9. How can the transmissal of information best be assessed?

10. How should records be kept (e.g., on computer) to trace and counsel persons at "high" risk?

Rare inborn errors and, more recently, chromosome abnormalities have traditionally intrigued medical geneticists. Leonard and her associates have focused on relatively common disorders. Why is this not being done more systematically by more medical centers? Do we not have some obligation to seek out families with common, serious genetic disorders and to provide counseling? Programs to detect sickle trait, the most common autosomal recessive condition in American blacks, are sprouting up everywhere. Should efforts be made to do the same thing for cystic fibrosis, the most common recessive disease in white children?

Just because we do not understand the molecular events in a disease, should we desist from supplying what knowledge we do have to all affected families? There are many families with relatively common, potentially catastrophic diseases such as neurofibromatosis and tuberous sclerosis, Marfan's syndrome and Huntington's chorea. All are autosomal dominant traits.

Should there be state or regional genetic registries to help follow such families and prod us into providing them with relevant genetic information? Such registries could be similar to those piloted recently on computer in Oregon and in Scotland, and named, respectively, FAMFL (Family File)[2] and RAPID (Register for the Ascertainment and Prevention of Inherited Disease).[3]

Probably the most poorly charted area in genetic counseling is that of polygenic disorders. These include diabetes mellitus, psoriasis, atopic disease, and essential hypertension. Also included are many of the most common congenital malformations such as cleft-lip-palate, congenital dislocation of the hip, cardiac malformations and possibly meningomyelocele, hydrocephalus, and anencephaly. As a rule of thumb these disorders are associated with a recurrence risk of about 5 per cent for subsequent sibs of affected children. How well are we counseling such families? A pilot study[4] in a congenital heart clinic with considerable genetic expertise indicates that after receiving genetic information, only about 25 per cent of families retained and understood the attendant recurrence risks.

What is the objective of genetic counseling? If it is to lessen the chance of subsequent affected sibs being born, the available data are discouraging. For instance, it has been found[5] that parents generally do not consider a risk of 10 per cent (or less) sufficient reason to limit family size.

What is the magnitude of the demand for genetic counseling? How should these services be funded? These crucial questions about genetic-counseling services are also currently without answers.

The foregoing questions should, we hope, suffice to suggest the extent of what we don't know. Now it is apparent that some answers are needed.

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INFORMED (BUT UNEDUCATED) CONSENT

THE trouble with informed consent is that it is not educated consent. Let us assume that the experimental subject, whether a patient, a volunteer, or otherwise enlisted, is exposed to a completely honest array of factual detail. He is told of the medical uncertainty that exists and that must be resolved by research endeavors, of the time and discomfort involved, and of the tiny percentage risk of some serious consequences of the test procedure. He is also reassured of his rights and given a formal, quasi-legal statement to read. No exculpatory language is used. With his written signature, the subject then caps the transaction, and whether he sees himself as a heroic martyr for the sake of mankind, or as a reluctant guinea pig dragooned for the benefit of science, or whether, perhaps, he is merely bewildered, he obviously has given his "informed consent." Because established routines have been scrupulously observed, the doctor, the lawyer, and the ethicist are content.

But the chances are remote that the subject really understands what he has consented to — in the sense that the responsible medical investigator understands the goals, nature, and hazards of his study. How can the layman comprehend the importance of his perhaps not receiving, as determined by the luck of the draw, the highly touted new treatment that his roommate will get? How can he appreciate the sensation of living for days with a multi-lumen intestinal tube passing through his mouth and pharynx? How can he interpret the information that an intravascular catheter and radiopaque dye injection have an 0.01 per cent probability of leading to a dangerous thrombosis or cardiac arrhythmia? It is moreover quite unlikely that any patient-subject can see himself accurately within the broad context of the situation, to weigh the inconveniences and hazards that he will have to undergo against the improvements that the research project may bring to the management of his disease in general and to his own case in particular. The difficulty that the public has in understanding information that is both medical and stressful is exemplified by the report starting on page 433 — only half the families given genetic counseling grasped its impact.

Nor can the information given to the experimental subject be in any sense totally complete. It would be impractical and probably unethical for the investigator to present the nearly endless list of all possible contingencies; in fact, he may not himself be aware of every untoward thing that might happen.

Extensive detail, moreover, usually enhances the subject's confusion. Epstein and Lasagna showed that comprehension of medical information given to untutored subjects is inversely correlated with the elaborateness of the material presented.[1] The inconsiderate investigator, indeed, conceivably could exploit his authority and knowledge and extract "informed consent" by overwhelming the candidate-subject with information.

Ideally, the subject should give his consent freely, under no duress whatsoever. The facts are that some element of coercion is instrumental in any investigator-subject transaction. Volunteers for experiments will usually be influenced by hopes of obtaining better grades, earlier parole, more substantial egos, or just mundane cash. These pressures, however, are but fractional shadows of those enclosing the patient-subject. Incapacitated and hospitalized because of illness, frightened by strange and impersonal routines, and fearful for his health and perhaps life, he is far from exercising a free power of choice when the person to whom he anchors all his hopes asks, "Say, you wouldn't mind, would you, if you joined some of the other patients on this floor and helped us to carry out some very important research we are doing?" When "informed consent" is obtained, it is not the student, the destitute bum, or the prisoner to whom, by virtue of his condition, the thumb screws of coercion are most relentlessly applied, it is the most used and useful of all experimental subjects, the patient with disease.

When a man or woman agrees to act as an experimental subject, therefore, his or her consent is marked by neither adequate understanding nor total freedom of choice. The conditions of the agreement are a far cry from those visualized as ideal. Jonas would have the subject identify with the investigative endeavor so that he and the researcher would be seeking a common cause. "Ultimately, the appeal for volunteers should seek . . . free and generous endorsement, the appropriation of the research purpose into the person's [i.e., the subject's] own scheme of ends."[2] For Ramsey, "informed consent" should represent a "covenantal bond between consenting man and consenting man [that] makes them. . . joint adventurers in medical care and progress."[3] Clearly, to achieve motivations and attitudes of this lofty type, an educated and understanding, rather than merely informed, consent is necessary.

Although it is unlikely that the goals of Jonas and of Ramsey will ever be achieved, and that human research subjects will spontaneously volunteer rather than be "conscripted,"[2] efforts to promote educated consent are in order. In view of the current emphasis on involving "the community" in such activities as regional planning, operation of clinics, and assignment of priorities, the general public and its political leaders are showing an increased awareness and understanding of medical affairs. But the orientation of this public interest in medicine is chiefly socioeconomic. Little has been done to give the public a basic understanding of medical research and its requirements not only for the people's money but also for their participation. The public, to be sure, is being subjected to a bombardment of sensation-mongering news stories and books that feature "breakthroughs" or that reveal real or alleged exploitations — horror stories of Nazi-type experimentation on abused human minds and bodies. Muckraking is essential to expose malpractices, but unless accompanied by efforts to promote a broader appreciation of medical research and its methods, it merely compounds the difficulties for both the investigator and the subject when "informed consent" is solicited.

The procedure currently approved in the United States for enlisting human experimental subjects has one great virtue: patient-subjects are put on notice that their management is in part at least an experiment. The deceptions of the past are no longer tolerated. Beyond this accomplishment, however, the process of obtaining "informed consent," with all its regulations and conditions, is no more than an elaborate ritual, a device that, when the subject is uneducated and uncomprehending, confers no more than the semblance of propriety on human experimentation. The subject's only real protection, the public as well as the medical profession must recognize, depends on the conscience and compassion of the investigator and his peers.

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CORRESPONDENCE

Letters to the Editor are welcomed and will be published, if found suitable, as space permits. Like other material submitted for publication, they must be typewritten *double spaced* (including references), must not exceed 1½ pages in length and will be subject to editing and possible abridgment.

DIAGNOSTIC VALUE OF SERUM FOLATE LEVEL

To the Editor: The paper by Rothenberg et al. (N Engl J Med 286:1335, 1972) presenting a rapid radioassay for serum folate is an admirable accomplishment. The value of serum folate levels, whether determined via radioassay or *Lactobacillus casei*, is questionable. Recently, 30 bone-marrow specimens from anemic patients were studied with the use of the "dU suppression" test.[1] This test is a measure of the mode of DNA synthesis in bone-marrow tissue — i.e., normoblastic or megaloblastic. A normal dU suppression test means absence of cellular megaloblastosis. Of the 30 patients tested there were nine who had a normal dU suppression test concomitant with low *L. casei* serum folate levels. None of these patients responded to folic acid or vitamin B_{12} therapy, and none were receiving antibacterial therapy.

A point to be made is that serum folate levels are a poor index of tissue folate content. Low serum folate levels in the presence of anemia do not necessarily mean that the anemia is due to bone-marrow tissue depletion of folate. As shown by others,[2] up to 45 per cent of hospitalized patients may have low serum folate levels. It would behoove the clinician to weigh the serum folate level against the medical history and peripheral blood and bone-marrow morphology. The technic that I have found the most reliable indicator to response to therapy (folate or vitamin B_{12}) when marrow is

Freebird Report.

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Eric.

Could you file with human subjects info?

Thanks

Ramon