Skin obtained from unrelated donors (allograft or homograft) has been used for many years as temporary cover, so cutting down the loss of fluid and heat from the wound, and, more nebulously, "preparing" the wound bed for final autografting. The immunosuppressed state of most severely burnt patients ensures that such allografts survive for considerably longer than they would in normal recipients. A recent and promising development in the use of full-thickness cadaver skin as an allograft has been to seed tiny patches of autograft through holes punched in the allograft cover. By the use of this method some very extensive burns, up to 95% of the body-surface area, have been successfully treated.¹

Skin from unrelated species, usually pigs (xenograft), has also been used to treat burn wounds. Pigskin is used solely to provide a temporary cover for the wound; it is said to be suitable for applying as a dressing to partial-thickness and superficial burns and has been claimed to provide analgesia and, possibly, to improve the final outcome of the injury. The claims made for pigskin are not, however, substantial enough to merit its widespread adoption for treatment.

More promising are methods being used to augment the supply from the patient himself. The process of harvesting the split skin causes additional injury and upset especially when very little has been left unburnt. The introduction of the mesh graft allowed expansion of the available skin by a factor of up to five.² Recent developments promise to improve greatly on this figure. O'Connor *et al*³ have reported the use of cultured epithelial cells for grafting. In this system a small split-skin sample is taken when the patient is admitted and cells are cultured to confluence by using a complex culture system.⁴ These sheets of differentiated epithelium may then be used to provide epithelial cover some four to six weeks after the initial sample has been taken. Potentially this method might enormously expand small donor areas, but simpler culture systems than those described by Green *et al*⁴ will need to be developed if the method is to come into widespread use.

One disadvantage to using split-thickness skin for full-thickness wounds is that it provides no new dermis, so that the grafted area may later contract. This problem is particularly important in reconstructive surgery and in attempting to make up losses in tissue caused by the contraction of existing scars. Burke *et al*⁵ have recently reported the use of an artificial dermis produced as a copolymer of collagen and mucopolysaccharide to provide fibrous infilling. This material requires to be over-grafted with split-thickness meshed grafts, but it may well prove effective in producing a stable, contracture-free closure. It should be accepted by the body since the collagen is non-antigenic.⁶ Indeed, the dermal collagen preparation described by Oliver *et al*⁶ has recently proved an effective implant substrate in preliminary studies in man.⁷

So surgeons can now provide their patients with new skin cells as sheets of cultured epithelium and an acceptable "dermis" either from a synthetic copolymer or from unrelated human tissue. The most exciting development will be to combine these two methods to provide a skin substitute tailored to the patient's own requirements. This goal is now in sight: Yannas *et al* have reported that burn wounds can be closed by the use of synthetic dermis seeded with epithelial cells to provide a complete skin substitute.⁸

Prospects are bright for research and development in practical skin substitutes that improve on existing methods of treatment. For some time yet these developments will be in the hands of the units with laboratory facilities for carrying out the demanding culture and preparation techniques. Though current methods of treatment are certainly adequate to treat

most patients with burn injury, at least in Britain, these recent developments promise great hope for the most severe burn injuries, where the treatment process itself poses considerable hazards.

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- ¹ Yang CC, Shih TS, Chu TA, Hsu WS, Kuo SY, Chao YF. The intermingled transplantation of auto and homografts in severe burns. *Burns* 1980;**6**:141-5.
- ² Tanner JC Jr, Vandeput J, Olley JF. The mesh skin graft. *Plast Reconstr Surg* 1964;**34**:287-92.
- ³ O'Connor NE, Mulliken JB, Banks-Schlegel S, Kehinde O, Green H. Grafting of burns with cultured epithelium prepared from autologous epidermal cells. *Lancet* 1981;i:75-8.
- ⁴ Green H, Kehinde O, Thomas J. Growth of cultured human epidermal cells into multiple epithelia suitable for grafting. *Proc Natl Acad Sci USA* 1979;**76**:5665-8.
- ⁵ Burke JF, Yannas IV, Quinby WC, Bondoc CC, Jung WK. Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury. *Ann Surg* 1981;**194**:413-28.
- ⁶ Oliver RF, Hulme MJ, Mudie A, Grant RA. Skin collagen allografts in the rat. *Nature* 1975;**258**:537-9.
- ⁷ Shakespeare PG, Griffiths RW. Dermal collagen implants in man. *Lancet* 1980;i:795-6.
- ⁸ Yannas IV, Burke JF, Orgill DP, Skrabut EM. Wound tissue can utilize a polymeric template to synthesize a functional extension of skin. *Science* 1982;**215**:174-6.

Artificial blood

The group of substances named perfluorochemicals enhance the oxygen carrying capacity of the circulation in mammals, including man.¹ These perfluorochemicals act as simple carriers of oxygen, but they have to be given as emulsions containing particles with diameters of around 0.1 micron to pass through the capillary nets. The dissolved oxygen is given up by diffusion in hypoxic tissues. So great is the oxygen carrying potential of perfluorochemicals, especially in hyperbaric conditions, that complete exchange perfusions have been performed in rats, which have then been kept alive with no red blood cells in their circulation.² In studies on animals some of the properties of the blood other than oxygen transport have been provided by glucose, bicarbonate buffer, electrolytes, and hydroxyethylstarch.

Much of the early work with perfluorochemicals was done in Japan and the United States.³ Recently Tremper and his colleagues in Los Angeles have reported their experience with Fluosol-DA, a 20% emulsion of two perfluorochemicals made by the Green Cross Corporation of Japan (Alpha Therapeutic Corporation).⁴ Seven severely anaemic patients were given Fluosol-DA before surgery. At ambient oxygen tensions there was little change, the emulsion acting simply as a non-toxic volume expander, but at higher tensions a substantial amount of oxygen was taken up and delivered to the tissues. The authors suggested several clinical conditions in which perfluorochemicals might be valuable including carbon monoxide poisoning, myocardial infarction, cerebral vasospasm, and sickle cell crisis.

One very obvious use for the perfluorochemicals is as oxygen carrying substitutes in the rare but difficult problem of religious objection to blood transfusion.¹ Other uses which have been explored are as initial treatment in haemorrhagic

shock, in emergency while awaiting delivery of fully cross matched blood,⁵ and as agents relieving both coronary⁶ and cerebral⁷ ischaemia. Further experience seems likely to open up a new and potentially very valuable approach to the immediate management by paramedical personnel of large numbers of casualties from disasters or armed conflicts. The perfluorochemicals might also be used instead of blood for priming extracorporeal pumps and for perfusing organs before transplantation.⁸ They might be tailored to remain in the circulation for long enough to be of value in patients with thalassaemia major or aplastic anaemia without the present risks of hepatitis or of iron overload. They might have a place in the management of severe anaerobic infections. One thought provoking suggestion by Geyer² is that they might be used in the targeting of malignant tumours for irradiation since the response is dependent on their oxygen content.

The list seems endless, for the emulsified perfluorochemicals have vast potential. To date they appear to be inert, non-toxic deliverers of dissolved oxygen to hypoxic tissue and of carbon dioxide to the lungs—a perfect present for the marathon runner. But first appearances may be deceptive, and, as Tremper and his colleagues suggest,⁴ their safety, as well as their efficacy, need to be shown in large scale clinical trials.

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¹ Yokoyama K, Suyama T, Naito R. Development of Fluosol-DA and its perspective as a blood substitute. In: *Oxygen and life. Proceedings of the second Priestley conference*. London: Royal Society of Chemistry, 1980:142-52. (Special Publication 39.)

² Geyer RP. Perfluorochemicals as oxygen transport agents in partial and total blood replacement. In: *Oxygen and life. Proceedings of the second Priestley conference*. London: Royal Society of Chemistry, 1980:132-41. (Special Publication 39.)

³ Clark LC, Gollan F. Survival of mammals breathing organic liquids equilibrated with oxygen at atmospheric pressure. *Science* 1966;**152**: 1755-6.

⁴ Tremper KK, Friedman AE, Levine EM, Lapin R, Camarillo D. The preoperative treatment of severely anemic patients with a perfluorochemical oxygen-transport fluid, Fluosol-DA. *N Engl J Med* 1982;**307**: 277-83.

⁵ Honda K, Hoshino S, Shoji M, et al. Clinical use of a blood substitute. *N Engl J Med* 1980;**303**:291-2.

⁶ Glogar DH, Kloner RA, Muller J, Déboer LWV, Braunwald E, Clark LC Jr. Fluorocarbons reduce myocardial ischemic damage after coronary occlusion. *Science* 1981;**211**:1439-41.

⁷ Peerless SJ, Ishikawa R, Hunter IG, Peerless MJ. Protective effect of Fluosol-DA in acute cerebral ischemia. *Stroke* 1981;**12**:558-63.

⁸ Geyer RP. Fluorocarbon-polyol artificial blood substitutes. *N Engl J Med* 1973;**289**:1077-82.

American group³⁻⁵ provided a detailed clinical picture of the fetal alcohol syndrome as well as confirming the risks of higher neonatal and infant mortality.⁶

From these curious beginnings of discovery, neglect, rediscovery, and independent rediscovery, the research output has grown with overwhelming rapidity over the last decade,⁷ but fortunately several recent reviews give excellent summaries.⁸⁻²⁰ The main impetus has come from the National Institute on Alcohol Abuse and Alcoholism (an American governmental agency), which has funded four major prospective studies of maternal drinking during pregnancy.²¹ Research on animals has also gone ahead rapidly.²² These initiatives in the United States provide a remarkable example of scientific energies being effectively directed towards a matter of public health concern and bears witness to the seriousness with which that country views its drinking problem. Some work on maternal drinking is now under way in Britain and other countries have made important contributions.^{12 22 23}

Among the mass of sometimes contradictory findings one conclusion stands out with certainty from the published data. The woman who continues to drink during pregnancy at a level deserving the clinical diagnosis of alcoholism is at severe risk of giving birth to a child who will manifest the fully developed triad of the fetal alcoholism syndrome—retardation in growth, a cluster of characteristic dysmorphic features, and mental retardation.^{2 4} The risk may be as high as 30%. This syndrome can no longer credibly be claimed to be due to confounding variables such as smoking or poor maternal nutrition, though these may interact with the effect of alcohol. As well as the fully developed syndrome a range of more minor degrees and clusterings of fetal damage may occur. The evidence shows that a range of drinking patterns may combine with compounding factors and individual vulnerabilities to give rise to a wide spectrum of disorders.^{6 13} The fetus is vulnerable at any stage of pregnancy.¹⁷ It is therefore insufficient to focus only on the extreme case. And, as already mentioned, the children of alcoholic mothers are also at risk of enhanced rates of stillbirth and infant mortality.⁶

So much for certain, but what is far more contentious is the relation between lesser and perhaps "social" degrees of maternal drinking and any type of harm to the fetus. As regards drinking and risk of spontaneous abortion, a recent prospective study of 32 000 pregnancies in California suggested that among women taking one or two drinks daily the risk of abortion in the second trimester was double that for non-drinkers,²⁴ while a study of 616 women from New York found an abortion rate of 25% among women who drank at least twice weekly, with a "minimal harmful dose" of two drinks on an occasion.²⁵ Aspects of both these studies have been criticised, however; in particular, any self-report of drinking may be an underestimate.²⁶

What about the effects of social levels of maternal drinking on fetal birth weight, the incidence of minor physical abnormalities, and subtle behavioural manifestations?²⁷⁻³³ The Seattle group has reported a prospective study of 263 women which appears to show that an average intake of about two drinks a day can reduce birth weight,³⁰ while a carefully controlled follow up of 500 women from the same group with "blind" assessment of the babies showed 19% with congenital abnormalities when maternal drinking was at four or more drinks a day, 11% with mothers taking two to four drinks, and 2% abnormal children when maternal drinking was fewer than two drinks a day.³² Again, however, both the evidence and interpretations are open to criticisms, and

Alcohol and advice to the pregnant woman

The adverse impact that a mother's drinking may have on the fetus was documented as long ago as 1899, when Dr William Sullivan published a report in the *Journal of Mental Science* showing that "female drunkards" incurred a stillbirth and infant mortality rate which was about two-and-a-half times greater than those in a comparison group.¹ Those observations were, however, largely lost from sight until 1968, when French research workers described mental retardation and physical deformities among children born to alcoholic mothers.² Somewhat later and independently an