a priori hypothesis that the risk would be seen in deaths from cancer. As the authors suggest, the association could be due to an increase in the incidence of cancer or to a reduced survival among those with the disease. Each explanation has potential weaknesses.

An effect on increased incidence seems unlikely because there is an increased risk at all sites of cancer. Even cigarette smoking restricts its effects to a small number of sites. This lack of specificity makes a causal association less likely. It also introduces a related problem. What plausible biological mechanism could explain the finding? The authors mention psychosocial factors, lifestyle factors, and neuroendocrine function but do not explain how these could have a carcinogenic effect on all body systems. Furthermore, in a subgroup analysis the authors show that adjusting for psychological distress does not reduce the risk of cancer associated with widespread pain.

Plausibility is also challenged because the increased risk of cancer is not restricted to a specific group of pain sufferers but is seen in the heterogeneous group with regional pain. It is unlikely that the risk is due to some small subgroup with regional pain, as a subgroup would have to have a substantially increased risk for the effect to be seen in the whole group. Plausibility is further threatened because this study was unable to take account of potential confounding factors. The authors have shown that the findings are robust to adjustment for current smoking status, but this is only one in a many potential lifestyle and environmental confounding factors. But if it were due to confounding, this would have to operate in a curious way. It is difficult to think of confounding factors that would act with such complete lack of specificity.

An effect on reduced survival would be more easily understood than an effect on an increase in incidence: psychosocial wellbeing or diet or other factors could have a generalised effect on survival. However, exclusion of participants with a previous diagnosis of cancer from the analysis led to an increased risk of mortality. This leaves the possibility that the pain is an early symptom of undiagnosed cancer.

We are thus left with an unexplained but potentially important finding. As the authors state the association needs to be assessed in other studies and possible mechanisms investigated. It seems unlikely that confounding could be the explanation. However the finding could be due to some unrecognised bias or may simply be a statistical fluke. It would be much more interesting if the effect were real because of the potential insights into the development of cancer. But, as so often, the answer will require further research.

Drug points

Premature osteonecrosis and sirolimus treatment in renal transplantation

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The incidence of osteonecrosis or avascular necrosis has fallen as a result of new advances in immunosuppression and lower corticosteroid regimens.[1 2] Mycophenolate mofetil and sirolimus are associated with an increase in surgical complications.[3 4] Sirolimus may also be associated with avascular necrosis in patients after renal allograft transplantation. This could be attributed to sirolimus's adverse lipid profile, its potent bone marrow suppressive effect, or perhaps an idiosyncratic effect

A 39 year old man with IgA nephropathy received a cadaveric renal transplant. He was a non-smoker and non-drinker. Seven months after receiving the transplant he developed an acute painful left leg. He was taking prednisone 10 mg, cyclosporin 300 mg, and sirolimus 5 mg daily. His trough sirolimus concentration was 20.7 ng/ml (range 5-20). Hip *x* ray and magnetic resonance imaging confirmed avascular necrosis in both hips. Sirolimus was discontinued, and tacrolimus and mycophenolate mofetil were introduced. Disodium pamidronate treatment produced symptomatic improvement.

A 49 year old man with polycystic kidney disease received a cadaveric renal transplant. He was a non-smoker and non-drinker. Six months after the transplantation he developed hip pain. Investigations confirmed bilateral avascular necrosis. He was taking prednisone 10 mg, cyclosporin 200 mg, and sirolimus 5 mg daily. His trough sirolimus concentration was 5.8 ng/ml. Sirolimus was changed to mycophenolate mofetil, and elective bilateral hip replacements were arranged.

Avascular necrosis, a recognised complication of transplantation, is commonly associated with prolonged high doses of corticosteroid.[1 2] Occurring 6-12 months after transplantation, it is less likely to result from corticosteroid treatment. In our transplant population the prevalence of avascular necrosis is 2% in patients on standard treatment, with less than 0.5% in the first year (unpublished data). In those patients receiving sirolimus the prevalence is 3.8% (2 from 52 cases). Data sheets suggest a frequency of 1-10% with corticosteroids. No other reports have been published. Although our data are compared with historical controls, we believe that sirolimus may be a cause of early post-transplant bone pain because of avascular necrosis.

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Endpiece

Death

Death is the dark backing a mirror needs if we are to see anything.

Saul Bellow