Genetic screening: Promises and pitfalls

Genetic disorders can be detected far more easily than most people realize. Fetuses can be screened for chromosomal abnormalities. Newborns can be screened for chromosomal, amino acid and red blood cell disorders. And adults can be tested to see whether they are genetic carriers of chromosomal, red blood cell or amino acid disorders. So should the American population undergo routine mass screenings to identify persons who have genetic diseases or are genetic carriers of these diseases?

Ideally, yes—but not until society comes more to grips with the medical, economic and ethical constraints of such screening. This is the emphatic response of the National Research Council's Committee for the Study of Inborn Errors of Metabolism. The committee made its views public this week in a 388-page report and at a press conference at the National Academy of Sciences, parent of the NRC.

The committee views mass genetic screening as a progressive health care concept. Family physicians would take blood samples routinely from patients and from fetuses. The blood samples or fetal cell samples would be run through automated regional or state laboratories and checked for genetic diseases and to see whether people are genetic carriers of these diseases. The family physician would then be in charge of treating persons found to have specific diseases. They would counsel women found to carry fetuses with genetic diseases about abortions and counsel couples found to be carriers of genetic diseases on whether they should reproduce.

However progressive the concept, the committee warns, it is fraught with medical, economic and ethical pitfalls that must be overcome before it is implemented.

On the medical front, for example, physicians are far from ready to participate in mass genetic screening. In fact, declares committee chairman Barton Childs of the Johns Hopkins University School of Medicine, "They are generally ignorant of its aims and uses." Even if physicians were prepared for action, there are questions about the safety of screening techniques. The only method available for diagnosing genetic diseases in the fetus, amniocentesis, is now being studied by the National Institutes of Health to be sure that it doesn't harm women or the fetuses they carry.

And even if physicians were ready and techniques were safe, the costs of routine mass screening would be prohibitive at present. Suppose a couple wanted to have all the tests for genetic disease carriers that are now available, to make sure that they will not pass genetic diseases onto their children. Such tests could easily cost them $500, estimates committee member Robert F. Murray Jr. of Howard University School of Medicine. Were all couples able to afford such stiff fees, the nation's laboratories could not begin to routinely screen all couples in a comparable way. In fact, says Murray, there are not even enough laboratories at this time to do an amniocentesis on all pregnant women over age 35 to see whether the fetuses they carry have Down's syndrome.

Then there is the question of value: Will routine screening help more than it will hurt? There is no doubt, the committee reports, that the only genetic screening that is now routinely done—the screening of newborns for phenylketonuria (PKU)—has reduced the incidence of mental retardation caused by the disease. But how many fetuses will be unfairly sacrified when they are diagnosed for diseases of lesser severity—say sickle cell anemia?

Being diagnosed for a genetic disease, the committee fears, might also lead to stigmatization by society. Psychiatrist Stanley Walzer and geneticist Park Gerald of Harvard Medical School studied the behavioral development of 40 children with chromosomal aberrations to determine the adverse effects associated with the aberrations and whether these effects might be modified by early recognition and proper therapy. The investigators have now stopped the study because a group charged that the study could stigmatize the children. Central to the issue was the study of boys with the XYY chromosomal makeup, which has been linked in the public mind to criminally aggressive behavior. (Several years ago a study found that a large proportion of prisoners showed this chromosomal pattern. Later evidence has tended to discount the finding.)

Still, Childs asserts, it is this kind of study that is needed if genetic screening is to be widely applied. Should evidence from a few people, such as prisoners, be extrapolated to the population at large? And precisely how might certain chromosomes lead to certain behaviors?

If and when mass genetic screening arrives, the committee concludes, it should be voluntary, including routine screening for PKU in newborns. □

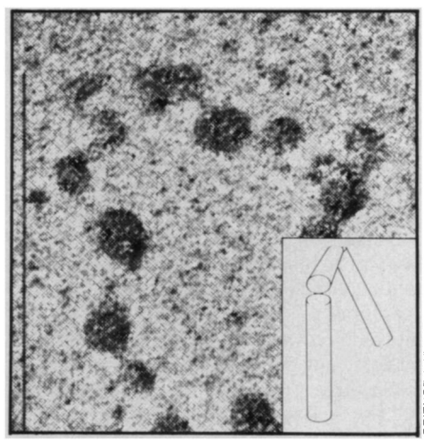
DNA in the nucleus: A kinky helix

A cell's nucleus is a bit like organic lace. A twisted cord of DNA a meter long plus some attached proteins called histones, are coiled and folded into a tiny orderly pattern capable of directing the cell's activities. Like other biomolecules, chromatin (DNA plus histones) is an integration of form and function. For this reason, biologists are studying the form of chromatin and hoping to learn more about the function. Just how, they wonder, does DNA really work? How does the same meter-long message, coiled into every nucleus, cause one cell to make hemoglobin and another to make red hair? The clues, some think, lie in the chromatin.

The most widely accepted theory of chromatin structure, emerging from a dozen or so pieces of research in the last year, is this: Strands of DNA and the attached histones are coiled into a connected series of tiny beads. Each bead, it is believed, contains perhaps 200 nucleic acid base pairs and is bent into a ball 100 angstroms across with histones on the inside and DNA segments on the outside. A bead's "label"—a short marker segment of DNA base pairs—could be recognized by activator molecules which select certain beads and turn them on. Although the activators are still a mystery, this theoretical system could explain how some DNA segments are turned on to produce, say, hemoglobin, while the rest are turned off.

There is an interesting question associated with this chromatin bead theory.

How could such a long DNA strand, with its characteristic double helix, be wrapped into such a tiny particle and still work correctly? Its function, too, depends on its form—its exact bond angles and energies, curves and diameters. If the strand were bent into a series of 90-degree turns, the bonding angles of the sugar phosphate backbone would be warped. Cambridge University biologists Francis H.C. Crick (honored for the double helix structure itself) and Aaron Klug propose in the June 12 NATURE a model for a "kinky helix" that just might work. The DNA, instead of bending diffusely, kinks—changes directions abruptly at a single spot on the backbone. This explanation, at least on paper, seems to reconcile the necessary bond angles and base pair sequence lengths observed experimentally. Although there is "no compelling evidence" for kinking rather than bending, the team intones with British understatement, the model seemed "sufficiently attractive" to present. Whether it's correct, they say, remains to be seen. □



Chromatin beads; DNA kinks (tube model).