treatment with DHEA. Treatment was also associated with an increase in insulin binding and degradation by T lymphocytes, and this was thought to reflect increased insulin sensitivity. No adverse effects were reported.

In the third study eight men and eight women aged 50-65 were given 100 mg of DHEA or placebo for six months.¹³ The investigators confirmed their previous observation¹⁰ that the intake of DHEA was associated with an increase in insulin like growth factor. Treatment at the higher dose led to an increase in lean body mass that reached statistical significance when both men and women were analysed together. Muscle strength at the knee was increased in men but not in women. Because the 100 mg dose of DHEA stimulated a greater increase in serum androgens in women than had been observed with a dose of 50 mg, the authors concluded that this amount "may induce undesirable androgenic effects with time." The effect of DHEA on well being was not discussed.

Writing in the *Lancet*, Herbert concluded: "Enough is known or suspected to warrant investigation of DHEA as an effective, worthwhile, and relatively risk-free replacement therapy in advancing age. This can only be done by a controlled prospective trial of DHEA treatment."⁸ This recommendation may be scientifically sound but it will be difficult to follow. The pharmaceutical industry may hesitate to support studies with DHEA, a molecule that cannot be patented. Similarly, it may not be easy to attract research funds from government agencies or private philanthropies at a time when support is shifting from clinical trials to fundamental research. Further research studies confirming or rejecting the reported results of DHEA replacement treatment seem unlikely to appear in the near future.

What advice should a doctor give when asked about the treatment? In my opinion there is not at present sufficient evidence for routinely recommending replacement treatment with DHEA to middle aged and elderly people. Furthermore, patients with a family or personal history of a tumour respon-

sive to hormones—for example, breast cancer or prostate cancer—should be dissuaded from taking DHEA. Treatment should be restricted to patients with low serum levels of DHEA and normal levels of prostate antigen. This means that patients who say that they want to take DHEA should have their serum DHEA and prostate antigen levels determined before treatment. All patients receiving DHEA should be asked to attend their doctor for regular clinical review and monitoring of their serum levels of DHEA and prostate specific antigen.

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- 1 Dehydroepiandrosterone (DHEA) and aging. Bellino FL, Daynes RA, Hornsby PJ, Lavrin DH, Nestler JE, eds. *Ann NY Acad Sci* 1995;774:1-350.
- 2 Bilger B. Forever young. *The Sciences* 1995 September/October:26-30.
- 3 Orentreich N, Brind JL, Rizer, Vogelman JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J Clin Endo Metab* 1984;59:551-5.
- 4 Orentreich N, Brind JL, Vogelman JH, Andres R, Baldwin H. Long-term longitudinal measurements of plasma dehydroepiandrosterone sulfate in normal men. *J Clin Endocrinol Metab* 1992;75:1002-4.
- 5 Barrett-Connor E, Khaw K, Yen SSC. A prospective study of DS, mortality end cardiovascular disease. *N Engl J Med* 1986;315:1519-24.
- 6 Helzouer KJ, Gordon GB, Alberg A, Bush TL, Comstock GW. Relationship of prediagnostic serum levels of HDEA and DS to the risk of developing premenopausal breast cancer. *Cancer Res* 1992;52:1-4.
- 7 Alternative medicine. *The Economist* 1996 February:28-31.
- 8 Herbert J. The age of dehydroepiandrosterone. *Lancet* 1995;345:1193-4.
- 9 Bagatelle CJ, Bremner WJ. Androgens in men - uses and abuses. *N Engl J Med* 1996;334:707-14.
- 10 Morales AJ, Nolan JJ, Nelson JC, Yen SSC. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J Clin Endocrinol Metab* 1994;78:1360-7.
- 11 Casson PR, Andersen RN, Herrod HG, Stentz FB, Straughn AB, Abraham GE, et al. Oral dehydroepiandrosterone in physiologic dose modulates immune function in postmenopausal women. *Am J Obstet Gynecol* 1993;169:1536-9.
- 12 Casson PR, Faquin LC, Stentz FB, Straughn AB, Andersen RN, Herrod HG, et al. Replacement of dehydroepiandrosterone enhanced T-lymphocyte insulin binding in postmenopausal women. *Fertil Steril* 1995;63:1027-31.
- 13 Yen SSC, Morales AJ, Khorram O. Replacement of DHEA in aging men and women. *Ann NY Acad Sci* 1995;774:128-42.

The prone position in acute respiratory distress syndrome

Small studies have shown that it improves oxygenation

Acute respiratory distress syndrome (ARDS) is characterised by radiographic diffuse bilateral infiltrates, decreased respiratory compliance, small lung volumes, and severe hypoxia.¹ Correcting life threatening hypoxia is one of the main goals of treatment, and a range of possible approaches has been suggested, including high airway pressures, jet ventilation, nitric oxide inhalation, and extracorporeal membrane oxygenation. However, no approach has yet proved definitive. Small case series have shown that the simple expedient of turning a mechanically ventilated patient with life threatening hypoxia to the prone position can bring dramatic improvements in oxygenation.² This manoeuvre may help to reduce some of the factors believed to damage the lungs of patients with acute respiratory distress syndrome, such as excessive inspiratory pressure and a high inspired oxygen fraction. Is the prone position really beneficial or just another good idea that cannot be proved?

Using the prone position to improve oxygenation in patients with acute respiratory distress syndrome was proposed 20 years ago.³⁻⁴ Research on animals suggests several mechanisms to explain the improvement in oxygenation, including re-expansion of gravity induced atelectasis (which may explain the very rapid improvement), alterations in ventilation-perfusion, increase in functional residual capacity, and correction of venous stasis.⁵⁻⁸ In fact, animal experiments with oleic

induced acute respiratory distress syndrome show that the move from supine to prone creates a transpulmonary pressure that is sufficient to exceed the airway opening pressure in the dorsal regions, where atelectasis is most severe. Ventilation is enhanced without any change in regional perfusion.⁵⁻⁶

Several small uncontrolled studies of between six and 16 patients with acute respiratory distress syndrome have all confirmed a rapid improvement in oxygenation in at least 70% of patients, though it is important to remember that such anecdotal reports are likely to include only successful cases. To date, however, no randomised trials are available. Langer *et al* reported 13 mechanically ventilated patients with acute respiratory distress syndrome who improved within two hours of being turned, and this improvement was maintained after repositioning the patients supine.⁹ Pappert *et al* reported similar results in 12 patients receiving pressure controlled ventilation, but the improvement disappeared when the patients were returned to the supine position.⁷ There was also a decrease in minute volume and an increase in arterial carbon dioxide pressure, suggesting a change in respiratory mechanics. Brusel *et al* reported a significant improvement in oxygenation without haemodynamic upset in patients with acute lung injury after coronary artery bypass surgery who were placed prone. Computerised tomography showed bilateral crest shaped densities in the dependent lung fields.¹¹ Gattinoni *et al*

Fig 1—In patients with ARDS lying supine (left), computed tomography shows bilateral crest shaped densities in the dependent lungs. When the patient is placed prone (right) the densities redistribute. Changes in arterial oxygen tension are shown adjacent to the scan

found that a few minutes after moving the patient from supine to prone, these densities moved from the previously dependent (dorsal) region to the dependent (ventral) region (fig 1¹). They found no relation between oxygenation and redistribution in lung densities.⁸

There is a natural reluctance in intensive care units to move such desperately ill patients. There are fears that infusions will become dislodged, as well as anxieties about moving the neck and placing the face of an intubated patient in an inaccessible position. In practical terms the patient needs to be turned for periods of four to six hours at least once a day. The frequency

is limited by difficulty in gaining access to the airway and providing the necessary hygiene and skin care. Facial oedema, pressure damage, bruising, and difficulty in keeping the tube strapped in place owing to saliva are common. The endotracheal tube needs to be tied in. Fixing the patient on pillows to permit free diaphragmatic excursion requires particular attention; this has proved less difficult than it sounds, but it requires a team of helpers.

The prone position may improve oxygenation and enhance removal of secretion in patients with respiratory failure, but prospective randomised trials are needed to define the real efficacy of this approach.

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- 1 Asbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967;iii:319-23.
- 2 Gattinoni L, Pelosi P, Valenza F, Mascheroni D. Patient positioning in acute respiratory failure. In: Tobin MJ, ed. *Principles and practice of mechanical ventilation*. New York: McGraw Hill, 1994:1067-76.
- 3 Pheil MA, Brown RS. Use of extreme position change in acute respiratory failure. *Crit Care Med* 1976;4:13-4.
- 4 Douglas WW, Rheder K, Froukje MB, Sessler AD, Marsh HM. Improved oxygenation in patients with acute respiratory failure: the prone position. *Am Rev Respir Dis* 1974;115: 559-66.
- 5 Mutoh T, Guest RJ, Lamm WJ E, Albert RK. Prone position alters the effect of volume overload on regional pleural pressures and improves hypoxaemia in pigs in vivo. *Am Rev Respir Dis* 1992;146:300-6.
- 6 Lamm WJ E, Graham MM, Albert RK. Mechanisms by which the prone position improves oxygenation in acute lung injury. *Am J Respir Crit Care Med* 1994;150:184-93.
- 7 Pappert D, Rossiant R, Slama K, Gruning T, Falke K. Influence of positioning on ventilation-perfusion relationships in severe adult respiratory distress syndrome. *Chest* 1994;106:1511-6.
- 8 Gattinoni L, Pelosi P, Vitale G, Persenti A, D'Andrea L, Mascheroni D. Body position changes redistribute lung computed tomographic density in patients with acute respiratory failure. *Anesthesiology* 1991;74:15-23.
- 9 Langer M, Mascheroni D, Marcolin R, Gattinoni L. The prone position in ARDS patients: a clinical study. *Chest* 1988;94:103-7.
- 10 Brussel T, Hachenberg T, Roos N, Lemzem H, Konertz W, Lawin P. Mechanical ventilation in the prone position for acute respiratory failure after cardiac surgery. *J Cardiothoracic Vascular Surg* 1993;7:541-6.
- 11 Anderton J. The prone position for the surgical patient: a historical review of the principles and hazards. *Br J Anaesth* 1991;67:452-63.

The prone position in respiratory failure¹¹

Indications

- Acute lung injury
- Cardiogenic oedema
- Permeability oedema

Contraindications

- Shock
- Acute bleeding
- Multiple trauma
- Spinal instability
- Pregnancy
- Raised intracranial pressure

- Recent abdominal surgery

Complications

- Nerve compression
- Crush injury muscle
- Venous stasis
- Airway security
- Diaphragmatic limitation
- Pressure sore
- Dislodging access lines
- Retinal damage

Second primary cancers after childhood cancer

Low absolute risk, but prevention and monitoring are high priorities

Over the past two decades, impressive advances have been made in the treatment and survival of children with cancer. Population based data from the United States document a 68% five year survival for children aged 0-15 years who were diagnosed with cancer in 1985.¹ In the vast majority of cases, five year survival represents cure. Accordingly, the number of children and young adults in the population who have been exposed to cancer treatments, which often include radiation and chemotherapy, continues to increase. These children, cured of their cancer, are at risk from adverse effects of the treatment they received.

Little is known about the long term consequences of cancer treatment. Rapid improvements in the treatment and survival of children with cancer were first realised in the early 1970s, and therefore the first large cohort of survivors of childhood cancer is now entering adulthood, a decade or more after being treated. A retrospective cohort of children in Britain diagnosed with cancer since 1940 has provided an opportunity to investigate the long term risk in a large population.^{2,3} The recent report by Hawkins and colleagues from the Childhood Cancer Research Group in Oxford describes the risk of bone cancer in over 13 000 children who survived three years after treatment.⁴

Hawkins *et al* emphasise the need to put the risks in perspective. Review of the literature gives a picture of massive excesses in risk, with observed to expected ratios in excess of 50—that is, 50 times the expected number of cases occurring in children with previous cancers.⁵ But from the patient's perspective, the relevant statistic is the cumulative probability or the absolute risk of developing a second cancer. Reports on large populations of patients have shown that the cumulative probability of second cancer can be quite low.⁶ Despite this low absolute risk, high priority should be given to characterising and preventing second neoplasms because they are often associated with high levels of morbidity and mortality.

Several questions remain regarding the future risk of cancer in child survivors. Firstly, what are the latencies between specific cancer treatments and subsequent cancers? While the risk of leukaemia associated with alkylating agents seems to be restricted to the first decade after exposure,⁷ data suggest that radiation will play a substantial role in the risk of non-leukaemic malignancies two and more decades later.^{7,8}

Secondly, what interactions exist between treatments? The possibility of interactions between radiation and some chemotherapeutic agents has been suggested.⁹ However, testing for