses that are to come
- People may need permission and encouragement to grieve and to stop grieving

Recent approaches to loss

A 1944 study of bereaved survivors of a night club fire focused attention on the psychology of bereavement, and led to the development of services for the bereaved and to other types of crisis intervention services.[4] It established grief as a distinct syndrome with recognisable symptoms and course, amenable to positive or negative influences. This, in turn, fuelled interest in the new fields of preventive psychiatry and community mental health. Elizabeth Kubler Ross's studies extended this understanding to dying people,[5] and helped to provide a conceptual framework for the humanitarian work of Dame Cicely Saunders and the other pioneers of the hospice movement.

More recently the improvements in palliative care have led to improvements in home care for the dying. Home care nurses have bridged the gap and general practitioners have had a central role, not only in caring for dying patients and their families but also in supporting people through many other losses. This is

The course of grief

- Numbness
- Pining
- Disorganisation and despair
- Reorganisation

the main theme of this series, which draws together authorities with special knowledge of the losses which afflict our patients and their families and looks at the practical implications for doctors.

The components of grief

Three main components affect the process of grieving. They include the urge to look back, cry, and search for what is lost, and the conflicting urge to look forward, explore the world that now emerges, and discover what can be carried forward from the past. Overlying these are the social and cultural pressures that influence how the urges are expressed or inhibited. The strength of these urges varies greatly and changes over time, giving rise to constantly changing reactions.

Most adults do not wander the streets crying aloud for a dead person. Bereaved people often try to avoid reminders of the loss and to suppress the expression of grief. What emerges is a compromise, a partial expression of feelings that are experienced as arising compellingly and illogically from within.

Much empirical evidence supports the claims of the psychoanalytic school that excessive repression of grief is harmful and can give rise to delayed and distorted grief—but there is also evidence that obsessive grieving, to the exclusion of all else, can lead to chronic grief and depression. The ideal is to achieve a balance between avoidance and confrontation which enables the person gradually to come to terms with the loss. Until people have gone through the painful process of searching they cannot "let go" of their attachment to the lost person and move on to review and revise their basic assumptions about the world. This process, which has been termed psychosocial transition, is similar to the relearning that takes place when a person becomes disabled or loses a body part.

The normal course of grief

Human beings can anticipate their own death and the deaths of others. Unlike the grief that follows loss, anticipatory grief increases the intensity of the tie to the person whose life is threatened and evokes a strong tendency to stay close to them.

Although the moment of death is usually a time of great distress, this is usually quickly repressed and, in Western society, the impact is soon followed by a period of numbness which lasts for hours or days. This is sometimes referred to as the first phase of grieving.[6] It is soon followed by the second phase, intense feelings of pining for the lost person accompanied by intense anxiety. These "pangs of grief" are transient episodes of separation distress between which the bereaved person continues to engage in the normal functions of eating, sleeping, and carrying out essential responsibilities in an apathetic and anxious way.

All appetites are diminished, weight is lost, concentration and short term memory are diminished, and the bereaved person often becomes irritable and depressed. This eventually gives place to the third phase of grieving, disorganisation and despair. Many find themselves going over the events which led up to the loss again and again as if, even now, they could find out what went wrong and put it right. The memory of the dead person is never far away and about a half of widows report hypnagogic hallucinations in which, at times of drowsiness or relaxation, they see or hear the dead person near at hand. These hallucinations are distinguished from the hallucinations of psychosis by the circumstances in which they arise and by their transience—they disappear as soon as the bereaved arouse themselves. A sense of the dead person near at hand is also common and may persist.

As time passes the intensity and frequency of the pangs of grief tend to diminish, although they often return with renewed intensity at anniversaries and other occasions which bring the dead person strongly to mind. Consequently the phases of grief should not be regarded as a rigid sequence that is passed through only once. The bereaved person must pass back and forth between pining and despair many times before coming to the final phase of reorganisation.

After a major loss such as the death of a loved spouse or partner, the appetite for food is often the first appetite to return. By the third or fourth month of bereavement the weight that was lost initially has usually returned, and by the sixth month many people have put on too much weight. It may be many more months before people begin to care about their appearance, and for sexual and social appetites to return. Most people will recognise that they are recovering at some time in the course of the second year.

Assessing the risk

Much research, in recent years, has enabled us to identify people at special risk after bereavement either because the circumstances of the bereavement are unusually traumatic or because they are themselves already vulnerable (box). These risk factors can give rise to complicated forms of grief that can culminate in mental illness. A

ADRIANA DORSETT

Factors increasing risk after bereavement

Traumatic circumstances
- Death of a spouse or child
- Death of a parent (particularly in early childhood or adolescence)
- Sudden, unexpected, and untimely deaths (particularly if associated with horrific circumstances)
- Multiple deaths (particularly disasters)
- Deaths by suicide
- Deaths by murder or manslaughter

Vulnerable people

General:
- Low self esteem
- Low trust in others
- Previous psychiatric disorder
- Previous suicidal threats or attempts
- Absent or unhelpful family

Specific:
- Ambivalent attachment to deceased person
- Dependent or inter-dependent attachment to deceased person
- Insecure attachment to parents in childhood (particularly learned fear and learned helplessness)

clear understanding of these factors will often enable us to prevent psychiatric disorder in bereaved patients.

Complicated grief

Bereavement has physiological as well as emotional effects (lower box). It also affects physical health: after bereavement, the immune response system is temporarily impaired[7 8] and there are endocrine changes such as increased adrenocortical activity and increases in serum prolactin and growth hormone,[2] as in other situations that evoke depression and distress.

A variety of psychiatric disorders can also be caused by bereavement, the commonest being clinical depression, anxiety states, panic syndromes, and post-traumatic stress disorder. These often coexist and overlap with each other, as they do with the more specific morbid grief reactions. These last disorders are of special interest for the light that they shed on why some people come through bereavement unscathed or strengthened by the experience while others "break down."

It is a paradox that people who cope with bereavement by repressing the expression of grief are more likely to break down later than are people who burst into tears and get on with the work of grieving. The former are more liable to sleep disorders, depression, and hypochondriacal symptoms resembling the symptoms of the illness that caused the bereavement ("identification symptoms"). Not all psychogenic symptoms, however, are a consequence of repressed or avoided grief. Some reflect the loss of security which often follows a major loss and causes people to misinterpret as sinister the normal symptoms of anxiety and tension.

At the other end of the spectrum of morbid grief are people who express intense distress before and after bereavement. Subsequently they cannot stop grieving and go on to suffer from chronic grief. This may reflect a dependent relationship with the dead person, or it may follow the loss of someone who was ambivalently loved. In the former case the bereaved person cannot believe that he or she can survive without the support of the person on whom they had depended. In the latter, their grief is complicated by mixed feelings of anger and guilt that make it difficult for them to stop punishing themselves ("Why should I be happy now that my partner is dead?").

Some degree of ambivalence is present in all relationships. To some degree its effects can be assuaged by conscientious care during the last illness, and many people will recall "We were never closer." If members the family have been encouraged and supported so that they have been able to care, and the death has been peaceful, anger and guilt are much less likely to complicate the course of grieving.

These two patterns of grieving often seem to occur in "avoiders" (people with a tendency to avoidance) and "sensitisers" (those with a tendency to obsessive preoccupation), respectively.[9]

Complications of bereavement

Physical
- Impairment of immune response system
- Increased adrenocortical activity
- Increased serum prolactin
- Increased growth hormone
- Psychosomatic disorders
- Increased mortality from heart disease (especially in elderly widowers)

Psychiatric

Non-specific:
- Depression (with or without suicide risk)
- Anxiety or panic disorders
- Other psychiatric disorders

Specific:
- Post-traumatic stress disorder
- Delayed or inhibited grief
- Chronic grief

Preventing and treating complicated grief

Doctors are in a unique position to help people through the turning points in their lives which arise at times of loss. In order to fulfil this role we need information and skills. One of our problems as caregivers is our ignorance of our patients' view of the world. Not only do we seldom know what they know or think they know about the situation they face, we do not even know how that situation is going to change their lives. It follows that we need to find out these things and, where possible, add to their knowledge or correct any misperceptions, taking care to use language that they can understand. (This is easier said than done when words like "cancer" and "death" mean different things to doctors than they do to most patients.) Above all, we should spend time helping them to talk through and to make sense of the implications of the information we have given. If need be, we should see them several times to facilitate this process of growth and change. General practitioners, because they are likely to know the person, are often well placed to provide this "trickle" of care. For most bereaved people the natural and most effective form of help will come from their own families, and only about a third will need extra help from outside the family.

Anticipatory guidance

Members of health care teams can often prepare people for the losses that are to come. People need time to

achieve a balance between avoidance and confrontation with painful realities, and we need to take this into account when we impart information that is likely to prove traumatic. One way is to divide the information that needs to be confronted into "bite sized chunks." Doctors do this when we break bad news a little at a time, telling a patient as much as we think he or she is able to take in. Patients seldom ask questions unless they are ready for the answers, and they will usually ask precisely what they want to know and no more. It follows that we should invite questions and listen carefully to what is asked rather than assuming that we know what the patient is ready to know. By monitoring the input of information, a person can control the speed with which they process that information.

Although a little anxiety increases the rate and efficiency with which we process information, too much anxiety slows us down and impairs our ability to cope, our thought processes become disorganised and we "go to pieces." Anything that enables us to keep anxiety within tolerable limits will help us to cope better with the process of change. If we are breaking bad news (box) it helps to do so in pleasant, home-like surroundings and to invite the recipient to bring someone who can provide emotional support. A few minutes spent putting people at their ease and establishing a relationship of trust will not only make the whole experience less traumatic for them but it will increase their chance of taking in and making sense of the information which we then provide.

Breaking bad news

- Consider social support (who to ask to be present)
- Consider setting (where to meet)
- Try to establish a relationship of mutual respect and trust
- Discover what the patient or the family knows or think they know already
- Invite questions
- Give information at a speed and in a language that will be understood
- Monitor what has been understood
- Recognise that it takes time to hear and understand bad news
- Give the patient or the family time to react emotionally
- Give verbal and non-verbal reassurance of the normality of their reaction
- Stay with the patient or the family until they are ready to leave
- Offer further opportunities for clarification, information, or support

Supporting bereaved people

A visit from the general practitioner to the family home on the day after a death has occurred enables us to give emotional support and to answer any questions about the death and its causes that may be troubling the family. Newly bereaved people often feel and behave, for a while, like frightened and helpless children and will respond best to the kind of support that is normally given by a parent. A touch or a hug will often do more to facilitate grieving than any words.

During the next few weeks bereaved people need the support of those they can trust. We can often reassure them of the normality of grief, explain its symptoms, and show by our own behaviour and attitudes that it is permissible to express grief. If we feel moved to tears at such times there is no harm in showing it. Bereaved people may need reassurance that they are not going mad if they break down, that the frightening symptoms of anxiety and tension are not signs of mortal illness, and that they are not letting the side down if they withdraw, for a while, from their accustomed tasks.

As time passes people may also need permission to take a break from grieving. They cannot grieve all the time and may need permission to return to work or do other things that enable them to escape, even briefly, from grief. It is only if they get the balance between confrontation and avoidance wrong that difficulties are likely to ensue.

The first anniversary is often a time of renewed grieving, but thereafter the need to stop grieving and move forward in life may create a new set of problems. People may need reassurance that their duty to the dead is done, as well as encouragement to face the world that is now open to them. The most important thing we have to offer is our confidence in their personal worth and strength. We should beware of becoming the "strong" doctor who will look after the "weak" patient for ever, but this does not mean that we become angry and dismissive, reprimanding the patient for becoming "dependent." In the end, most bereaved people come through the experience stronger and wiser than they went into it. It is rewarding to see them through.

Appendix

In the acute stages it is usually best to give support by personal contact, preferably in the client's home. Later the help of a group in which bereaved people can learn from each other, as well as a counsellor, may be helpful. Organisations such as Cruse Bereavement Care and the member organisations of the National Association of Bereavement Services may be able to provide either of these types of help. The Compassionate Friends (for bereaved parents), Lesbian and Gay Bereavement, Support after Murder and Manslaughter (SAMM), and the Widow-to-Widow programmes that exist in the United States and other parts of the world provide mutual help by bereaved people for others with the same types of bereavement.

Further reading

Markus AC, Parkes CM, Tomson P, Johnstone M. *Psychological problems in general practice.* Oxford: Oxford University Press, 1989.

Parkes CM. *Bereavement: studies of grief in adult life.* 3rd ed. Harmondsworth: Pelican, 1998.

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1 Clark S. Loss and grief in general practice: a pilot study. National convention of the Royal Australian College of General Practitioners, 1986.
2 Jacobs S. *Pathologic grief: maladaptation to loss.* Washington, DC: American Psychiatric Press, 1993.
3 Clegg F. Grief and loss in elderly people in a psychiatric setting. In: Chigier E, ed. *Grief and mourning in contemporary society.* Vol 1. *Psychodynamics.* London: Freund, 1988:191-8.
4 Lindemann E. The symptomatology and management of acute grief. *Am J Psychiatry* 1944;101:141.
5 Ross EK. *On death and dying.* London: Tavistock, 1970.
6 Bowlby J, Parkes CM. Separation and loss within the family. In: Anthony EJ, ed. *The child in his family.* New York: Wiley, 1970.
7 Bartrop RW, Lazarus L, Luckhurse E, Kiloh LG, Pennry R. Depressed lymphocyte function after bereavement. *Lancet* 1977;i:834-6.
8 Schleiffer SJ, Keller SE, Camerino M, Thornton JC, Stein M. Suppression of lymphocyte stimulation following bereavement. *JAMA* 1983: 250:374-7.
9 Horowitz, M. *Stress response syndromes.* Northvale, NJ: Aronson, 1986.

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