MEDICINA NEI SECOLI ARTE E SCIENZA, 14/3 (2002) 793-811
Journal of History of Medicine

Articoli/*Articles*

HISTORICAL ASPECTS OF GENETIC COUNSELING: WHY WAS MATERNAL AGE 35 CHOSEN AS THE CUT-OFF FOR OFFERING AMNIOCENTESIS?

ROBERT G. RESTA
Division of Perinatal Medicine Swedish Medical Center
Seattle, WA, USA

SUMMARY

The justification for offering amniocentesis to women age 35 or older is that by age 35 the risk of having a child with a chromosome problem is greater than the risk of amniocentesis. In fact, this seemingly objective statement is not supported by historical analysis. Maternal age 35 was chosen for the cutoff based mostly on economic cost-benefit analysis rather than objective medical assessment. The story of why 35 was chosen illustrates how collective memory can affect, and be influenced by, the guiding ethical principles of a medical profession.

Most genetic counselors maintain that the focus of their work is helping families cope with the psychological, emotional, social, and medical effects of genetic disease[1]. Cognizant of the eugenic roots of medical genetics, genetic counselors try to differentiate current genetic counseling practice from past eugenic abuses by emphasizing the importance of nondirective counseling, a client-centered ethos and patient autonomy. However, some aspects of genetic counseling can still be construed as eugenic and in conflict with the profession's ethical values and philosophy.

In this article I will briefly review the history of genetic counseling and amniocentesis in the United States. I will then discuss the development of amniocentesis guidelines during the 1970's,

Key words: Genetic counseling – Amniocentesis - Cost-benefit analysis – Eugenics - Collective memory

and show how the historical reasons are discordant with the reasons that genetic counselors currently cite as the justification for offering amniocentesis at maternal age 35. The discrepancy between the history of amniocentesis and the current counseling practice illustrates the concept of "collective memory" - the historical memory shared by a professional or social group.

Genetic Counseling

The term "genetic counseling" was coined in 1946 by Sheldon Reed of the Dight Institute of Human Genetics in Minnesota[2]. Reed had a doctorate in laboratory genetics but developed an interest in the clinical and psychological issues raised by families affected with genetic diseases. Reed envisioned genetic counseling *"as a kind of genetic social work without eugenic connotations"*[3].

For Reed, genetic counseling was a medical and psychological interaction rather than a form of eugenics (although Reed, like other medical geneticists of his time, supported eugenic goals)[4]. Reed's concept of genetic counseling laid the groundwork for the development of the genetic counseling profession in the United States, even though Reed played no direct role in the establishment of genetic counseling training programs.

During the 1960's geneticists recognized the need for a professionally trained specialist with genetic counseling skills and a philosophy of genetic counseling that focused on the psychological impact of genetic disease[5]. However, it was only with the establishment in 1969 of a genetic counseling graduate training at Sarah Lawrence College in New York City that the concept of a genetic counseling specialist became a reality. Currently in the United States, genetic counseling is usually conducted by more than 2000 genetic counselors who have graduated from one of the more than twenty genetic counseling training programs in the United States.

The profession of genetic counseling developed and diffused during the 1970's at the same time that amniocentesis was being introduced into medical care. Many of the first students who graduated from genetic counseling training programs found em-

ployment in prenatal diagnosis programs. To this day, more than half of all genetic counselors are employed in a prenatal diagnosis clinic[6]. Thus, genetic counseling and prenatal diagnosis share a long and intimate history.

Genetic Counseling and Eugenics

Genetic counselors usually view eugenics as "misguided genetics" that took place prior to World War II, and is embodied in the works of Charles Davenport, Harry Laughlin and the Eugenics Record Office. After World War II, as the story usually goes, geneticists renounced eugenics and encouraged the principals of patient autonomy and nondirectiveness[7]. In reality, through at least the 1970's, some medical geneticists, if not genetic counselors, continued to espouse eugenic goals[8].

Cognizant of the eugenic origins of medical genetics, genetic counselors have been careful to distinguish between eugenics and genetic counseling. Following Sheldon Reed's lead, genetic counselors have focused on the emotional and psychological impact of genetic disease on families. In the psychosocial approach, the primary goal of genetic counseling is to help families cope with the emotional, social, psychological and medical effects of genetic diseases. Eugenic goals are not typically supported by genetic counselors, and in fact, genetic counselors actively espouse a philosophy of nondirectiveness which dictates that patient decision-making should be autonomous and free from social and political pressure[9].

Amniocentesis

The first prenatal diagnosis of a fetal defect was reported in 1916 when radiologist James Case used x-rays to diagnose anencephaly in a third trimester fetus. Over the next twenty years, several fetal defects were identified by x-rays[10], laying the groundwork for obstetrical interest in prenatal diagnosis of fetal disorders.

Although the German physician Schatz is generally credited with proposing amniocentesis in the 1880's, the first amniocentesis was not reported until 1919[11]. In the 1930's, amniocentesis

was used in conjunction with x-rays in a technique called amniography. Amniography involves withdrawing amniotic fluid and replacing it with a radioopaque liquid, permitting enhanced x-ray visualization of the fetus and placenta. By the 1950's amniocentesis was used to determine the severity of erythroblastosis fetalis in Rh-sensitized pregnancies, to relieve polyhydramnios, and to determine fetal lung maturity before labor induction[12].

In 1956 Tjio and Levan reported that human cells have a modal number of 46 chromosomes[13]. A few years later, Lejeune and colleagues identified trisomy 21 as the chromosomal basis for Down syndrome[14]. With improvements in cell culturing techniques by the mid-1960's, amniotic fluid cells could be used to diagnosis fetal chromosomal defects in utero[15]. The development of chromosomal banding techniques in the early 1970's improved the identification of individual chromosomes and also allowed for detection of structural chromosome defects such as deletions and small translocations[16].

Legal and social factors also influenced the integration of amniocentesis into obstetric care, perhaps the most important of which was the legalization of abortion. Because chromosomal diseases are not treatable, the availability of abortion gave patients the option to terminate pregnancies in which amniocenteses had revealed cytogenetic abnormalities. The 1973 Supreme Court ruling in *Roe v. Wade* made abortion legal – and ultimately safe. The availability of safe abortion also fit well with eugenic goals and cost-benefit analyses (see below).

State and other local courts ruled that physicians could be held legally liable if they did not offer amniocentesis to high-risk patients. In1971, a state court ruled that a physician could not be held liable for not offering amniocentesis to a patient[17]. By the late 1970's, several courts had ruled that physicians were negligent for not offering amniocentesis to women aged 35 and older[18].

In addition to legal factors, social trends helped integrate amniocentesis into obstetric care. As Ruth Cowan Schwartz has pointed out, women themselves were very active in making am-

niocentesis available[19]. These women were probably fueled by the Feminist Movement and the increasing demand for patients' rights, both of which encouraged women to take a more active role in their medical care.

By 1978, the American College of Obstetricians and Gynecologists told its membership that amniocentesis should be considered a clinical, not a research, procedure[20].

The Symbiotic Relationship between Amniocentesis and Genetic Counseling

The introduction of amniocentesis into routine medical practice has helped foster the growth of the genetic counseling profession. The link between genetic counseling and amniocentesis was evident when genetic amniocenteses were performed in the mid-1960's. In the words of Cecil Jacobsen, one of the first physicians to perform amniocentesis, "*Culturing amniotic fluid for* counseling *in chromosomal diseases was first advanced by Fuchs....*" [non italics added][21]. During the 1970's, the availability of amniocentesis and genetic counseling spread hand-in-hand.

As amniocentesis worked its way into medical practice, many authors and professional organizations stated the need for genetic counseling prior to amniocentesis[22]. By explaining the risks, benefits and limitations of amniocentesis, as well as exploring the underlying psychosocial issues, genetic counselors helped patients decide whether or not to undergo prenatal testing. Genetic counseling also afforded legal protection for obstetricians, since genetic counseling provided informed consent for their patients.

Almost all genetic counselors work as part of a team of healthcare professionals that provides medical genetics services and testing. Many health insurance plans in the United States did not - and still do not - provide coverage for genetic counseling by genetic counselors. Furthermore, the time commitment of a genetic work-up is such that even if insurance reimbursement were universally available, it would be inadequate to cov-

er the cost of the service[23]. The salaries of genetic counselors are therefore often drawn from the department's budget.

The advent of amniocentesis provided income for genetics departments through the charges for performing amniocentesis and particularly with the charges for cytogenetic studies of amniotic fluid. Although genetic counselors' salaries are not based on the number of patients they persuade to undergo amniocentesis, the income generated by prenatal diagnosis is vital to the employment of genetic counselors.

Thus, the provision of amniocentesis to a large extent depends on the availability of genetic counseling, and the continued employment of genetic counselors depends upon the counseling opportunities and departmental income provided by amniocentesis. This symbiotic relationship poses an ethical and philosophical dilemma for genetic counselors: on the one hand, genetic counselors specifically reject eugenic doctrine; on the other hand, the net effect of amniocentesis is eugenic[24].

Establishing eligibility criteria for amniocentesis

Not all women could have access to prenatal testing because of the limited availability of specialty centers where amniocentesis and chromosomal analysis could be performed, as well as the expense and risks of amniocentesis. Therefore, eligibility criteria needed to be established, and the most obvious and simplest criterion was maternal age.

From it's inception to the present, the most common reason for performing amniocentesis has been "advanced maternal age." In the United States, women who are 35 years or older at the time of delivery of the pregnancy are considered appropriate candidates for amniocentesis.

Why was thirty-five years old chosen as the age cut off for offering amniocentesis? Most genetic counselors, obstetrics books and articles state that by age 35, the benefits of amniocentesis outweigh the risks. That is, the risk of miscarriage associated with amniocentesis is about 0.5%[25]. By age 35, the risk of a chromosomal abnormality in the fetus is slightly greater than 0.5%. The cutoff is determined simply on the basis of medical

risk-benefit analysis. But a closer look reveals that the reason for choosing age 35 as the cutoff for offering amniocentesis is more complex.

In the early 1930's Lionel Penrose firmly established the association between older maternal age and an increased risk for Down syndrome in her offspring[26]. Penrose was also the first to identify 35 as a crucial maternal age in understanding the epidemiology of Down syndrome:

"Though some of these imbeciles have young mothers, most of the cases (about 70%) are born after the mother has reached the age of 35 years" [27].

In fact, the percentage of Down syndrome cases due to advanced maternal age varies with demographics and reproductive patterns. To a large extent, it is dictated by the numbered of women over 35 having babies compared to the number of younger women having babies. The proportion is further influenced by social factors, such as the availability of abortion and contraception, and social pressures to delay or not delay childbearing.

In 1967, when Cecil Jacobson and Robert Barter reported some of the earliest experience with genetic amniocentesis, they did not include maternal age as an indication for undergoing the procedure[28]. In 1968, the American College of Obstetricians and Gynecologists did not consider the mother's age as an indication for amniocentesis[29]. By the early 1970's, the primary indication for amniocentesis was maternal age, though it was not clear which maternal age was the best cut-off for offering amniocentesis[30]. By the mid-to late 1970's, maternal age 35 or older was firmly entrenched as the standard of care for offering amniocentesis. In 1976, the American College of Obstetricians and Gynecologists, in a Technical Bulletin sent to its membership, stated that 35 years of age should be the appropriate age at which to start offering amniocentesis[31]. In 1979, a consensus conference convened by the United States National Institute of Child Health and Development made the same recommendation[32].

By 1979, James Sorenson and Judith Swazey could confidently say:

> *"It is fairly well accepted medical practice now to tell pregnant women 35 and older of their increased risk for having a child with a chromosomal aberration, and to offer amniocentesis"*[33].

The reason why maternal age 35 or older became the medical standard is the result of three related factors:

- economic cost-benefit analysis
- eugenic ideologies
- medical risk-benefit analysis

These factors are discussed below.

Economic Cost-Benefit Analysis: A Modern Form of Eugenics?

During the 1970's and early 1980's numerous researchers utilized economic cost-benefit analyses to determine the best maternal age cut-off for offering amniocentesis[34]. These studies asked the same question – At what maternal age is the economic cost of amniocentesis lower than the economic cost of caring for people with Down syndrome?

The studies used slightly different approaches, made slightly different assumptions, and were conducted in settings where reproductive demographics varied. Given the different methodologies, assumptions and study populations, it is not surprising that the studies came to slightly different conclusions about the best maternal age to start offering amniocentesis. However, most studies suggested that age 35 was the break-even point for economic cost-benefit. Conley and Milunsky summarized this in the conclusion of their 1975 cost-benefit analysis:

> *"In the past, over half of all offspring born with Down syndrome were to women over 35....In short it is economically feasible, on the basis of the limited benefits that were measured, to prevent the birth of over half of all cases of Down syndrome"*[35].

Economic cost-benefit analysis, when applied to genetics, has underlying eugenic connotations, though geneticists seem reluctant to admit this. Traditionally, eugenics focused on the quality of the gene pool. In cost-benefit analysis, the goal is not to eliminate "bad genes" so much as it is to minimize the economic losses generated by caring for people with disabilities.

These eugenic connotations can be illustrated by examining two of the implicit and explicit assumptions of the study - the risks of amniocentesis and the alternatives to a prenatal diagnosis program.

With one exception, *none* of the studies included the risk of amniocentesis in the cost calculation. The exception was the Stein *et al.* study, which acknowledged the risks of amniocentesis but downplayed their economic consequences. It is surprising that little attention was given to the risks of amniocentesis, given that there are some medical costs associated with miscarriage, as well as the economic loss of the earnings that these normal children would eventually have produced had they not miscarried. Indeed, one article even went so far as to say that amniocentesis did not carry any excess risks and therefore the complications did not need to be taken into account in the cost-benefit analysis:

> *"We assume no adverse effects, leading to increased costs, due to risks associated with the amniocentesis procedure itself. In our literature survey, we found three large-scale studies in the United States and Canada which indicated there is no excess risk to women undergoing amniocentesis"*[36].

While ignoring the risks of amniocentesis is not eugenic *per se*, it does suggest that some of the researchers' beliefs may have subtly influenced the assumptions of the studies, and therefore the outcome of cost-benefit analysis. That some of these researchers had a eugenic agenda is evident in this quote from the Stein *et al.* cost-benefit study:

> *"We are less certain about the balance of costs, at current rates, of screening the whole pregnant population. But is a detailed estimate of money costs required? The lifelong care of severely retarded persons is so burdensome in almost every human dimension that no preventive program is likely to outweigh the burden"*[37].

Besides not considering the risks of amniocentesis, none of the cost benefit analyses compared the costs of the prenatal elimination of Down syndrome with the costs of alternatives to elimination. All of the studies compared the cost of amniocentesis with the current medical, custodial and educational costs of caring for individuals with Down syndrome. No study compared the cost of amniocentesis to the cost of developing better programs to improve the medical care, economic opportunities, and education of people with Down syndrome.

Thus, while cost-benefit analysis appears on the surface to be an objective and rational approach to allocating limited resources, the underlying assumptions of the studies indicate that the studies reflect some eugenic ideologies and biases. And whatever the intentions of cost-benefit analysis, the net social effect is eugenic, *i.e.*, a reduction in the number of people with Down syndrome.

Conservative Eugenics

Some authors justified amniocentesis on traditional eugenics grounds - that is, improvement of the gene pool by reducing the number of low IQ individuals. These authors were also concerned that amniocentesis could be dysgenic by encouraging heterozygous parents, who may have refrained from having children if amniocentesis were not available, to reproduce, knowing that they could terminate affected fetuses. The net effect would be dysgenic, *i.e.*, an increase in the number of carrier children, because parents would not terminate heterozygous fetuses.

However, overall, amniocentesis was believed to have the potential to improve the gene pool: *"In general, antenatal diagnosis is likely to have beneficial (eugenic) effects on the gene pool"*[38].

Terrance Swanson, a lawyer with the Department of Forensic Studies at Indiana University, expressed the eugenic justification for amniocentesis in 1970:

> *"If we allow our genetic problems to get out of hand by not acting promptly to ameliorate the situation, we as a society run the risk of over committing ourselves to the care and maintenance of mentally deficient patients at the expense of other urgent social program"*[39].

Swanson further expressed his conservative eugenic beliefs when he stated:

> *"A major problem has been that while upper and middle income groups have embraced the family planning concept, it has not yet reached the lower income groups to any great extent. Thus, while the birth rate and number of births have declined in recent years, the quality of this year's crop might be considered lower too"*[40].

Swanson was not alone in his concern about the apparent increase in the number of mentally deficient individuals, an alarmist cry that harks back to the early twentieth century eugenicists. In the Stein *et al.* cost-benefit analysis discussed above, the authors suggested that the prevalence of Down syndrome may have increased by over 100-fold during the course of the twentieth century. They felt that the rise was due in part to money spent on improved care for people with Down syndrome, the net effect of which was a longer life span for individuals with Down syndrome. Their concern for the public effects of this apparent increase is reflected in their suggestion that the prenatal diagnosis program in New York City should be carried out under the auspices of the Department of Health[41].

Eugenic goals were sometimes couched in medical terminology. In a discussion following Jacobsen and Barter's seminal 1967 paper on amniocentesis, one physician stated:

> *"With further expansion of these important studies...we can increasingly establish the normality of the fetus, thereby guaranteeing one of the basic rights of the unborn - the right to be 'well born'"* [42].

Basically, the eugenic justification for a maternal age cut-off was that should be offered to women at the age where it would have the greatest impact on the incidence of Down syndrome. As Hagard and Carter declared in their 1976 cost benefit analysis:

"To make a major impact on the problem [Down syndrome], however, would require mass prenatal diagnostic programs directed, in the first instance, towards all older pregnant women - that is, those at higher risk"[43].

Medical Risk-Benefit Analysis

Some physicians were concerned about the fetal risks of amniocentesis, and felt that those risks should be considered when offering amniocentesis. Geneticists Herbert and Marie-Louise Lubes acknowledged this in 1972:

"Since preliminary indications are that the risk of amniocentesis is less than 1%, it is not generally indicated unless the risk of an abnormal test is 1% or greater" [44].

The Lubs were not alone in expressing this view[45]. However, the difficult part was establishing the risks of amniocentesis. During the 1970's and 1980's, many studies tried to pinpoint the fetal loss rate due to amniocentesis. All the studies agreed that the risk for fetal loss was low, but the studies generated slightly differing risks, ranging from no increased risk to about a 1% increased risk of miscarriage[46]. Most surprisingly, not one of these studies found a miscarriage risk of 0.5%, the oft-quoted rate that genetic counselors claim forms the basis for offering amniocentesis at age 35!

In the study by Crandall *et al.*, the authors do state that the loss rate of amniocentesis is 0.5%:

"The authors believe that there is a small risk of early spontaneous abortion associated with second trimester amniocentesis (estimated to be @ 0.5%)...".[47]

However, a careful look at data from the Crandall study shows that the miscarriage rate in the amniocentesis group is in fact only 0.2% greater than the control groups, a difference that was not statistically significant. Thus, even though the authors "believe" the amniocentesis-related miscarriage rate is 0.5%, their data does not support their belief.

And even if Crandall *et al.*'s assertion were correct, why should the results of this one study be any more valid than the results of the other studies that found slightly higher or lower miscarriage rates? Presumably, if important decisions about the availability of amniocentesis are to be based on the risks of the procedure, the risks should be firmly established by several well-designed studies. And besides, as noted above, the age cut-off of 35 was established several years *before* the 1980 publication date of the Crandall *et al.* study.

Discussion

Maternal age 35 was chosen as the cutoff for offering amniocentesis primarily because of the results of economic cost-benefit analysis. Medical risk–benefit analysis and strict eugenic concerns played secondary roles in establishing eligibility criteria for amniocentesis. Indeed, I suspect that even if amniocentesis were indisputably shown to have a 0.5%miscarriage rate, but economic cost-benefit analyses showed that such programs were not profitable, then it is unlikely that large scale prenatal diagnosis programs would have developed to the extent that they did.

While 0.5% may be a reasonable approximation of the risk, no studies on the safety of amniocentesis support it. The amniocentesis risk figure of 0.5% appears to be a figure of convenience. Obstetricians and genetic counselors feel that they have to provide their patients with information about the risk of amniocentesis and patients typically demand very precise data. The 0.5% risk figure has become accepted because it has been repeated so often in the medical literature and daily medical practice that it has taken on a life of its own. That such a risk figure fit in well with the recommendations of economic cost-benefit analysis further encouraged its acceptance.

Indeed, it is likely that the "true" risk of amniocentesis will never be identified. Miscarriages that occur after amniocentesis rarely have unique characteristics that identify the amniocentesis as the cause for the miscarriage. Many studies have compared the loss rate between amniocentesis and control groups.

However, determining the loss rates in control and experimental groups, and comparing results across studies, can be hampered by technical factors such as different and sometimes flawed study designs, imperfect selection or matching of control groups, and the variable experience and skills of physicians performing amniocenteses.

If medical risk-benefit analysis played only a relatively minor role in the determination of amniocentesis eligibility, why is medical-risk benefit cited as the primary reason for offering amniocentesis at age 35? I suggest that this practice stems largely from the desire of genetic counselors to divorce themselves from eugenics. Genetic counselors view their role as helping people make emotionally difficult decisions. Economic cost-benefit analyses seem out of place during sensitive and psychologically intimate counseling sessions. Economic cost-benefit analysis is also antithetical to the cherished counseling ideology of non-coercion. However, genetic counselors cannot disassociate themselves from amniocentesis since the procedure is so vital to the employment of genetic counselors. Therefore, to avoid the awkward eugenic implications of economic cost-benefit analysis and amniocentesis, genetic counselors frame counseling decisions in terms of medical factors, i.e., the patient's risk of having a child with Down syndrome versus the risk of amniocentesis, and focus on the emotional and psychological implications of those decisions. Of course, while genetic counselors are trying to avoid eugenic implications, they work within a larger medical system that tolerates and even condones certain forms of eugenics.

It is also fair to say that many aspects of genetic counseling are not eugenic. Although most critics of genetic counseling have focused on reproductive issues, many genetic counselors work in settings where reproduction and eugenics are not relevant[48]. Such work settings include families at risk for adult onset diseases (e.g., breast cancer, colon cancer, neurogenetic disorders), newborn screening programs where treatment is the primary focus, or as liaisons between laboratories and the medical community. Genetic counselors also support non-eugenic

programs that prevent birth defects without becoming directly involved with reproductive decisions. Examples of such programs are the use of folic acid to prevent neural tube defects, rubella vaccination to prevent congenital rubella syndrome, and patient education about teratogens such as isotretinoin. In these situations, counselors are trying to prevent the defect rather than the person with the defect.

The oft-told story about the medical risk-benefit justification of amniocentesis is an example of "collective memory" - the memory of history shared by a particular group. Collective memory is not necessarily in agreement with the historical record. When applied to the history of science and medicine, collective memory has been shown to play a key role in legitimizing scientific practices[49]. Thus, genetic counselors have a collective memory of the risks of amniocentesis being 0.5%, and this risk forms the basis for offering amniocentesis at age 35. This collective memory meshes nicely with the non-eugenic philosophy and patient-centered practice of genetic counseling, and this philosophy helped shape the collective memory.

Economic cost-benefit analysis still plays a key role in determining the availability and justification for prenatal diagnosis services. The same type of economic cost-benefit analyses of amniocentesis that were performed in the 1970's are still being conducted today, although maternal serum screening and ultrasonography are combined with maternal age as the basis for offering amniocentesis[50]. And so perhaps a new collective memory will arise about the use of maternal serum screening and ultrasonography as a justification for amniocentesis.

BIBLIOGRAPHY AND NOTES

1. The idea for this article first emerged in a discussion with Diane Paul about 10 years ago. She has since provided several helpful references and discussion. Bruno Strasser introduced me to the concept of "collective memory." I would also like to thank the very helpful archive librarians at the American College of Obstetricians and Gynecologists (ACOG) for their assistance in obtaining ACOG documents.
2. RESTA R.G., *Sheldon Reed and 50 years of genetic counseling*. J. Genet. Counsel. 1997; 6:375-377.
3. RESTA R.G., ref. 2., p. 376.

4. RESTA R.G., *Eugenics and nondirectiveness in genetic counseling*. J. Genet. Counsel 1997; 6: 255-258.
5. BARTUSKA D.G., *Genetic counseling*. Clin Obstet Gynecol 1996; 9:699-706. TIPS R.L., LYNCH H.T., *The impact of genetic counseling upon the family milieu*. J. Amer. Med. Assoc. 1963; 184:117-120. TIPS R.L., SMITH G.S., LYNCH H.T., MCNUTT C.W., *The "whole family" concept in clinical genetics*. Amer. J. Dis. Children 1964; 107:67-76. TIPS R.L., MEYER D.L., PERKINS A.L., *The dynamics of genetic counseling*. Eugenics Quarterly 1962; 9:237-240. LYNCH H.T. *Dynamic genetic counseling for clinicians*. Springfield, CC Thomas.1969. RESTA R.G., ref. 2, p. 376.
6. FARMER J.M., CHITTAMS J., *Professional status survey 2000*. Perspectives in Genetic Counseling 2000; 22(4):S1-S12.
7. FINE B., *The evolution of nondirectiveness in genetic counseling and implications of the Human Genome Project*. In BARTELS D., LEROY B., CAPLAN A. (eds), *Prescribing our future: Ethical challenges in genetic counseling*. Hawthorne, NY, Aldine de Gruyter, 1993, pp. 101-118. WHITE M., *"Respect for autonomy" in genetic counseling: An analysis and a proposal*. J. Genet. Counsel. 6:297-314. MICHIE S., BRON F., BOBROW M., MARTEAU T.M., *Nondirectiveness in genetic counseling: An empirical study*. Amer. J. Hum. Genet. 1997; 60:40-47.
8. RESTA, ref. 4, pp. 256-257. PAUL D.B., *Controlling human heredity 1865 to the present*. New Jersey, Humanities Press, 1995. MCKUSICK V.A., *Human genetics*. New Jersey, Prentice-Hall, 1964, pp. 140-141.
9. NATIONAL SOCIETY OF GENETIC COUNSELORS. *Code of Ethics*. J. Genet. Counsel. 1992; 1:41-44.
10. RESTA R.G., *The first prenatal diagnosis of a fetal defect*. J. Genet. Counsel. 1997; 6:81-84.
11. HENKEL M., *Akutes Hydramnion, Leberkompression, enges Becken. Punktion des Hydramnion*. Zentrallblatt für Gynäkologie 1919; 43:841.
12. SCRIMGEOUR J.B., *Amniocentesis: Techniques and complications*. in EMERY A. (ed), *Antenatal diagnosis of genetic disease*. Edinburgh and London, Churchill Livingstone, 1973, pp. 11-39.
13. TJIO J.H., LEVAN A., *The chromosome number of man*. Hereditas 1956; 42:1-6.
14. LEJEUNE J., GAUTIER M., TURPIN R., *Les chromosomes somatique des enfants mongoliens*. Comptes Rendus des Academy des Science, Paris 1959; 248:1721-1722.
15. JACOBSON C.G., BARTER R.H., *Intrauterine diagnosis and management of genetic defects*. Amer. J. Obstet. Gynecol. 1967; 99:796-807.
16. SEABRIGHT M., *A rapid banding technique for human chromosomes*. Lancet 1971; 2:971-972. CASPERSSON T., ZECH L., JOHANNSON C. *Differential banding of alkylating fluorochromes in human chromosomes*. Exp. Cell Res. 1970; 60:315-319.
17. MILUNSKY A., *Medico-legal issues in prenatal genetic diagnosis*. in MILUNSKY A., ANNAS G.J. (eds), *Genetics and the law*. New York, Plenum Press, 1975, p. 54.
18. *Berman v. Allan*, 80 N.J. 421, 404 A.2d 8 (1978). *Becker v. Schwartz*, 46 N.Y. 2d 401, 413 N.Y.S. 2d 895, 386 N.E. 2d 807 (1978). FINEBERG K.S., PETERS J.D., *Amniocentesis in medicine and law. Practice standards and legal ramifications*. Trial 1984; 20:56-59.
19. COWAN R.S., *Women's roles in the history of amniocentesis and chorionic villi sampling*. in ROTHENBERG K.H., THOMSON E.J. (eds), *Woman and prenatal testing. Facing the challenges of genetic technology*. Columbus, Ohio State University Press, 1994, pp. 35-48.
20. AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS. *Statement of Policy As Issued by the Executve Board of ACOG. Statement on amniocentesis*. 1978.

21. JACOBSON C.G., BARTER R.H., ref. 24, p. 796.
22. AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS. Technical Bulletin Number 19. *Antenatal diagnosis of genetic disorders*. 1972. HAGARD S., CARTER F.A., *Preventing the birth of infants with Down's syndrome: a cost-benefit analysis*. Brit. Med. J. 1976; 1:753-756. PRITCHARD J. A., MACDONALD P.C., *Williams Obstetrics*. Fifteenth Edition. New York, Appleton-Century Crofts, 1976, p. 834.
23. BERNHARDT B.A., PYERITZ R.E., *The economics of clinical genetics services. III. Cogntive genetic services are not self-supporting*. Amer. J. Hum. Genet. 1989; 44:288-293.
24. BIESECKER B.B., HAMBY L. *What difference the disability community arguments should make for the delivery of prenatal genetic information*. In PARENS E., ASCH A. (eds), *Prenatal testing and disability rights*. Washington, D.C., Georgetown University Press, 2000, pp. 340-357.
25. AMERICAN COLLEGE OF OBSTETRICANS AND GYNECOLOGISTS. Technical Bulletin Number 108. *Antenatal diagnosis of genetic disorders*. 1987. NUSSBAUM R.L., MCINNES R.R., WILLARD H.F. *Thompson and Thompson. Genetics in Medicine*. 6th edition. Philadelphia: W.B. Saunders, 2000, p. 361. JORDE L.B., CAREY J.C., BAMSHAD M.J., WHITE R.L., *Medical genetics*. St. Louis, Mosby, 1999, pp. 276-277.
26. PENROSE L.S., *The relative effects of paternal and maternal age in mongolism*. J. Genetics 1933; 27:219-224.
27. PENROSE L.S., *The relative aetiological importance of birth order and maternal age in mongolism*. Trans. Royal Soc. 1934; 115:431-450.
28. JACOBSON AND BARTER, ref. 24, p. 797.
29. AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS. *Technical Bulletin Number 8. Amniocentesis - Indications, Technic, and complicatons*. 1968.
30. NADLER H.L, GERBIE A.B., *Role of amniocentesis in the intrauterine detection of genetic disorders*. New Eng. J. Med. 1970; 282:596-599. AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS. *Technical Bulletin Number 19. Antenatal diagnosis of congenital disorders*. 1972.
31. AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS. *Technical Bulletin Number 38. Antenatal Diagnosis of Genetic Disorders*. 1976.
32. NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT. *Report of a consensus conference sponsored by the National Institute Of Child Health And Human Development*. NIH Publication 79-1973, 1979, p. I-15.
33. SORENSON J.P., SWAZEY J.P., 1979, *Sex and the single chromosome*. In MILUNSKY A, ANNAS G.J. (eds), *Genetics and the law II*. New York, Plenum Press, 1979, p. 264.
34. HAGARD S.A., CARTER F.A., ref. 35. CONLEY R., MILUNSKY A., *The economics of prenatal genetic diagnosis*. In MILUNSKY A. (ed) *The prevention of genetic disease and mental retardation*. Philadelphia: W.B. Saunders, 1975, pp. 442-455. STEELE H.F., HOLMES D.W., *The growing demand for midtrimester amniocentesis: a systems approach to forecasting the need for facilities*. Amer. J. Public Health 1979; 69:574-580. ANDREANO R.L., MCCOLLUM D.W., *A benefit-cost analysis of amniocentesis*. Social Biol 1983; 30:347-373. SADOVNICK A.D., BAIRD P.A., *Maternal age-specific costs of detecting Down syndrome and neural tube defects*. Can. J. Public Health 1982; 73: 248-250. GLASS N., *Economic aspects of the prevention of Down's syndrome (mongolism)*. in BAILEY N.T.J., THOMPSON M. (eds), *Systems aspects of health planning*. Amsterdam, North-Holland Publishing, 1975, pp. 203-213. FU-

DENBBERG H.H., *Fiscal returns of biomedical research*. J. Invest. Dermatology 1973; 61:321-329. HOOK E.B., CHAMBERS G.M., *Estimated rates of Down syndrome in live births by one year maternal age intervals for mothers aged 20-49 in a New York State study - Implications of the risk figures for genetic counseling and cost-benefit analysis of prenatal diagnosis programs*. Birth Defects: Original Article Series 1977; XIII(3A):123-141. STEIN Z., SUSSER M., GUTERMAN A.V. *Screening programme for prevention of Down's syndrome*. Lancet 1973; 1(7798):205-210. MIKKELSEN M., NIELSEN G., RASMUSSEN E. *Cost-effectiveness of antenatal screening for chromosome abnormalities*. Edinburgh, Edinburgh University Press, 1976, pp. 209-216.

35. CONLEY AND MILUNSKY, ref. 51, pp. 453-454.
36. ANDREANO R.L., MCCOLLUM D.W., ref. 53, p. 358.
37. STEIN ET AL., ref. 58, p 308.
38. SMITH C., *Implications of antenatal diagnosis*. in Emery A. E.H., *Antenatal diagnosis of genetic disease*. Edinburgh, Churchill Livingstone, 1973, p.153.
39. SWANSON T.E., *Economics of mongolism*. Annals of N.Y. Acad. Sci. 1970; 171:p.682.
40. SWANSON T.E., ref. 65, p. 680.
41. STEIN ET AL, ref. 58, pp. 305,309.
42. JACOBSEN AND BARTER, ref. 24, p. 806.
43. HAGARD AND CARTER, ref. 35, p. 753.
44. LUBS H.A., LUBS M-L. E., *Indications for amniocentesis*. In DORFMAN A. (ed), *Antenatal diagnosis*. Chicago: Univ. of Chicago Press, 1972, p. 18.
45. SMITH G.F., BERG J.M., *Down's anomaly*. Edinburgh: Churchill Livingstone. 1976. p. 273. MILUNSKY A. *The prenatal diagnosis of hereditary disorders*. Springfield, CC Thomas, pp 24-25. NADLER H.L., GERBIE A.B., ref. 46, p. 599. ETZIONI A., *Issues of public policy in the U.S.A. raised by amniocentesis*. J. Med. Ethics 1976; 2:8-11.
46. CRANDALL B.F., HOWARD J., LEBHERZ T.B., RUBINSTEIN L., SAMPLE W.F., SARTI D., *Follow-up of 2000 second-trimester amniocenteses*. Obstet, Gynecol, 1980; 56:625-628. NICHD National REGISTRY FOR AMNIOCENTESIS STUDY GROUP. *Midtrimester amniocentesis for prenatal diagnosis. Safety and accuracy*. J. Amer. Med. Assoc. 1976; 236:1471-1476. PHILIP J., BANG J., *Outcome of pregnancy after amniocentesis for chromosome analysis*. Brit. Med. J. 1978; 2:1183-1184. SIMPSON N.E., DALLAIRE L., MILLER J.R., SIMINOVICH L., HAMERTON J.L., MILLER J., MCKEEN C., *Prenatal diagnosis of genetic disease in Canada: Report of a collaborative study*. Can. Med. Assoc. J. 1976; 115:739-746. GOLBUS M.S., LOUGHMAN W.D., EPSTEIN C.J., HALBASCH G., STEPHENS J.D., HALL B.D., *Prenatal genetic diagnosis in 3000 amniocenteses*. N Eng J Med 1979; 300:157-1763. PORRECO R.P., YOUNG R.E., RESNIK R., COUSINS L., JONES O.W., RICHARDS T., KERNAHAN C., MATSON M., *Reproductive outcome following amniocentesis for genetic indications*. Am. J. Obstet. Gynecol. 1982; 143:653-660. WORKING PARTY ON AMNIOCENTESIS. MEDICAL RESEARCH COUNCIL, *An assessment of the hazards of amniocentesis*. Br. J. Obstet. Gynaecol. 1978; 85(Suppl 2):1-41. TABOR A., MADSEN M., OBEL E.B., PHILIP J., BANG J., NØRGAARD-PEDERSEN B., *Randomised controlled trial of genetic amniocentesis in 4606 low-risk women*. Lancet 1986;1:1287-1292. GALLE P.C., MEIS P.J., *Complications of amniocentesis: A review*. J. Reprod. Med. 1982; 27:149-155.

47. CRANDALL ET AL., ref. 73, p. 628.
48. BIESECKER B.B., MARTEAU T.M., The future of genetic counselling: an international perspective. Nat. Genet. 1999; 22:133-137.

49. STRASSER B., In press, *Linus Pauling's "Molecular Diseases:" Between History and Memory*. Am J Med Genet/Sem Med Genet.
50. GILBERT R.E., AUGOOD C., GUPTA R., ADES A.E., LOGAN S., SCULPHER M., van der MEULEN J.H.P., *Screening for Down syndrome: effects, safety, and cost effectiveness of first and second trimester strategies*. Brit. Med. J. 2001; 323:1-6. CUSICK W., VINTZILEOS A.M., *Fetal Down syndrome screening: a cost effectiveness analysis of alternative screening programs*. J. Matern. Fetal Med. 1999; 8:243-248. SHACKLEY P., *Economic evaluation of prenatal diagnosis: a methodological review*. Prenatal Diagn. 1996;16:389-395.

Correspondence should be addressed to:
Robert G. Resta, Division of Perinatal Medicine, Swedish Medical Center, Seattle, WA - USA