antenatal complications develop in an obese woman she is at greater risk of losing her baby than a woman of normal weight with the same complication, though if there are no antepartum complications maternal weight does not alter perinatal mortality.⁸

Obese women tend to have large babies.⁶⁻¹¹ They might therefore be expected to have increased risks of cephalopelvic disproportion, shoulder dystocia, and caesarean section, but the evidence on this question is not clear.¹¹ Some studies have reported increased rates of caesarean section,^{8 11} but others have not.^{7 10} When operative intervention is required, however, there is increased morbidity and wound infection.^{7 11} Among normal women the baby's birth weight is related both to the mother's weight before pregnancy^{13 14} and to her weight gain during pregnancy,^{13 15} but among severely overweight women the birth weight is related only to the weight before pregnancy and is not influenced by weight gain.¹³ The mother's weight also affects the baby's growth after birth: both normal⁷ and low birthweight¹⁶ babies put on weight more quickly if their mother is fat than if she is underweight. Whether this is due to genetic or intrauterine factors or to differences in later feeding patterns is unknown.

To what extent can obstetric risks be modified by dietary adjustment in pregnancy? Pregnant women are traditionally urged to eat for two, and concern has been expressed that enthusiasm for slimming may adversely affect fetal growth.¹⁷ Encouraging non-obese women to achieve an "appropriate" weight gain¹⁸ reduces the proportion of low birthweight babies,¹⁹ and in developing countries women may be given energy supplements for this purpose, though recently doubt has been cast on the need for such supplementation in the absence of obvious food shortages.^{20 21} Nevertheless, there is little evidence that perinatal mortality can be improved by dietary measures aimed at increasing birth weight.

Recommendations for a minimum weight gain in pregnancy should take account of the weight before pregnancy: underweight women need to gain more than overweight women.²²⁻²⁴ If, then, there is no need to encourage fat women to gain weight in pregnancy¹³ should they be encouraged to lose weight? Dietary restriction for women who gain a lot of weight can reduce the birth weight of their babies, but once again there is no evidence that this reduces the risk of pregnancy complications.¹² A Scottish study¹² has concluded that "dietary restriction cannot be advocated even in the obese primigravida as it is possibly detrimental to the baby and of no benefit to the mother: it is probably better to try and reduce the obese woman's weight either before or after the pregnancy."

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Licensed to kill

About 5-10% of human peripheral white blood cells spontaneously and rapidly kill in vitro a wide range of cultured cell lines, tumour cells, and virus infected cells. These natural killer cells were described more than 10 years ago, and they are becoming of interest in several of the clinical medical specialties. As well as being an important component of natural resistance to infection, they may also play a part in limiting the growth and metastatic spread of some tumours and in graft versus host disease. They may even prove to be useful in treating some tumours.

Natural killer cells are large, low density lymphocytes rich in azurophilic cytoplasmic granules, that can be isolated by density gradient centrifugation from peripheral blood. They are also found in lymphoid tissues and may be detected in inflammatory sites.¹ Natural killer cells isolated from peripheral blood lymphocytes are non-phagocytic, do not bear surface immunoglobulin, and, in contrast to T lymphocytes, do not require products of the HLA locus either for their activation or to recognise target cells. Although several pan natural killer markers have been described—(for example, those recognised by the monoclonal antibodies B73-1² and Leu 11a³—the operational definition of natural killer cells is still based on their cytotoxic activity. They are a heterogeneous population and therefore cannot yet be given a single phenotype relating to their function.

Although derived from bone marrow, the lineage of natural killer cells remains controversial. They can express phenotypic markers of myelomonocytic as well as of T cell origin.⁴ Most can form rosettes with sheep red blood cells, and many of these can also express the M1 marker (monoclonal antibody defined monocyte-macrophage antigen). The CD3 antigen, which is associated with the antigen recognition site of T lymphocytes, is found on a subset of natural killer cells although they use a target recognition mechanism distinct from that used by cytotoxic T cells.⁵ The phenotypic heterogeneity may reflect differences in the stage of differentiation or ontogeny of natural killer cells. Natural killer effectors recognise glycosylated structures on target cell membranes by as yet undefined receptors.⁶ It was thought that developing techniques for culturing and cloning natural killer effector cells would allow them to be more

precisely defined, but it was not to be. Cloned natural killer cells were also found to display a wide range of phenotypes and target cell preferences.⁷

The interferons are probably the major common activation pathway for natural killer cells. A brief incubation with interferons rapidly increases natural killer activity in vitro. Purified populations of natural killer cells can also produce interferon after exposure to inducing agents such as poly I-poly C, BCG, retinoids, and some target cells.⁸ In addition, interleukin 2 (T cell growth factor) can directly induce the proliferation of highly purified natural killer populations as well as increase their natural killer activity.⁹ The activity of natural killer cells can be inhibited by prostaglandins, histamine, and lipomodulin.^{10 11}

Since the first description of natural killer activity in the early 1970s it has been suggested that natural killer cells were an integral part of natural resistance. In conjunction with interferons, which can inhibit viral replication and also recruit cells of the immune system, natural killer cells could play a part in early non-specific attack against virus infected cells. Some evidence that natural killer cells represent a rapidly inducible effector mechanism for eliminating virus infected cells has come from the study of experimental viral infections in animals.^{12 13}

Among tumour immunologists, renewed interest in natural killer cells has followed a recent report showing a correlation between decreased class I antigen expression by lymphoma variants, with increased susceptibility to natural killer lysis.¹⁴ The authors proposed that this would complement the target specificity of cells of the adaptive immune system in which foreign antigens are recognised in the context of self determinants coded for by the HLA locus. Support for this hypothesis in man comes from studies of the sensitivity of human neuroblastoma cells to lymphocyte mediated cytotoxicity.¹⁵ Neuroblastoma derived cell lines express very low concentrations of HLA antigens, and these are sensitive to natural killer lysis but not to cytotoxic T lymphocyte mediated cytotoxicity. Host differences in natural killer effector function may thus be important in the establishment and rate of growth of this type of tumour. In addition, the sensitivity of different types of tumours to T cell or natural killer mediated lysis may have important therapeutic implications.

The study of natural killer cell mediated cytotoxicity has extended into research in rheumatology, maternofetal immunobiology, and particularly transplantation.¹⁶ The last is of particular interest as natural killer cells have been implicated in the rejection of parental bone marrow graft in hybrid resistance and are implicated as possible effector cells in graft versus host disease.^{17 18}

Although the natural killer assay is unlikely yet to become a routine clinical test, therapeutic modulation of natural killer activity may soon become a reality. The natural killer cell may then become more important in clinical medicine.

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Doctors and the drug industry: too close for comfort

The drug industry spent £169m promoting its products to doctors in 1983, and the estimated expenditure was almost £200m for 1985. That works out at £2500 for each doctor, but almost 80% of the expenditure (£160m) is on general practitioners—over £5000 is thus spent for each general practitioner. In contrast, the NHS spends about £2m refunding expenses incurred by general practitioners attending postgraduate education—less than £70 for each doctor.

The drug industry does, of course, have a perfect right to promote its products. The 14 years and £100m needed on average to produce a new drug mean not only that the company will want to retrieve that money but also that the company is likely to have come to believe strongly in its product: although it might look like "just another β blocker" to the doctor, to the company it is a much valued baby and superior to its competitors. When so much is at stake and so much promotional money is being spent ample room exists for the unscrupulous company or doctor to abuse the relationship that has to exist between doctors and the drug industry. But, more worryingly, room also exists for scrupulous doctors to be overinfluenced by a company's promotion and for a company to be overzealous in its promotion.

The Association of the British Pharmaceutical Industry has a (much criticised) code designed to restrain the over-zealous company, and now the Royal College of Physicians has produced guidelines that are supposed to make sure that doctors remain thoroughly "professional" in their relationships with drug companies.¹ The college—almost, I sense, with regret—has desisted from suggesting that doctors do not accept gifts, hospitality, or travelling expenses from drug companies and instead has produced a code full of words like "acceptable," "moderate," "reasonable," "relevant," and "appropriate." The college admits that judging what is acceptable may be difficult, and the truth is that a weekend in