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Cancer in organ transplant recipients: part of an induced immune deficiency syndrome

Treatment of patients with renal failure by dialysis and renal transplantation has been one of the great contributions to healing. Nevertheless, the necessary use of immunosuppressive drugs has made the recipients susceptible to a wide variety of complications, most resulting from induced immune deficiency. Among these must be included liability to cancer.

Only a few years after the recognition of the dangers of tumours being transferred with organs taken from donors dying of cancer[1 2] came the first reports of cancer arising afresh in transplant recipients.[3 4] Since then it has been abundantly confirmed that recipients of organ transplants, with their immune systems suppressed, are at much greater risk of cancer than the general population. The incidence of cancer in transplant recipients varies considerably in different geographical areas. Cancer occurred de novo in 1·6% of transplant recipients in one series in Europe[5] compared with 3·3% in Scandinavia,[6] 5·6% in an American series,[7] and 24% in an Australian report.[8] Much of the variation is because of an increased incidence of skin tumours in those areas at high risk for these cancers. If malignancies of the skin are excluded an incidence of cancer of 4% to 7% in transplant recipients is usual. Penn calculated that this incidence was roughly 100 times greater than that in the age matched general population.[9]

The incidence of cancer calculated by comparing the number of transplant recipients with cancer with the total number surviving after transplantation may prove unduly optimistic, since most patients surviving with organ grafts are in the early years after transplantation, while the greatest incidence of cancer occurs in later years. Furthermore, the incidence of cancer in transplant recipients increases at a rate disproportionately greater than occurs in the general population. A more revealing method is to determine the proportions of patients surviving for the same interval after transplantation who do or do not have cancer. Use of this method in Australia and New Zealand showed that of those surviving 10 years only 65% had never had cancer—30% had skin malignancy, 9% other forms of cancer, and some patients had both.[10] The final incidence of cancer in transplant recipients will become known only when large numbers of patients have survived for long periods after transplantation.

The most common malignancies encountered in allograft recipients are those of the skin. Cancers include Bowen's disease, basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. In contrast to the pattern in the general population, squamous cell carcinoma occurs much more frequently than basal cell carcinoma.[11] In "high risk" areas its frequency (calculated to be at least 20 times that expected in a comparable population) is a cause of considerable morbidity and some mortality.[12] Though squamous cell carcinoma occurs mostly in parts of the body exposed to the sun, this is by no means always so. Some unfortunate patients develop almost generalised squamous cell carcinomas of the skin and require repeated operations for removal of lesions. Lesions tend to be multiple, aggressive, and prone to recurrence and metastasis.[13] Squamous cell carcinoma may affect the vulva or vagina. It is still not clear whether the frequency of basal cell carcinoma is increased in recipients of transplants, but melanoma seems to be occurring about five times more commonly than expected.[10 14 15]

As with skin cancer, the distribution of other malignancies recorded in transplant recipients differs from that of the age matched general population. The most frequent are tumours of the reticuloendothelial system, which make up 30% of non-skin malignancies in recipients of transplants as against 3% in the general population.[16] Hoover and Fraumeni estimated that this form of cancer occurs 30-40 times more frequently than expected.[17] Most common of the reticuloendothelial malignancies are large cell lymphomas described as reticulum cell sarcomas or microgliomas, which account for half of such tumours. The whole range of reticuloendothelial malignancies has been recorded, however, including lymphosarcoma, plasma cell lymphoma, lymphoreticular sarcoma, Hodgkin's disease, and several poorly defined malignancies. Interestingly, Hodgkin's disease accounts for only 2% of lymphomas in organ transplant recipients as against one third of reticuloendothelial malignancies in the general population.[18] A striking feature of the lymphomas which occur in recipients of organ transplants is the frequency with which these affect the central nervous system.

Another unusual tumour, Kaposi's sarcoma, accounts for 3% of new cancers in organ transplant recipients.[19] This neoplasm has a multicentric origin and is characterised by tumours with vascular and fibroblastic elements. It affects the skin or oropharyngolaryngeal mucosa when localised or the gastrointestinal tract or respiratory system when more generalised. It is endemic in certain areas of Africa but rare elsewhere.

Though the distribution of cancers in transplant recipients

is thought to differ from that found in the general population even when lymphomas and skin malignancies are excluded, this conclusion should remain under review. Early reports suggested that cancers of the prostate, colon and rectum, breast, and lung occurred with less frequency than in the general population.[20] Transplant recipients are relatively young, however, and such tumours should be rare. Others have pointed out that most malignancies recorded in the general population are gradually being recorded in transplant recipients, and for the most of these the frequency is increased compared with that expected.[8]

The latent period between transplantation and the development of cancer is much shorter than that which applies to known oncogenic influences such as tobacco, ultraviolet light, ionising radiation, and aniline dyes. Lymphomas and skin malignancies have been reported in the early months after transplantation. At the other end of the scale, first malignancies have been reported as long as 17 years after transplantation. The average time for appearance of lymphomas is about two years, though the excess risk of lymphoma persists indefinitely.[17] A similar continuing risk seems to apply to skin cancers, where again average times of development are in the range two to three years. The time of appearance of carcinomas of the various organs is later, with average times of four years.[10] On average leukaemias and carcinomas of the uterine cervix appear about five years after transplantation. As would be expected, most cancers occur in the older patients with transplants. In the Australian and New Zealand series the mean age of patients with cancer was 47, whereas the mean age of the population with transplants was 40.[10] Notable exceptions were lymphomas and cancers of the cervix, vagina, and vulva, where the mean age of patients was 40.

Among the aetiological factors which may play a part in the increased risk of cancer in immunosuppressed recipients of allografts are diminished immune surveillance, allowing survival of potentially neoplastic cells arising by somatic mutation or viral infection; protracted antigenic stimulation of the lymphoreticular system by the resident allograft; direct neoplastic action of immunosuppressive drugs; the defective humoral and cell mediated immunity of uraemia; and genetic differences in individual recipients. Probably all of these mechanisms contribute, their relative importance varying with the type of cancer. Recent attention has focused on oncogenic viruses. These include lymphoma (Epstein-Barr virus), hepatoma (hepatitis B virus), Kaposi's sarcoma (herpes virus), some cancers which derive from warts including (rarely) skin cancers, and vulval and perianal cancers, where the viruses thought to be concerned are herpes simplex type 2 and human papilloma virus.

We might expect the occurrence of cancer in the transplant recipient to worsen prognosis. Though this is certainly true for some patients, there are paradoxes in the relation between cancer and survival after transplantation. Because the incidence of cancer increases with time after transplantation it follows that cancer occurs most in those otherwise doing best in terms of graft function. Furthermore, many cancers (such as those of the skin and uterine cervix) are controllable by treatment, while others including some lymphomas are amenable to treatment if the diagnosis is made early. On the other hand, visceral cancers and leukaemias are highly malignant. With all these conflicting influences, the outlook for patients who develop cancer is as good and perhaps better than for those who do not with respect both to graft function[21] and to survival, at least for the first several years after transplantation.[22] Possibly immunosuppressive treatment results in a more profound inhibition of immune responses in the patients prone to cancer, or they may have innate reduced ability to mount immune responses. In either case the result might be a decreased ability to reject organ grafts but also an inability to withstand viral oncogenesis or to eliminate malignant clones. Nevertheless, those recipients with benign early courses and good graft function are those most likely to be exposed for long periods to any direct oncogenic effect of immunosuppressive drugs and to antigenic stimulation from the graft.

The danger of death from cancer must be placed in perspective. Overall mortality in most transplant programmes is roughly half in the interval up to 10 years. The causes of death are legion, but most deaths are due to infections and other complications of treatment, rejection of allografts, or progression of vascular disease resulting in strokes or myocardial infarction. Of the deaths, only some 6% are due to cancer, making it of relatively low importance. For those who survive all the early dangers and are otherwise doing well, however, cancer becomes a cruel threat as years go by—for example, in one report cancer accounted for a third of deaths which occurred beyond five years after transplantation.[22]

Those transplant recipients treated with standard immunosuppressive agents seem certain to continue to be at risk of developing cancer. In whatever way the complex aetiological factors interrelate the cancers seem to be consequent on an induced immune deficiency syndrome. Indeed, the types of cancers recorded in recipients of organ grafts are broadly similar to those described in the acquired immune deficiency syndrome (AIDS).

Possibly, however, the advent of new immunosuppressive agents may bring a change. This might happen, for instance, with cyclosporin A. Though standard immunosuppressive treatment relies on antimetabolite activity to produce immunosuppression, cyclosporin A acts completely differently, thought to be by inhibiting the secretion of lymphokines necessary for initiation of a new immune response, leaving established immune reactivities largely unaffected. Though those malignancies in which non-specific immunosuppression and oncogenic viruses play important aetiological parts may continue in patients treated with cyclosporin A,[23 24] those which seem especially dependent on use of antimetabolites may be diminished. The latter include most skin cancers, and there is early evidence that their incidence may be decreased under treatment with cyclosporin A.[25] We must also hope that early detection of virus induced illnesses and appropriate treatment by decreasing the amount of immunosuppression used and by the use of the new antiviral agents may diminish the incidence of virus induced tumours. Finally, the isolation and characterisation of specific causative viruses may lead ultimately to prevention by prophylactic immunisation.

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1 Martin DC, Rubini M, Rosen VJ. Cadaveric renal homotransplantation with inadvertent transplantation of carcinoma. *JAMA* 1965;**192**:752-4.
2 McPhaul JJ, McIntosh DA, Hall W. Tissue transplantation still vexes. *N Engl J Med* 1965;**272**:105.
3 Doak PB, Montgomerie JZ, North JDK, Smith F. Reticulum cell sarcoma after renal homotransplantation and azathioprine and prednisone therapy. *Br Med J* 1968;iv:746-8.
4 Penn I, Hammond W, Brettschneider L, Starzl TE. Malignant lymphomas in transplantation patients. *Transplant Proc* 1969;**1**:106-12.
5 Jacobs C, Brunner FP, Brynger H, *et al.* Malignant diseases in patients treated by dialysis and transplantation in Europe. *Transplant Proc* 1981; **13**:729-32.

[6] Birkeland SA. Malignant tumors in renal transplant patients. The Scandia transplant material. *Cancer* 1983;**51**:1571-5.
[7] Penn I. *Malignant tumors in organ transplant recipients*. Berlin: Springer-Verlag, 1970.
[8] Sheil AGR, Mahony JF, Horvath JS, *et al.* Cancer following successful cadaveric donor renal transplantation. *Transplant Proc* 1981;**13**:733-5.
[9] Penn I. The incidence of malignancies in transplant recipients. *Transplant Proc* 1975;**7**:323-6.
[10] Disney APS, ed. *Sixth report of the Australian and New Zealand Combined Dialysis and Transplant Registry*. Woodville, South Australia: The Queen Elizabeth Hospital, 1983.
[11] Walder BK, Robertson MR, Jeremy D. Skin cancer and immunosuppression. *Lancet* 1977;ii:1282-3.
[12] Hardie IR, Strong RW, Hartley LCJ, Woodruff PWH, Clunie GJA. Skin cancer in Caucasian renal allograft recipients living in a subtropical climate. *Surgery* 1980;**87**:177-83.
[13] Sheil AGR. Cancer in renal allograft recipients in Australia and New Zealand. *Transplant Proc* 1977;**9**:1133-6.
[14] Greene MH, Young TI, Clark WH Jr. Malignant melanoma in renal-transplant recipients. *Lancet* 1981;i:1196-8, 9.
[15] Kinlen L, Doll R, Peto J. The incidence of tumors in human transplant recipients. *Transplant Proc* 1983;**15**:1039-42.
[16] Silverberg E, Grant RN. Cancer statistics 1970. *CA* 1970;**20**:11-23.
[17] Hoover R, Fraumeni JF. Risk of cancer in renal-transplant recipients. *Lancet* 1973;ii:55-7.
[18] Penn I. Malignant lymphomas in organ transplant recipients. *Transplant Proc* 1981;**13**:736-8.
[19] Penn I. Kaposi's sarcoma in organ transplant recipients. Report of 20 cases. *Transplantation* 1977;**27**:8-11.
[20] Penn I. Development of cancer as a complication of clinical transplantation. *Transplant Proc* 1977;**2**:1121-7.
[21] Sloan GM, Cole P, Wilson RE. Risk indicators of de novo malignancy in renal transplant recipients. *Transplant Proc* 1977;**9**:1129-32.
[22] Sheil AGR, Mahony JF, Horvath JS, *et al.* Cancer and survival after cadaveric donor renal transplantation. *Transplant Proc* 1979;**7**:1052-4.
[23] Calne RY, Rolles K, White DJG, *et al.* Cyclopsorin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. *Lancet* 1979;ii:1033-6.
[24] Beveridge T. Cyclosporin-A: an evaluation of clinical results. *Transplant Proc* 1983;**15**:433-7.
[25] Sheil AGR, Hall BM, Tiller DJ, *et al.* Australian trial of cyclosporin A (CSA) in cadaveric donor renal transplantation. *Transplant Proc* (in press).

Repetitive publication: a waste that must stop

Like most other journals the *BMJ* receives far more original articles than it can print. Yet sometimes we learn that a paper we have published has appeared virtually unaltered elsewhere, either before or after its publication in the journal. Not only is this practice wasteful of time and money spent assessing, preparing, and publishing the article: it also means that some other, perfectly sound article has been elbowed out of the journal and that the retrieval services (such as *Index Medicus*) become clogged by duplicate items of "literature."

This problem is not confined to the *BMJ* (though we have had recent experience of it): I know of at least five recent instances of articles printed in the specialist journals published by the BMA that have also appeared in others, and American editors have expressed concern at the practice.[1] Nevertheless, there is no lack of advice for authors: the *BMJ* Instructions state, "All material submitted for publication is assumed to be submitted exclusively to the *BMJ* unless the contrary is stated"[2]; our copyright form says, "Papers are accepted on condition that they have not been published by any other journal"; and the Vancouver code, to which the *BMJ* was a founder signatory, has an entire paragraph devoted to prior and duplicate publication.[3]

The *New England Journal of Medicine* was one of the first journals to discuss this question. In September 1969 an editorial formulated what has since become known as the "Ingelfinger rule," named after its then editor.[4] "Papers are submitted," the editorial stated, "with the understanding that they or their essential substance have been neither published nor submitted elsewhere (including news media and controlled circulation publications). This restriction does not apply to (*a*) abstracts published in connection with meetings, or (*b*) press reports resulting from formal and public oral presentation." Explaining the rule (which has since been slightly modified) 12 years later, today's editor of the *New England Journal*, Arnold Relman, spelt out the principal reason for it: the public's need for medical information is not well served by the distribution of opinions and claims that have not been peer reviewed or carefully edited.[5]

Although the Ingelfinger rule is mainly concerned with a different type of repetitive publication, its principles and practice are applicable to the broader dilemma. And, as with any rule, questions immediately arise about details of the process. So I give here the *BMJ*'s answers to three of the commonest questions that are asked by authors who do not want to be accused of repetitive publication.

Firstly, how long and detailed does an abstract have to be before it is considered as a substantive contribution? Obviously, brief (250-400 word) abstracts of contributions to meetings of learned societies cannot, and are not, held to be a challenge to publication of the substantive paper; on the other hand, a larger abstract that contains data given in the text, illustrations, or tables together with a discussion of their implications is a definitive article. Similarly, a letter to the editor commenting on published work that uses some of the writer's own findings does not rule out publication of a full report of this work.

The second question concerns the "salami" series of articles —a preliminary study in 25 patients (often published in a general journal); a substantive paper based on work in another 25, lumped together to total 50 (with lengthy details, in a specialist journal); and a further offering based on 75 or 100. The difficulty may be that the more patients are studied the more the results change; as one of our referees commented on a similar series of articles that have been appearing over the years: "the statistical significance in 30 subjects was said to be strong, but in 60 is much less so. I suspect that by the time the group has studied 100 it will have ceased to exist altogether." So does the editor who published the first article have a moral obligation to set the record straight? Possibly he does—and he may allow the authors a letter to the editor, a Short Report, or an Unreviewed Report for this purpose—but a better solution would be for editors to insist that any article subsequent to the preliminary one is based on a substantial amount of work in new patients.

The third question is the point made by authors who when challenged claim that they have to inform two different audiences of their findings. Thus one of the authors recently detected attempting repetitive publication wrote:

> We elected to send a letter to the *Inquirer* as a preliminary communication; this is merely a brief description of the results and comment. We then preferred to submit a full article to a Pinealological Journal which might be read by the Pinealological and Pinealo-surgical fraternities. I acknowledge that there is duplication of information in both the letter and the paper but I am most keen as a Pinealologist that the fuller description of our work be published in a Pinealological Journal. In view of the wide interest in our work, my basic science colleagues were then keen that this important information be available in preliminary form to scientists not receiving Pinealological Journals.

A similar plea is often made by Americans for publication in British journals and vice versa—but almost always after the attempt at dual publication has been detected. The solution