making processes that can be further improved to achieve legitimacy and fairness (p 1316).[1] An ethical approach to fair process must build on their findings.

A fair process requires publicity about the reasons and rationales that play a part in decisions. There must be no secrets where justice is involved, for people should not be expected to accept decisions that affect their well being unless they are aware of the grounds for those decisions. The study found that transparency was important to participants in the decisions, though it did not state whether the rationales for decisions were then made transparent to all affected by them. This broader transparency is a hallmark of fair process. Fair process also involves constraints on reasons. Fair minded people—those who seek mutually justifiable grounds for cooperation—must agree that the reasons, evidence, and rationales are relevant to meeting population health needs fairly, the shared goal of deliberation. The kinds of reasons described in the study meet this condition, but the institutions studied—committees concerned with implementing new technologies—did not face the more difficult task of comparing quite different benefits across different groups of patients under budget limits.

Fair process also requires opportunities to challenge and revise decisions in light of the kinds of considerations all stakeholders may raise. Though the committees studied by Singer et al gave evidence that decisions improved—that is, became more sensitive to patient variations—through revision, there should be a mechanism for appeals to decisions by those affected by them. The fact that a single lay member of the cardiac committee did not function as effectively as the three lay members of the cancer committee is a lesson that must be taken seriously in designing fair procedures.

Accountability for reasonableness makes it possible to educate all stakeholders about the substance of deliberation about fair decisions under resource constraints. It facilitates social learning about limits. It connects decision making in healthcare institutions to broader, more fundamental democratic deliberative processes.

Accountability for reasonableness also occupies a middle ground in the debate between those calling for "explicit" and "implicit" rationing.[10] Like implicit approaches, it does not require that principles for rationing be made explicit ahead of time. But, like explicit approaches, it does call for transparency about reasoning that all can eventually agree is relevant. Since we may not be able to construct principles that yield fair decisions ahead of time, we need a process that allows us to develop those reasons over time as we face real cases. The social learning that this approach facilitates provides our best prospect of achieving agreement over sharing medical resources fairly.

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The endometrium and embryo implantation

A receptive endometrium depends on more than hormonal influences

How embryos attach and implant remains a mystery. Implantation represents the remarkable synchronisation between the development of the embryo and the differentiation of the endometrium. As long as these events remain unexplained, improvement in the success of in vitro fertilisation treatment and the development of contraception that modifies implantation is likely to be difficult.

In most animals, the endometrium undergoes a series of changes leading to a period of uterine receptivity called the "window of implantation." Outside of this time the uterus is resistant to embryo attachment. In a study by Hertig et al in 1956, women were asked to record their menstrual pattern and dates of unprotected intercourse before they had a hysterectomy for benign gynaecological disease.[1] With their informed consent, their uteruses were carefully examined after operation, and the authors found that a number of them had conceived just before surgery. In these cases, embryos found in the uterus before the 20th day of the menstrual cycle were "free lying"—that is, not attached to the endometrium. Embryos found on or after the 21st day of the menstrual cycle were attached. Naturally, such research would not be performed today, but data from in vitro fertilisation programmes have substantiated these findings.[2] During in vitro fertilisation treatment embryos replaced before the 20th day may implant; those replaced after the 24th day do not.

The architectural changes that occur to the endometrium during a 28 day menstrual cycle were also investigated in the 1950s using light microscopy.[3] Alterations in the endometrium during days 16 to 20 mainly affect the epithelial glands, which show increased secretory activity, prominent subnuclear vacuoles, and a decrease in mitotic activity. The stroma abruptly becomes oedematous on day 21. In the 1980s, electron microscopy studies identified epithelial protrusions into the uterine cavity called pinopodes; these appear between day 19 and day 21.[4] In animals

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and humans their appearance coincides with a receptive endometrium.

Changes in the expression of molecules on the cell surface have also been observed in the conversion of the endometrial surface from a non-receptive to a receptive state. The mucins, a group of antiadhesive molecules, seem to have the most profound effect. They make up part of a thick layer, the glycocalyx, on the luminal epithelial surface of the uterus. In mice the glycocalyx prevents the embryo from direct contact with the endometrium, but changes in concentrations of oestrogen and progesterone after ovulation cause this layer to thin. This exposes the endometrium and enables it to react with the cells of the embryo.[5] In humans the mucins, specifically MUC-1, are also under hormonal control, but in contrast to mice the endometrial epithelium continues producing MUC-1 while it is receptive to embryo implantation.[6] This suggests that implantation is different in humans. It is conceivable that a decrease in MUC-1 is localised to specific but as yet unidentified receptor sites in humans and that this decrease is directed by the embryo itself. Alternatively, hormonal changes during the receptive phase may cause a subtle alteration in the structure of MUC-1 that allows the embryo to attach and implant. Furthermore, in both animals and humans the MUC-1 mucin has been found in the fallopian tube. Although it is not known whether it is under hormonal control at this site, it clearly could prevent ectopic pregnancy because of its antiadhesive properties.

Although the regulation of antiadhesion molecules, such as mucin glycoproteins, is undoubtedly important, this alone is not sufficient to support the attachment of the embryo to the uterine epithelial cells. The expression of adhesion molecules, such as integrins, selectins, cadherins, and the immunoglobulin superfamily, is also thought to be involved in the development of a receptive state. In the endometrium, the profile of expressed integrins varies according to the phase of the menstrual cycle; the combined presence of certain integrins has been proposed as a means of distinguishing receptive endometrium from non-receptive.[7] The pattern of temporal expression of the selectins, cadherins, and immunoglobulin superfamily is less well defined in humans because much of the data are derived from animal studies.

Because of the ethical and moral dilemmas faced by researchers investigating embryo implantation, most of the in vivo data are from studies that have examined the endometrium or embryo in isolation. It is therefore not surprising that the coordination of the process of human embryo attachment has been attributed to oestrogen and progesterone and to "quality embryos."[8] The embryo is not passive but is an active orchestrator of its attachment and fate. The spatiotemporal expression of embryonic proteins and their influence on the endometrium may prove to be critical. Consequently, co-culture techniques using donor embryos and endometrial epithelial cells with or without their stroma are being developed. Such in vitro approaches will contribute to our understanding of the complex interaction between the embryo and the endometrium. Unravelling the mystery of the mechanisms controlling the receptivity of the human endometrium remains an exciting challenge.

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Treatment of bipolar affective disorder

New drug treatments are emerging, but more clinical evidence is required

Bipolar affective disorder is a common condition which, among mental illnesses, ranks second only to unipolar depression as a cause of worldwide disability.[1] Classically, it manifests itself as repeated periods of illness with complete recovery. However, many patients have a poor outcome: a third suffer chronic symptoms and some 13-24% develop rapid cycling disorder, where four or more episodes occur within a year. The lifetime risk of bipolar disorder is at least 1.2%, with a recognised risk of completed suicide of 15%. Young men, early in the course of their illness, are at highest risk, especially those with a history of suicide attempts or alcohol abuse and those recently discharged from hospital. Despite its shortcomings, lithium has long been the mainstay of treatment for bipolar affective disorder. Several newer drugs have emerged over the past 10 years, but evidence of their effectiveness remains disappointingly thin.

Ideally, mood stabilisers should treat both mania and depression and prevent their recurrence. Importantly, treatment itself should not precipitate mania or depression or induce rapid cycling. Lithium has been used as a mood stabiliser in bipolar disorder for 50

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