Appendixes

Appendix A

Reproductive Dysfunction in the Population

Introduction

Analysis of incidence rates and trends in reproductive dysfunction in the general population, along with evidence of nonoccupational causal factors, is important to this report because:

1. such analysis provides background rates against which to identify unusual increases in incidence that may be related to occupational hazards within population subgroups;
2. correlation of background rates with demographic and other variables may yield clues to the etiology of certain reproductive disorders;
3. nonoccupational exposure to reproductive health hazards may have synergistic effects with factors existing in workplace settings; and
4. a better understanding of the etiology of reproductive dysfunction may allow identification of hazards and development of preventive or protective measures that could be applied in the workplace.

The following review is organized according to the two populations affected by reproductive hazards—adults and offspring. Recent trends and possible causes of infertility in both men and women are discussed, and major impairments manifested in the offspring—including infant mortality, low birth weight, and birth defects—are examined. Depending on available data, incidence rates are analyzed for correlation with demographic variables such as age, race, geographic region, and socioeconomic level.

Infertility

Incidence of Infertility

There have been three national surveys of reproductive capacity among married American couples, in 1965 (128), 1976 (163), and 1982 (117). Despite methodological differences between the first and the latter two surveys, some trends in infertility emerge from the data.

It is important to note that infertility is often a temporary phenomenon. Estimates of infertility may therefore vary widely, according to the specified interval of inability to conceive. The common medical definition of infertility is used here: inability to conceive after 1 or more years of marriage during which contraception is not used. This 1-year period appears reasonable since almost 90 percent of the infertile couples surveyed were infertile for 18 months or more, and almost half for 30 months or more (117).

In 1982, approximately 2.4 million married American couples, or 8.4 percent of those in which the wives were of childbearing age (15 to 44), were classified as "unintentionally" infertile. Of these couples, 70 percent wanted to have a child. Thus, in 1982, a total of 6 percent of married couples involving women of childbearing age who wanted to have a child were thwarted by infertility (117). The epidemiologic profile of infertile couples in the United States reveals a tendency for them to be black, the wife to be age 30 or over and have less than a high school education, and for the couple to have experienced one or no previous live births (117a).

In the 1965-82 period, the overall unintentional infertility rate for all women aged 15 to 44 appeared to drop from 11.2 to 8.4 percent (table A-1). However, the percentage of couples in which one or both partners had been surgically sterilized more than doubled in this period, from 16 to 39 percent (117), thus reducing the population at risk for infertility. If the infertility rate is calculated only for the at-risk population (i.e., excluding those who were surgically sterilized), overall infertility did not in fact change (table A-2). There was, however, a significant increase (3.6 to 10.6 percent) in infertility among the 20 to 24 age group of wives during this period (117). The still-sizeable gap in infertility between couples in which the wife is over 30 and those in which the wife is younger may therefore be narrowing.

Although the 1982 data have not yet been analyzed by racial subgroups, the 1965 and 1976 data reveal significant race-specific trends. Unintentional infertility increased by 350 percent among black couples in which the woman was 20 to 24, and 58 percent among those in which the woman was 25 to 29. Smaller but significant increases were found among white couples in which the women were in the same age group (117a). Blacks exhibited consistently higher overall infertility than whites: 55 percent higher in 1965, and 92 percent higher in 1976.

These racial differences may also be partly explained by trends in surgical sterilization: the percentage of couples seeking surgical sterilization is rising more rapidly among whites than blacks, reducing the num-

Table A-l.— Percent Distribution of Currently Married Women 15 to 44 Years of Age by Infertility Status: United States, 1965, 1976, and 1982[a]

A~e and ~aritv	Number in thousands			Total	Infertility status (percent distribution)								
					Surgically sterile			Infertile			Fecund		
	1965	1976	1982		1965	1976	1982	1965	1976	982	1965	1976	1982
Total .,	26,455	27,488	28,231	**100.0**	15.8	28.2	38.9	11.2	10.3	8.5	73.0	61.6	52,6
Age:													
15-19 years	1,032	1,043	612	**100,0**	0.6[c]	1.0[c]	**0.3**[c]	**0.6**[c]	**2.1**[c]	**2.1**[c]	**98.9**	**96.6**	**97.7**
20-24 years	4,397	4,977	4,130	100.0	3.1	4.5	8.2[c]	3.!i	[c] 6.4	9.7[c]	93.4	89.2	82.1
25-29 years	4,953	6,443	6,442	100.0	9,5	16.6	19,6	6.5	9.0	7.0[c]	84.0	74,4	73,4
30-34 years	5,074	5,736	6,482	100,0	17,0	36.2	43.6	11.6	10.3	7,7'	71.3	53.5	48.7
35-39 years	5,700	4,814	5,783	100.0	22.8	45.3	58.1	14.2	12.5	0.3	**63.0**	**42.2**	**31.6**
40-44 years	5,298	4,474	4,783	100.0	26.8	49.0	66.7	20.2	15,9	9.0[c]	52.9	35,2	243
Parity:													
o	—	*5,235*	*5,098*	100,0	7,3	5.6	9.9	14.5	18.1	19.6	78.2	76.3	70.5
1	–	5,571	5,891	100.0	7.5	8,8	17.7	17,2	12,4	10.8	75.3	78.8	71.7
2 ,.,	–	7,638	9,042	**100.0**	14,2	32.3	46.9	9,3	6.0	**5.0**	**76.6**	**61.7**	**48.1**
3 or more	–	9,045	8,201	100.0	21.5	49,8	63.3	9.4	7.9	3.8	69.0	42.3	32.9

astallsllcs are based on samples of the household population of the Conterrmmous Umted states
bwelgflted numbers not avatlable by Parlly for 1965
clnrj,~ales that the stallstlc has a relatwe standard error of O **3 or 9r6ater**

SOURCE W O Mosher Fecundity and Infertility (n the Uruted States, 1965 -1982," NCHS, paper presented al the annual meetmg of the Populahon Assocla'lon of America, Mmneapolls, MN, May 3-5, 1984

Table A.2.— Percent of Women, Presently Married, 15 to 44 Years of Age, Who Were Infertile, Excluding Those Surgically Sterile, United States

Age and parity	Percent infertile		
	1965	1976	1982
15-44 years.	13.3	14.3	13.9
15-19 years	0.6[a]	2.1[a]	2.1[a]
20-24 years	3.6	[a] 6.7	10.6
25-29 years.	7.2	10.8	8.7
30-34 years.	14.0	16.1	13.6
35-39 years	18.4	22.8	24.6
40-44 years	27.7	31.1	27.2
All parities	13.3	14.3	13.9
0	15.6	19.2	21.8
1	18.6	13.6	13.1
2	10.8	8.9	9.3
3 “o; rno;e” I I I I 1 I I I ; I I I I 1 I I	12.0	15.8	lo.3a

alndi~ates that the statistic has a relative standard error of 0.3 or greater.

SOURCE W. D Mosher, “Fecundity and Infertility in the Urrtted States, 1985-1982, ” NCHS, paper presented at the annual meeting of the Population Association of America, Minneapolis, MN, May 3-5, 1984.

ber of white couples at risk for unintentional infertil - it.v. Black couples seek surgical sterilization less often, perhaps because they are more likely to have already experienced infertility (11 7a). IMany other factors, including economic and cultural differences, ma-v contribute to this phenomenon.

The 1982 data were analyzed for differences in sexual acti\~ity that may cause a couple to be classified as infertile. No difference was found in the frequency of intercourse of infertile couples compared with those that ciid not report fertilit~~ problems (1 17).

A large proportion of couples classified as infertile at the time of these surve}s were probably only temporarily affected and later recovered. In a longitudinal study of infertile couples, 38 percent eventually achieved pregnancy following a mean infertility duration of 3 years (21). Furthermore, a large percentage of these recoveries were treatment-independent: 35 percent of untreated couples recovered spontaneoLrdy, compared with 41 percent of treated couples. Added to the category classified as “treatment-independent” were 31 percent of the treated couples who became fertile more than 3 months after the last medical treatment or 12 months after therapeutic surgery. ’ In sum, ‘(treatment-independent” pregnancies constituted 61 percent of all pregnancies that occurred in this study (21). In other words, most of the infertile couples who regained their reproductive capacity did so independently of medical treatment.

Spontaneous Abortion

Spontaneous abortion, defined here as embryonic or fetal death before the 20th week, [z] is usually not included in the medical dej”inition of infertility. However, since the inability to bring a pregnancy to term causes virtual infertility, spontaneous abortion is discussed here. Spontaneous abortion may also indicate

[y] **The specified intervals were later criticized as being too short to be certain that subsequent pregnancies were treatment-independent (43,93).**

[z] **Fetal deaths beyond 20 weeks are included in perinatal mortality statistics and are considered obstetrical ratber than fertility effects [67).**

fetotoxicity and/or severe physiological or genetic defects; in about 50 percent of first trimester spontaneous abortions, the fetus exhibits a chromosomal abnormality (50). One study of couples with a history of 3 or more consecutive spontaneous abortions identified possible causative abnormalities in 56 percent of the couples. The most common defects were anomalies of the uterus (15 percent), infections of the uterine lining (15 percent), and cervical incompetence (13 percent). Hormonal dysfunction was identified in 5 percent and chromosomal abnormalities in 3 percent of the couples (145). Several additional factors associated with birth defects (discussion follows) are also thought to increase the risk of spontaneous abortion.

The incidence of spontaneous abortion is difficult to determine, largely because most occur during the first few weeks after conception when the woman may not yet know she is pregnant and embryo/fetal loss is difficult to detect. Estimates of spontaneous abortion range from 30 to 75 percent of all pregnancies (1). One prospective study using very sensitive pregnancy indicators found that 43 percent of the conceptuses were lost by the 20th week of pregnancy. Only one-fifth of these losses (9 percent of the total) were clinically apparent (110).

While retrospective abortion data are often more accessible than medical records or prospective data, there may be limits to the usefulness of recalled abortion data. Failure to recall an abortion may be related to:

- the time elapsed since the event,
- the total number of births or spontaneous abortions experienced by the woman,
- a woman's age at the time of pregnancy,
- the gestational age of the fetus at the time of abortion,
- medical treatment and hospital admission, and
- social class and education.

A 1984 study of the accuracy of spontaneous abortion recall found that one of every four recorded spontaneous abortions was not later recalled (179).

The likelihood of spontaneous abortion increases with maternal age, especially after age 40, and is greater among those who have previously had spontaneous abortions (124). One estimate for clinically apparent spontaneous abortion among first pregnancies in women under age 30 ranges from 8 to 11 percent; in women over age 35, estimates range from 15 to 22 percent (67).

causes of Infertility

Infertility is attributed in roughly equal proportions to husbands and wives among married infertile couples (54). The etiology of a given reproductive disorder may differ from situation to situation, and is often difficult to pinpoint: estimates of the percentage of infertility cases for which no cause can be pinpointed ranges from 6 (168) to 50 percent (81).

The multiplicity of factors that frequently contribute to a given case of infertility can further obscure the etiology and thus hinder effective treatment: in one study, 40 percent of 141 extensively examined infertile couples were found to have multiple factors contributing to their reproductive impairment—7 percent had 3 or more identified contributing factors (168). In addition, individuals may be affected differently by a given agent due to differences in characteristics such as age, health, and personal habits that can affect the risk of reproductive damage.

A separate in-depth study of about 500 infertile couples found that the three major primary causes of infertility were ovulation defects, tubal disease, and "male factor" problems, including sperm count below 10 to 20 million sperm per milliliter (million/ml) of semen, impaired sperm motility, or psychiatric problems leading to impotence or loss of libido. Approximately 20 percent of diagnosed cases were attributable to each of these disorders, which therefore collectively caused infertility in 60 percent of diagnosed couples. No diagnosis was possible for 25 percent of the couples (77). Among major secondary causal factors were unreceptive female mucus (severe infection or immune response to sperm causing agglutination), endometriosis (unusual location, proliferation, and dispersal of tissue resembling that of the uterine lining), cervical abnormalities, and luteal phase deficiency (insufficient secretion of hormones necessary to maintain the uterine lining). In this study, 52 percent of the infertile couples eventually bore a viable infant; 90 percent conceived within 1 year of initial medical consultation (77).

The proportion of fertile[3] couples in the United States fell from 73 to 53 percent between 1965 and 1982. This drop is paralleled by a twofold increase—from 16 to 39 percent—in the percentage of couples in which one or both partners have been surgically sterilized by tubal ligation, vasectomy, or hysterectomy (117). While this trend in surgical sterility is not further explored here, it is useful for isolating, and sometimes explaining, trends in unintentional infertility.

The following two sections discuss the rates and possible causes of specific conditions contributing to reproductive impairment among women and men. Depending on available information, the following categories of causal factors are discussed for both women

[3]Couples defined hereas t ertile em'{) repass all those capable of conceiving, including those who are using (writ raception

and men: 1) **environmental factors,** including pollutants; 2) **pathological factors,** including infectious disease; 3) **heritable factors,** such as inherited syndromes; 4) **iatrogenic factors** (i.e., side effects of medical treatment), including contraception and therapeutic drugs; 5) **nutritional factors**; and 6) **sociobehavioral factors,** including "recreational" drugs, stress, exercise, and paternal or maternal age.

Women.—The six causal factors listed may contribute to the following female reproductive impairments, all of which can contribute to infertility: amenorrhea (absence of menstrual cycle), oligomenorrhea (reduced frequency of menstrual cycles), anovulatory cycles (a cycle during which no egg is released), premature menopause (cessation of menstrual cycling before the mid to late 40s) and spontaneous abortion.

Environmental Factors.—Two trends in exposure to environmental reproductive hazards may contribute to the increase in infertility among younger couples: 1) the increasing proportion of women entering the work force and thus potentially being exposed to reproductive health hazards in the workplace (6); and 2) the possible increased exposure of couples to environmental toxins that impair fertility (12).

Among the many environmental pollutants that may impair fertility among women are DDT analogs and polycyclic aromatic hydrocarbons. The banned pesticide DDT and the DDT analogs currently in use, such as methoxychlor, mimic the action of the sex hormone estrogen. Laboratory animals exposed to these pesticides exhibit impaired fertility and disturbances in mating behavior (57,90,171) (see chapter 4). Polycyclic aromatic hydrocarbons are common environmental pollutants produced by the burning of fossil fuels (e.g., oil, gasoline) and cigarettes, and the production of synthetic fuels (98,129). In experiments with laboratory animals, these hydrocarbons have been shown to destroy developing egg cells (37,101,102), produce ovarian tumors (70), and decrease fertility (91,100).

Pathological Factors.—Both the rise in infertility among younger couples and the concurrent decrease in infertility among older couples have been linked to trends in sexually transmitted disease. The rise in infertility among young couples may be partially due to the rising incidence through the 1960s and early 1970s of gonorrhea among young women (153). Gonorrhea can cause pelvic inflammatory disease (PID) with accompanying infertility (174). Reported cases of gonorrhea tripled between 1965 and 1975 (24) with the highest rates evident for women aged 20 to 24, who have also shown the largest increases in infertility (157). Since 1975, the number of reported gonorrhea cases has exhibited a slow decline. Even with declining morbidity, persons aged 20 to 24 continued to account for 30 to 40 percent, and persons 15 to 19 for nearly 25 percent of all reported cases of gonorrhea each year. By 1982, rates for women 15 to 19 exceeded those for women aged 20 to 24 (153).

Sexually transmitted infection by the chlamydia organism is a sometimes-unrecognized cause of infertility, although it has been described as epidemic in the United States (63). A study of pregnant women attending a prenatal clinic reported chlamydial infections in 5 to 10 percent of the women, a rate up to 10 times higher than that for gonorrhea, which was found in only 1 percent of the patients (63). Like gonorrhea, chlamydial infections can cause PID. In fact, chlamydial PID may be more likely to cause infertility than gonorrhea-induced PID (63). The high rate of "silent" chlamydial infections that are not clinically apparent, the lack of national incidence data, and frequent misdiagnosis have caused this disease to be both underestimated and undertreated.

From 1975 to 1981, the hospitalization rate for PID rose slightly overall for women aged 15 to 44 (174). High-risk groups included women in their 20s, divorced or separated women (1.7 times more likely to be hospitalized than single or married women), and nonwhite women (whose hospitalization rate was 2.5 times that of white women). Other factors that may have contributed to the recent rise in PID include the early age at which the baby-boom generation became sexually active, the tendency to have intercourse with a greater number of partners (187), and the shift away from contraceptives, like the condom, that protect against PID (117a,148). It has been projected that if these rises in venereal and pelvic inflammatory diseases continue among young women, 11 percent of women born in 1955 will become involuntarily sterile as a result of these diseases alone (24).

This rise in PID has also been linked to a near threefold increase in the incidence of ectopic pregnancy, from 4.8 per 1,000 live births in 1970 to 14.5 per 1,000 live births in 1980 (155). Ectopic pregnancy consists of implantation of the fertilized egg outside the uterus, often in the fallopian tubes that normally guide the egg from the ovary to the uterus. PID causes about 50 percent of ectopic pregnancies (63). Ectopic pregnancies must virtually always be terminated to save the mother's life and can cause temporary infertility. The infertility can be permanent if there is irreparable damage to the fallopian tubes. In one study of women with recent removal of an ectopic pregnancy, only about 20 percent eventually achieved live birth and only after at least 1 year of infertility (126).

Heritable Factors.—Maternal sickle cell anemia has been associated with increased risk of spontaneous abortion (115). Myotonic dystrophy, an inherited degenerative neuromuscular disease, can cause amenorrhea, although afflicted females in the younger age

groups sometimes manage to conceive (133). Several inborn hormonal imbalances, when untreated, can compromise fertility in females. For example, imbalanced synthesis of steroids by the adrenal gland (congenital adrenal hyperplasia) is the most common cause of ambiguous external genitalia at birth. Without hormone replacement therapy, this disorder can result in infertility among these females (132). Untreated gonadotropin deficiency can result in amenorrhea and the failure of female secondary sex characteristics to appear. Untreated hypothyroidism has been associated with increased stillbirth rates and decreased fertility (66).

Some gross chromosomal abnormalities have also been linked to female infertility. Females born with only one of the normal pair of X chromosomes exhibit impaired ovarian function and are infertile (135). Women born with an extra X chromosome sometimes undergo premature menopause (139; for an in-depth review of heritable disorders that adversely affect female fertility, see ref. 135).

Iatrogenic Factors.—The use of oral contraceptives, which has rapidly increased since their release to the public in 1960 (166), can cause temporary infertility. Women may take longer to conceive after discontinuing use of oral contraceptives than those who use other or no methods of contraception (88). Two recent studies have linked IUD use to pelvic inflamatory disease and primary tubal infertility (22,25). Relative risk of developing primary tubal infertility differs depending on type of IUD used.

Both radiation and chemotherapy treatments for cancer can cause reproductive impairment in women. The effects of both treatments are age- and dose-related (20); both can cause ovarian damage and impaired fertility, to which prepubertal girls are more resistant than older females. Abnormal ovarian function can surface as irregular, anovulatory, or absent menstrual cycles or abnormal levels of certain sex hormones. The risk of complete ovarian failure due to chemotherapeutic drugs increases after the late 20s with clinical symptoms, including amenorrhea and low postmenopausal-like levels of certain sex hormones, that produce insomnia, irritability, and depressed libido (20). Furthermore, use of combinations of such drugs seems to increase the risk of ovarian failure.

Finally, most treatments for infertility (including many drugs that induce ovulation and some surgery) are associated with increased risks of spontaneous abortion among ensuing pregnancies. This effect may be a direct result of the treatment or due to an incomplete cure of the original reproductive impairment (67).

Nutritional Factors.—Changes in diet and body composition, many of which are associated with exercise, can affect female reproductive function. Substantial weight loss, low body weight-for-height, low percentage of body fat (40,41,42), and high energy consumption (173) have all been implicated in amenorrhea. The higher prevalence of menstrual disorders reported among college women compared with the general population has been associated with weight loss of 20 pounds or more—11.3 percent of college women reported oligomenorrhea and 2.6 percent reported amenorrhea (9) compared with 10 percent and less than 1 percent, respectively, in the general population (150). The severity of menstrual irregularity among those college women tested was associated with older age at menarche (9).

Malnutrition and starvation, including that induced by anorexia nervosa, can also delay menarche in young girls, who may then be permanently sterile. Malnutrition and starvation can also result in amenorrhea in older women (10).

Sociobehavioral Factors.—The recent tendency to delay childbearing to later years (161), when infertility is comparatively high, may result in an overall rise in infertility, especially in the older age groups (6). The reason for this age-related rise in infertility is unknown but may be partially due to the cumulative impact of infectious, occupational, and environmental agents as well as endogenous changes with age. The latter, "normal" age-related changes, could include changes in neuroendocrine hormone function, ovarian dysfunction, and increased incidence of spontaneous abortion.

Although many so-called recreational drugs, both licit and illicit, are suspected to have detrimental effects on reproductive ability, chronic cigarette smoking and heavy alcohol consumption have been most strongly implicated. Cigarette smoke can cause a dose-related lowering of the age of menopause, a sign of oocyte depletion (99). Smoking also increases the risk of spontaneous abortion to almost twice that of nonsmokers, according to one study (79). Women who drink the equivalent of one or more ounces of absolute alcohol twice a week (or at least four drinks per week) are almost twice as likely to abort spontaneously than women who drink less (78).

Other widely used licit and illicit drugs have been more tentatively linked to fertility problems. Barbiturates, some tranquilizers, marijuana, and narcotics may affect neural input into the hypothalamus, the brain center that orchestrates many of the body's endocrine functions, including the secretion of sex hor-

mones. Marijuana can alter patterns of sex hormone secretion and inhibit ovulation in lab animals (138). Narcotics, such as heroin, may impair libido, potency, menstrual regularity and fertility, and may increase the incidence of spontaneous abortion (176).

Women who exercise strenuously, such as marathoners and ballet dancers, may exhibit some reproductive dysfunction, including delayed menarche, amenorrhea, and an abbreviated, dysfunctional luteal phase of the menstrual cycle. The reasons for these effects are largely unknown. However, exercise-induced decrements in reproductive function can usually be reversed through changes in lifestyle (23,143).

Men.—Major male reproductive dysfunction is associated with abnormalities in semen or sperm, ejaculatory failure, and impotence. The three characteristics of semen that are most strongly associated with infertility are low sperm count, reduced sperm motility, and abnormal sperm morphology—all of which may be interrelated (14,96). Most infertility clinics base their evaluations on all three of these parameters (see chapter 5). Standards of normalcy for these characteristics, however, as well as the degree to which the semen must deviate in order to cause infertility, remain controversial (86,105).

Although sperm count is commonly used as a measure of male fertility, neither a distribution of sperm counts among normal men nor a "normal" sperm count have been established. Sperm counts vary considerably between men and even within the same man according to age, sexual activity, season of the year, general health, and quantitation technique used (54). For example, daily sperm production declines significantly with age (68)—the number of sperm per ejaculation has been reported to decline by 30 percent in the 60 to 70 age group and by a further 20 percent in men 70 to 80 (48). In general, however, sperm counts below 10 million/ml are thought of as low and are correlated with increased risk of infertility (105,188). Yet people with "low" sperm counts are not always infertile. For example, one clinical study reported that 50 percent of men with sperm counts below 10 million/ml were able to initiate a pregnancy (2).

Sperm motility may also decline with age, especially after age 40 (92). Antisperm antibodies in the semen or in the cervical mucus of the female are associated with sperm agglutination, impaired motility, and infertility (96). Such antibodies can impede sperm penetration of the female's cervical mucus and egg (3). Antisperm antibodies are often found in the blood of infertile couples (53). One study reported that in more than 30 percent of infertile couples tested, at least one partner possessed antisperm antibodies in the blood, and that these couples had a lower incidence of subsequent pregnancy (108) (see chapter 5 for further discussion of seminal abnormalities as indices of reproductive impairment).

An 8-year study of donor semen at one infertility clinic reported a decline in semen quality, including lower sperm counts and more morphological abnormalities. Sperm motility remained constant. If this trend continues, and increasing numbers of donors have to be rejected, in 5 or 6 years none of the prospective semen donors will meet minimal standards (85). The significance of and reason for this decline are unknown.

Environmental Factors.—Analogs of DDT and certain other pesticides, some of which are still in use, mimic the action of estrogen and may affect male fertility (see chapter 4). Whether background levels of pesticides in the environment affect male reproductive function is unknown. (A comprehensive review of chemicals affecting human sperm appears in (184).)

Pathological Factors.—Several infectious diseases can cause inflammation of the testes and subsequent failure of spermatogenesis. These diseases include mumps, tuberculosis, gonorrhea, syphilis, typhoid, influenza, and smallpox (52). Testicular failure, accompanied by androgen deficiency, may also occur as a result of hypothalamic or pituitary disease. Estimates of the incidence of primary (i.e., testicular) endocrine defects among subfertile men range from 0.5 to 3 percent (26,167,169). Most infertile men have hormonal imbalances that are attributable to other infertility-causing pathological conditions (183).

Varicocele, or abnormal dilatation of the veins leading from the testes, may contribute to male infertility. Because varicocele is correctable by surgery (149), this disorder has been the subject of much recent research as a possibly reversible cause of male infertility.

Infants who are born with both ovarian and testicular tissue (for reasons that are usually unknown) are known as "true hermaphrodites." Due to the characteristic testicular degeneration, hermaphrodites are usually infertile as males, but have occasionally been shown to be fertile as females (135).

Some major psychiatric illnesses, such as schizophrenia, manic-depression, depression, and anorexia nervosa, are associated with infertility (10). The problem is complicated by the fact that psychotropic drugs used to treat these disorders may also impair fertility. Stress may lower testosterone levels in men and may be associated with decreased sperm count (104).

Impotence can be caused by pathological factors such as injury or cancer of the spinal cord or brain, cardiovascular disease, and hormone imbalances (including diabetes), and is generally associated with debilitating illnesses (55).

Heritable Factors.—Several congenital disorders, including cystic fibrosis, are associated with infertility

(52) (table A-3). Diabetes, sickle cell disease, and renal failure may also depress sperm production. Gonadotropin deficiency can cause loss of libido, impotence, infertility, and lack of sexual development. Another inborn hormonal disorder involving abnormally high levels of prolactin (a hormone secreted by the pituitary gland) typically causes impotence, but there is no general agreement about its effect on spermatogenesis (183). Myotonic dystrophy, an inherited degenerative neuromuscular disease, is associated with testicular atrophy accompanied by decreased libido, impotence, and infertility in afflicted males (133). Certain congenital urogenital or neurological abnormalities can cause retrograde ejaculation, the most common form of ejaculatory failure, in which the semen passes backwards into the bladder. However, this condition is more commonly acquired than inherited, whether as a side effect of surgery or trauma to the urogenital region (55) or of neurological disorders.

Klinefelter's Syndrome, whose frequency among males is estimated at 0.1 percent (19), is caused by possession of an extra X chromosome and usually results in azoospermia (absence of sperm). The testes of males with this disorder are typically small and devoid of germ cells.

Iatrogenic Factors.—Radiation and chemotherapeutic treatments for cancer can cause germ cell abnormalities and destruction in human males. Common side-effects are azoospermia, oligospermia (low sperm count), impaired sperm motility, abnormal serum levels of certain sex hormones, and decreased sperm synthesis (11,20). Permanent sterility is a common side effect of chemotherapeutic drugs, although some degree of potency and libido is usually retained. Most men experience decreased libido during combination chemotherapy and one-third experience impaired potency and decreased sexual pleasure after such therapy ends (20,178). These side effects are generally less severe in prepubertal boys than in men. Clinical knowledge of the extent, synergism, and variability of gonadal toxicity for many of these chemotherapeutic treatments remains inadequate, however.

Antihypertensives, anticonvulsants, and psychotropic drugs can all cause impotence. In addition, adrenergic-blocking agents and surgery to the prostate and bladder neck may cause retrograde ejaculation (55).

Nutritional Factors.—Some food additives may be reproductive hazards: estrogenic hormones fed to cattle to promote growth may be ingested by the human consumer in amounts large enough to affect fertility (52).

Sociobehavioral Factors.—Many commonly used recreational drugs (licit and illicit) affect male fertility. Chronic intensive use of marijuana, for example, is thought to inhibit normal secretion of gonadotropins, the pituitary hormones directing gonadal function (138), and cause significant reduction in sperm count and changes in sperm morphology (58). Alcohol depresses the synthesis and secretion of testosterone by the testes (69,106). Chronic alcohol consumption and alcoholic cirrhosis lead to multiple hormonal disturbances, growth of the male mammary glands, decreased size and functioning of the gonads, and sometimes impotence (55). Narcotics also cause impotence and decreased sex drive. Heroin addicts show depressed levels of certain sex hormones (76,107) along with decreased sperm count and motility (138).

Chronic use of anabolic steroid hormones, composed of testosterone and its synthetic derivatives, can cause the body to manufacture less of its own testosterone and result in testicular atrophy, decreased sperm count, and temporary infertility in males (189). Anabolic steroids have been employed to build up muscle mass by some athletes, particularly body builders and weight lifters, for years. More recently, the appeal of anabolic steroids has broadened to other groups, such as runners, swimmers, and cyclists.[4] Steroids appear to be the class of chemicals most consistently affecting sperm characteristics (184).

Chronic sniffing of paint or lacquer thinner can produce tissue abnormalities in the testes along with

Table A-3.—Conditions That May be Associated With Azoospermia. Some of These Factors May Cause Reversible Azoospermia

- Genetic disorders:
  - Klinefelter's syndrome
- Congenital disorders:
  - cystic fibrosis
  - myotonic dystrophy
- Hormonal defects:
  - hypothalamus
  - pituitary gland
  - adrenal gland
  - thyroid
  - testes
- Severe illness or malnutrition
- Infection:
  - mumps
  - smallpox
- Drug therapy:
  - cytotoxic drugs
- Irradiation

SOURCE: Office of Technology Assessment.

[4]Women, as well as men, may use anabolic steroids in sports training. Because their bodis produce only tiny amounts of testosterone, female athletes potentially will experience more of an effect on muscle mass from steroid use than will male atheletes (189).

faulty or suppressed sperm production (146). Smoking can impair sperm production and increase the number of malformed sperm in the ejaculate (52).

Demand for Infertility Services

The proportion of all private physician visits devoted to infertility counseling rose by more than so percent between 1968 and 1980 (6). Several demographic and sociological factors may have contributed to this phenomenon:

- an increased number of infertile couples in the population,
- an increased proportion of infertile couples aware of and seeking infertility services,
- a growing number of physicians providing infertility services, and
- an increasingly pro-family social and political climate *(6).*

In 1976, about 6.9 percent of nonsterile,[5] married women aged 15 to 44 reported that they had used infertility services recently (i.e., consulted a doctor or other trained person within the previous 3 years) (164). Women aged 15 to 29 were significantly more likely to seek infertility services than those aged 30 to 44 [table A-4). Among childless women, blacks were nearly twice as likely to have recently used infertility services than whites. AS might be expected, women of low parity[G] were also more likely to have had an infertility consultation **than** women of higher parity. The only statistically significant regional difference was found among white women: white women in the west were more likely to have recently sought services than those in the Northeast, North-Central, or South regions (164).

Further study of trends in demand for infertility services and of the relevant demographic and sociopolitical variables may allow the health care delivery system to prepare for future demand, and to reach those subgroups expressing the greatest need.

— . . —

[5]Nonsterile is defined here as not being sterile due to contraceptive surgery, accident, or previous **illness.**

[6]Parity refers to the number of pregnancies a woman has carried to at least 20 weeks gestation (or 500-gram fetal weight).

Table A-4.—Percent of Nonsterile Women (Currently Married, 15 to 44 Years of Age, United States, 1976) Who Had an Infertility Consultation in the Previous Three Years

Characteristic	All races[a]	Race: White	Race: Black
Aii characteristics	6.9°io	6.70/o	7.4 "/0
Age:			
15-29 years	8.5	8.4	8.8
30-44 years	5.0	4.7	5.9
Parity:			
0-1 parity	12.1	11.6	15.5
2 parity or more	*2.6*	*2.6*	*2.3*
Geographic region:			
West	*8.6*	*8.8*	*3.4*
Nonwest	6.5	6.2	7.9

alncludes white, black, and other races.

NOTE Statistics are based on a sample of the household population of the conterminous United States.

SOURCE: Adapted from National Center for Health Statistics, "Use of Family Planning and Infertility" United States, " National Survey of Family *Growth* **Vital** *and Health Statistics,* Series 23, No. 8, 1981.

Infant Mortality, Low Birth Weight, and Birth Defects

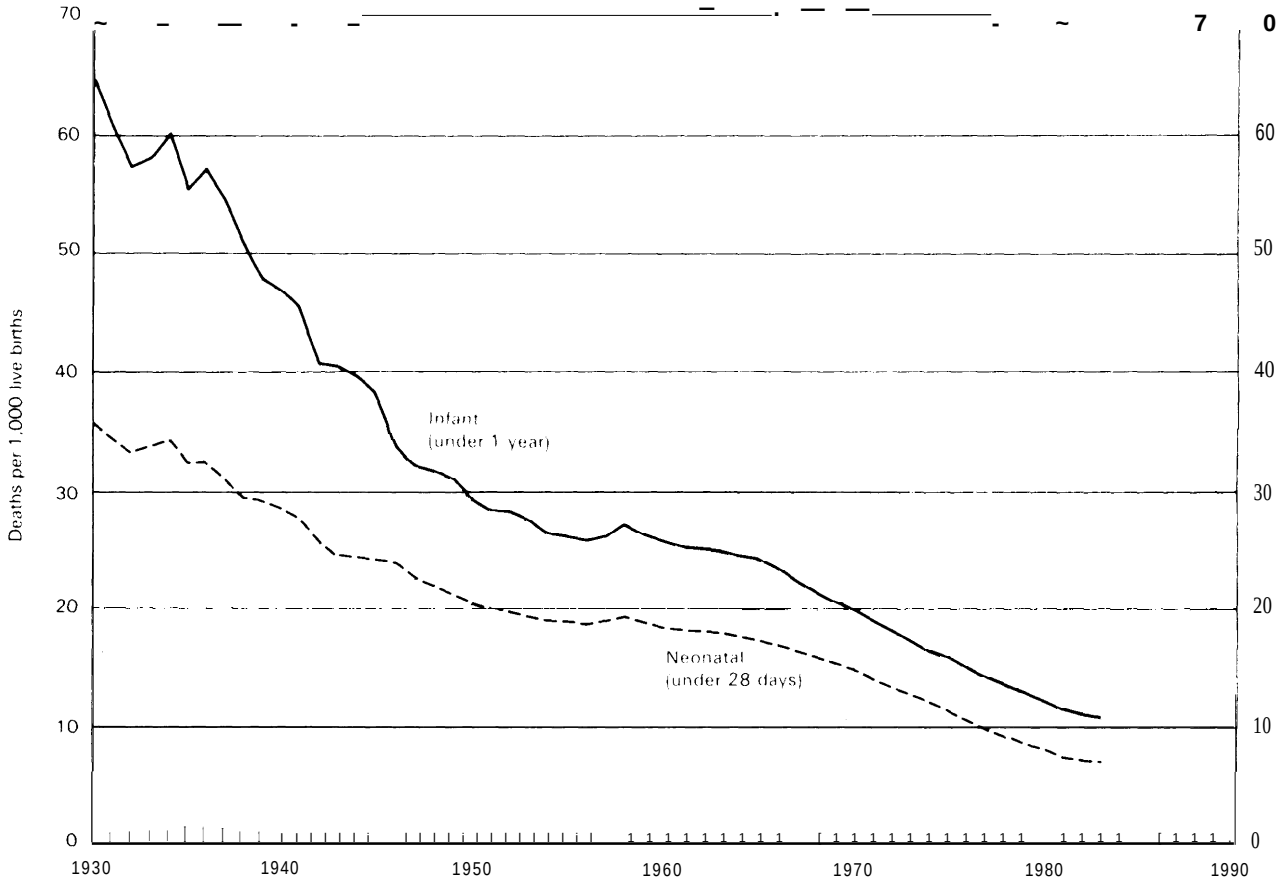
Background rates for infant mortality, low birth weight, and birth defects are important since many of the chemical, physical, and biological agents present in the workplace are suspected to adversely affect the gametes and/or fetus. A "baseline" rate is needed against which to compare abnormally high rates observed in certain settings and thereby pinpoint the responsible hazards. Causal factors and regional differences in these rates are identified where information is available.

Infant Mortality Rates

Death rates among both newborns (aged under 28 days) and infants (aged under 1 year) have dropped steadily since 1930 (see figure A-1). In 1982, 21 percent of all infant deaths were attributed to congenital anomalies (table *A-5).* This proportion has risen steadily in the 1900s (from 7 percent in 1916 to 18 percent in 1977) because the rate clf congenital anomalies has dropped less rapidly than the overall infant death rate (figure A-2), and also because of improvements in pre- and post-natal care that have reduced the impact of other causes of infant death. Despite the recent decline in infant mortality in this country, however, the United States ranks 14th irl an international comparison of infant death rates (94).

Almost 70 percent of infant deaths occur in neonates (i.e., within the first 28 days of life) (table A-5). More than half of infant deaths and three-fourths of neonatal deaths occur in low-birth-weight infants (162). The death rate remains substantially higher among black infants (figure A-3) and was almost twice that of white infants in 1982 (160). Black infants exhibit higher death rates for et'ery major category in the National Center for Health Statistics data, except for cystic fibrosis (though there is overlap for specific defects within the congenital anomalies category). The rate among blacks is more than three times that of whites for deaths due to low birth weight or prematurity. This may be par-

Figure A.I.— Infant and Neonatal Mortality Rates, United States, 1930-83



SOURCE National Center for Health Statistics, "Annual Summary of Births, Deaths, Marriages, and Divorces United States, 1983," Monthly Vital Statistics Report, VOI 32, No 13, Sept, 21, 1984.

tially due to the larger proportion of black mothers exhibiting maternal risk factors associated with bearing low-birth-weight infants.

Incidence of Low Birth Weight

Low birth weight, defined as 5 pounds 8 ounces (2,500 grams) or less, is strongly associated with both infant mortality and birth defects, including congenital malformations, mental retardation, and other physical and neurological impairments (159). Extremely low birth weight (4 pounds 7 ounces or less) is a leading cause of death among infants and a major factor in childhood disability (94). The percentage of newborns that are of low birth weight has declined in recent years, but less sharply than the neonatal death rate (figure A-4). In addition, the decline is due largely to the 21-percent drop in the incidence rate of **full-term** low birth-weight infants from *1970* to 1980, compared with only a 7-percent drop in the rate of **preterm low** birth-weight infants (74). These trends probably reflect improved neonatal care, but little improvement in the prevention of prematurity and fetal growth retardation (94).

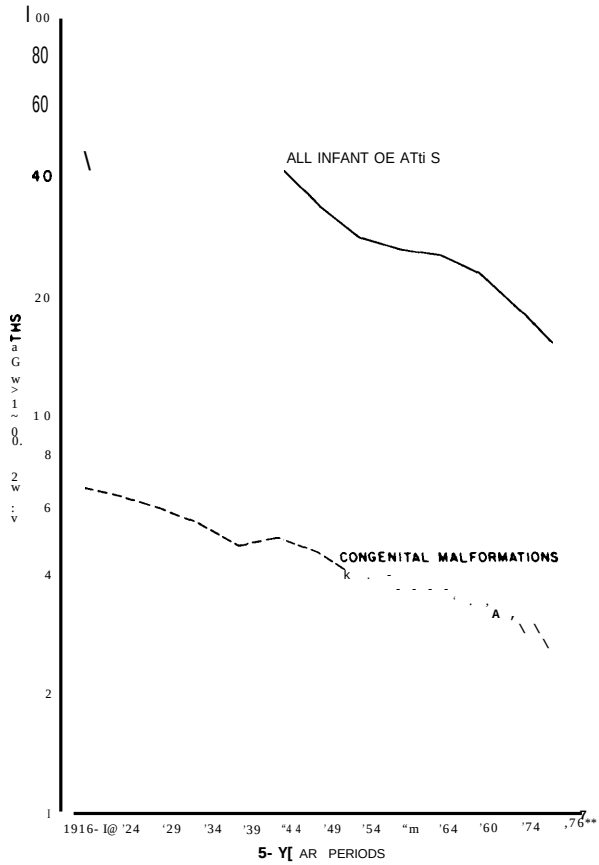
1n 1981, 6.8 percent of all infants born were of low birth weight (1.5s3). The proportion of black infants of low birth weight was more than double that of white infants: 12.5 percent of black infants v. 5.7 percent of white infants. 1n a typical year with approximately s..5 million births, the expected number of low birth-weight infants exceeds zoo, ooo (44). The racial difference in low birth weight has been attributed equally to racial differences in: 1) incidence of prematurity and z) incidence of low birth-\ veight infants that are full- or post-term infants (there are few racial differences among preterm infants). 1n 1981, 17 percent of black infants were preterm compared with 7'.9 percent of white infants. Among full- and post-term babies, the racial difference in low birth weight may be at least partially due to the larger proportion of all

Table A.5.—Infant Mortality Rates by Age and for Ten Selected Causes of Death, Based on a 10-Percent Sample of Deaths, United States

Age and cause of death	1982 (estimated) (rates per 100,000 live births)	Percent of total deaths
Total:		
Under 1 year	1,124.5	100.0
Under 28 days	762.4	67.8
28 days to 11 months	362.0	32.2
Congenital anomalies	237.0	21.1
Sudden infant death syndrome	127.2	11.3
Respiratory distress syndrome	107.2	9.5
Disorders relating to short gestation and low birth weight	98.8	8.8
Intrauterine hypoxia and birth asphysia	39.7	3.5
Pneumonia and influenza	20.0	1.8
Birth trauma	15.4	1.4
Certain gastrointestinal diseases	7.3	0.6
Other conditions originating in the perinatal period	295.1	26.2
All other causes	177.1	15.7

SOURCE: Adapted from National Center for Health Statistics, "A Study of Infant Mortality From Linked Records by Birth Weight, Period of Gestation, and Other Variables: United States, " Vital *and Hea/th Statistics,* Series **20, No. 12, 1982.**

Figure A"2.—Infant Mortality Rates in the United States, 19{6-76



" = 4-year period; "" = 2-year period.

SOURCE: G. P. Oakley, "incidence and Epidemiology of Birth Defects, " ***Genef/c*** Issues in Pediatric and Obsts4ric Practice, M. M. Kaback (ed) (Chicago: Year Book Medical Publ shers, Inc , 1981),

black mothers who possess characteristics associated with bearing low birth-weight infants. These characteristics (159) include:

- being unmarried (81.4 percent of black mothers ~~. 18.2 percent of white mothers),
- having less than a high school education (s.5 percent of black mothers v. 20 percent of white mothers),
- prenatal care beginning after the second trimester or not at all ($I percent of black mothers v. q percent of white mothers), and
- multiple delivery (i.e., twins or triplets) (24.7 L'. 18.8 per 1,000 live births for black and white mothers, respectively).

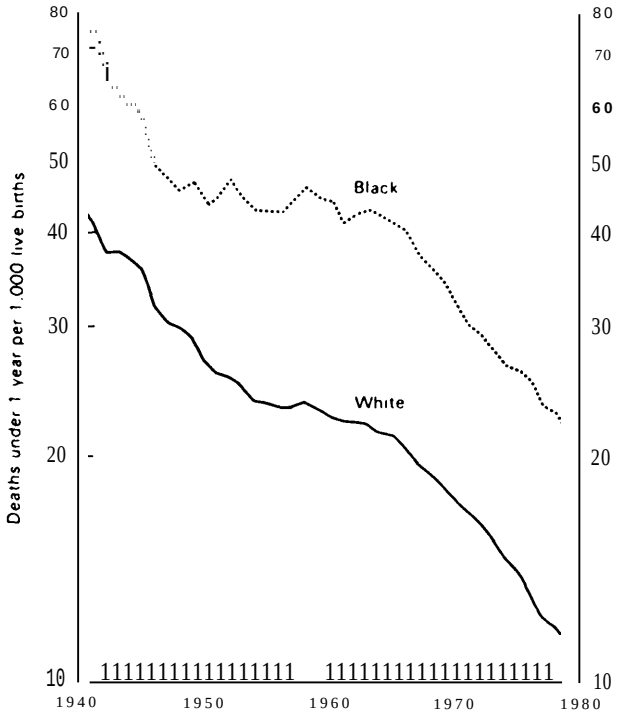
However, both the extent of prenatal care and the educational attainment of black mothers have improved in recent years (159).

In contrast, smoking and drinking during pregnancy—both of which are associated with low birth weight—are more prevalent among white women compared with both black and Hispanic women: 41 percent of white women drink during pregnancy compared with 24 percent of black women and 29 percent of Hispanic women; 26 percent of white women smoke during pregnancy compared with 22 percent of black women and 17 percent of Hispanic women; 12 percent of white women both smoke and drink during pregnancy compared to 9 percent of black women and 7 percent of Hispanic women (47,125). (Information on smoking and alcohol consumption during pregnancy appears in ref. 125.) Since the proportion of low birth-weight infants remi~ins relatively low among white mothers despite these maternal risk factors, the adverse affects of smoking and drinking are either better-treated in white mctthers, or compensated for by low prevalence of other maternal risk factors.

Women aged 25 to 34 years are the least likely to bear a low birth-weight inf,mt: 5.8 percent of all births to this age class were of low birth weight. The percentages for those over age *40* and under age ***15*** are almost twice and three times as great, respectively (159).

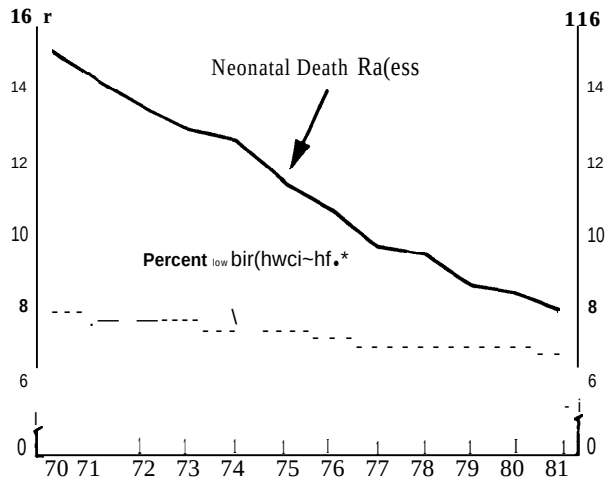
There is substantial variation from State to State in the percentage of low birth-weight newborns. The

Figure A-3.-infant Mortality by Race, United States, 1940-80



SOURCE National Center for Health Statistics, "Annual Summary of Births, Deaths, Marriages, and Divorces: United States, 1982," Monthly *Vital Statistics Report,* vol. 31, No 13, 1983

Figure A-4.— Neonatal Deaths and Low Birth Weight, United States, 1970.81



•Deafhs under28 days per *1,0001ive births*

•* Percent of live births weighing 2,S00 grams (5!4 lbs.) or less

SOURCE March of Dimes, Facts/1984 (White Plalns, NY: March of Dimes Btrtt-Defects Foundation, 1984).

seven West North-Central States[7] have the lowest aggregate rate of low birth weight (5.8 per 100 total live births), while the nine South Atlantic States[8] haie the highest rate (8.0 per 100 total live births). Howe\7er, this regional variation may be due largely to the disproportionate number of black children born in those States with the highest low birth-weight rates. The fit~e States with the highest rates of low weight births (District of Columbia, South Carolina, Mississippi, Louisiana, and Georgia) all reported substantially more black than white babies born in 1981. The regional variation observed within racial groups is largely reduced when the States with relatively few black births are excluded from the analysis (159).

Recent data demonstrate the strong nonrandomness of the geographical distribution of loiv birth ~veight in the United States, Clusters of loiv birth }treight in the Rocky Mountain region and in certain Northern industrialized States suggest the strong influence of environmental factors such as altitude, mineral-extraction industries (e.g., lead, uranium, and silver mining), heavy industries (e.g., steel, automobile, and chemical), and agricultural spraying (44).

Birth Defects

A "birth defect" is defined here as any structural, functional, or biochemical abnormality, whether genetically determined or induced during gestation, that is not due to injuries suffered during birth. Birth defects afflict 1 of every 14 live-born infants (about 7 percent), or more than a quarter-million in the United States each year. Twice as many miscarriages and stillbirths occur annually, most of which are due to impaired fetal development **(94).** 1n **1982, 21** percent of all infant deaths were attributed to congenital anomalies, a proportion second only to that claimed by unspecified perinatal conditions (161) (table A-5). It is important to note that the problem of birth defects is not limited to infants: approximately 1.2 million people of all ages are hospitalized and 60,000 die as a result of birth defects each year (94).

Most of the birth-defects statistics used in this review are from the Birth Defects Monitoring Program (BDMP), which is based on the newborn discharge data (i.e., diagnosis at birth of both li~e- and still-born babies) of 955 participating hospitals nationwide (156). Although the BDMP data do not represent a random sample, the program remains the largest single source

[7]Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska and Kansas.

[8]Delaware, Marvland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, and Florida

of uniformly collected and processed birth defect data on newborn infants. Data from the NCHS include only live births (which lowers the reported incidence of commonly fatal conditions like anencephaly, absence of the brain), and are based solely on information gleaned from birth certificates. Birth certificates tend to underreport the more subtle birth defects not immediately apparent at birth. Therefore, this review employs NCHS data solely as a source for analyses of maternal data and other variables not considered by BDMP.

It is important to note that analysis of temporal changes in incidence rates of birth defects is often limited by some degree of incomparability among data from different years. BDMP data are subject to changes in defect classification and are influenced by improvements in diagnostic abilities and public awareness that can elevate reported incidence.

Incidence of Selected Birth Defects.—For this discussion, 67 birth defects have been selected, according to incidence, severity of impact on those afflicted, and availability of data. The selected birth defects data ha~e been divided into 11 categories, according to the physiological consequence of the defect. Table A-6 lists these birth defects and their incidence in the United States in 1982,

Some of the most common defects involve the male urogenital system, including hydrocele (accumulation of fluid around the testes), hypospadias (opening of the urethra on the underside of the penis or on the pelvic floor) and undescended testicles (table A-6). Also relatively common are hip dislocation, patent ductus arteriosus (failure of the opening between the aorta and pulmonary artery to close after birth), clubfoot, and hemangioma (birthmark formed by blood vessels). Congenital metabolic disorders are the least common category overall, with incidence ranging from 0.1 to 0.6 per 10,000 total births. The other two rarest defects among those selected are congenital rubella syndrome and congenital glaucoma. Although the BDMP data do not provide an incidence figure for all chromosomal abnormalities combined, the aggregate rate has been estimated at 62 per 10,000 births (64).

Many of these birth defects have relatively low incidence rates, but the impact of their severe physiological effects on the families involved, and on society, is significant. Do~vn syndrome, for example, has a relatively low incidence rate of 8 per 10,000 total births. Yet, because of the severity of its physiological and functional effects, it is the leading cause of major mental retardation in the United States (82). Similarly, neural tube defects (NTDs) such as spina bifida (incomplete closure of the spinal column) and anencephaly (absence of the brain) are relativelJ~ rare (table A-6), but have such devastating effects that their trends and etiology have been the subject of intense research.

The BDMP data are further subdivided into four regions of the United States: North East, North Central, South, and West (156) (figure A-5). Substantial variations are evident for only a handful of the selected birth defects. There are two major regional differences: one for NTDs and one for the North East region in general.

Three of the NTDs—anencephaly, spina bifida, and hydrocephalus (excess fluid in the brain) -exhibited incidence that are highest in the South (156). The reason for this regional trend is unknown. Data from BDMP and the Metropolitan Atlanta Congenital Defects Program (associated with the Centers for Disease Control) revealed that the incidence of "single" NTDs (those with no major associated defects) follows a decreasing East-West gradient and occurrs most frequently in white and in female newborns (75). Multiple NTDs do not fit this epidemiological profile. This indicates that there may be at least two distinct categories of causes for NTDs: one for single NTDs that is sex-race-region dependent, and another for multiple NTDs that is not dependent on these v;miables. Although several genetic and environmental mechanisms for the epidemiology of single NTDs have been postulated, they are not supported by conclusive evidence (75).

The second major regional difference extracted from the BDMP data is that, of the seven defects other than NTDs that exhibited substarltial regional variation, six have much higher incidence rates in the North East compared with other regions: ventricular septal defect, Down syndrome, hip dislocation without CNS anomalies, rectal atresia and stenosis, clubfoot, and hypospadias (156). The rates are lowest for the first three birth defects in the South, and for the latter three in the West. Again, the reason for this regional variation is not clear, but valuable clues to the etiology of these defects may surface as more data are collected and more epidemiological correlations are made with environmental and genetic factors.

Causes of Birth Defect s.—The causes of a given birth defect may vary from case to case, are often multiple, may involve synergistic effects such as the interaction of genetic and environmental factors, and are usually not known. Neural tube defects, for example, may be caused by a variety of chromosomal anomalies, maternal infections, genetic disorders, and teratogens (75). The causal role of chromosomal anomalies in NTDs has been questioned, however (66). Although the list of possible causal factors continues to grow, many birth defects are of unknown or, at best, speculative origin. Individuals may be affected differently by a given causal agent, and some may not be affected at all. Individual characteristics such as age, health,

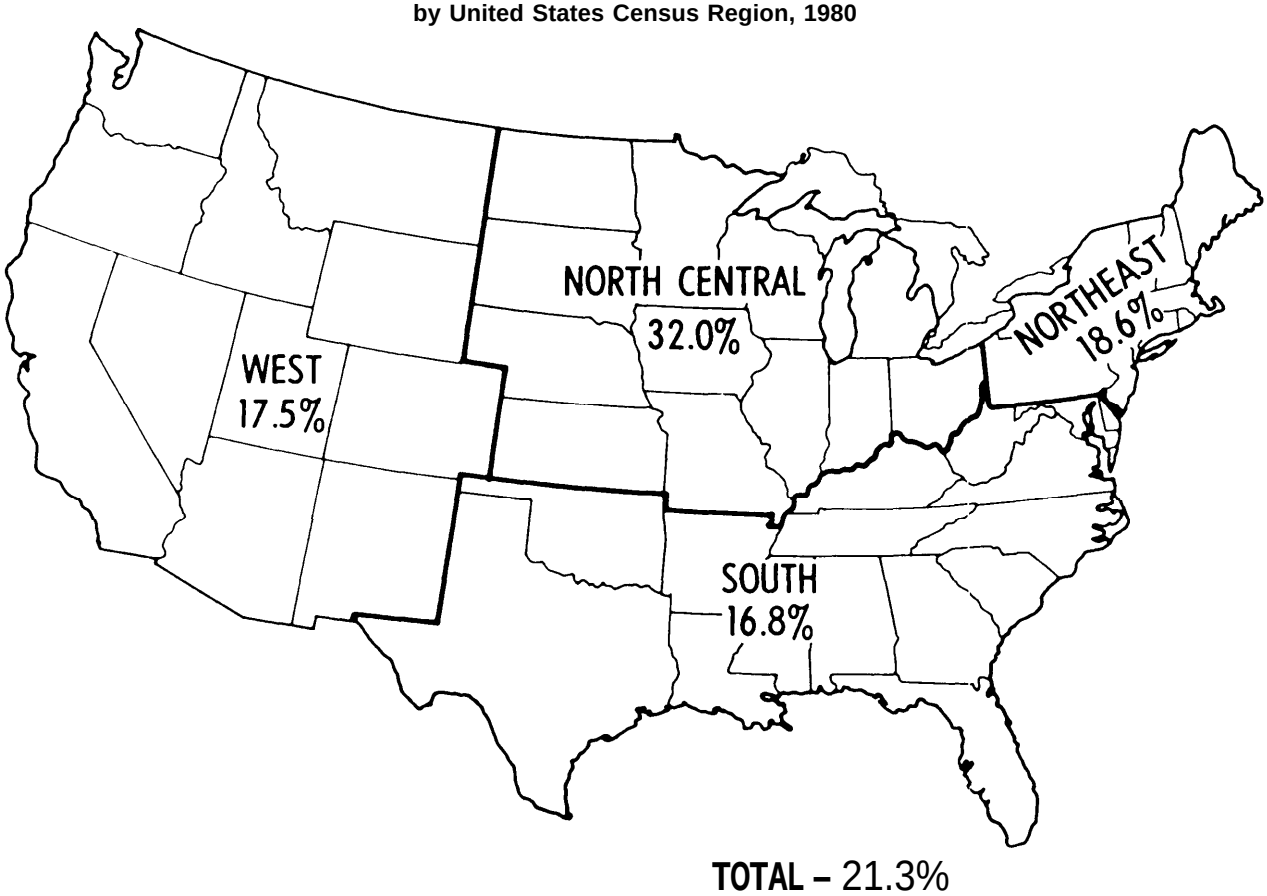
Table A-6.–incidence Rates Per 10,000 Total Births of Selected Birth Defects, 1982

Condition	Incidence rate
Central nervous system:	
Total congenital anomalies of nervous system	18.4
Hydrocephalus (water on the brain)	5.6
Spina bifida (open spinal column)	4.9
Anencephaly (absent brain)	3.3
Microcephaly (small brain)	2.2
Encephalocele (hernia of brain)	1.0
Heart and circulatory system:	
Patent ductus arteriosus (failure of the opening between aorta and pulmonary artery to close at birth)	25.4
Ventricular septal defects (hole between lower chambers of heart)	14.7
Absence of umbilical artery	3.2
Valve defect, absence, or closure	2.2
Atriai septal defect (hole between upper chambers of heart)	1.5
Endocardial fibroelastosis (thickness of inner lining of heart)	1.2
Tetralogy of Fallot (a combination of congenital heart defects)	0.9
Transposition of great arteries	0.8
Other anomalies of the heart (not all-inclusive)	26.6
Urogenital system:	
Hydrocele (collection of fluid in membrane surrounding testes)	30.7
Undescended testicle	27.5
Hypospadias (urethral opening on underside of penis or on the pelvic floor)	27.0
Renal agenesis (absence of kidney)	1.6
Congenital ureteral obstruction	1.6
Cystic kidney disease	1.2
Indeterminate sex	0.6
Male genital anomaly N. E.C.[a]	5.3
Respiratory system:	
Agenesis (absence) of the lungs	2.5
Total anomalies of the nose	2.2
Anomalies of the larynx and/or trachea N. E.C. [a]	2.2
Congenital multi-system syndromes:	
Blood type ABO isoimmunization	144.8
Rh hemolytic disease in newborns	15.6
Down syndrome	7.9
Total monitored infections	4.2
Autosomal abnormalities (i.e., not on sex chromosomes) except Down syndrome	1.8
Total congenital syphilis	1.7
Fetal alcohol syndrome	1.2
Abnormalities of the sex chromosomes N. E,C.[a]	0.7
Congenital rubella	0.2
Congenital Metabolic Disorders:	
Total congenital amino acid disorders	0.6
Cystic fibrosis	0.6
Steroid metabolism disorder	0.2
Phenylketonuria	0.1
Total congenital carbohydrate metabolism disorders	0.1
Total congenital lipid metabolism disorders	0.1
Gastrointestinai tract:	
Total cleft lip and cleft palate	13.4
Intestinal anomalies N. E.C.[a]	4.9
Rectal defect, absence, or closure	3.0
Tracheal-esophageal fistula (opening between trachea and esophagus)	1.8
Congenital pyloric defect	0.6
Other anomalies of the alimentary canal	2.6
Visual system:	
Congenital cataract	0.9
Congenital glaucoma	0.2
Other anomalies of the eye	2.9
Ear, face, and neck:	
Branchial cleft (vestigial, gill-like structure)	1.7
Anomaly of the ear with impaired hearing	0.6
Other anomalies of the ear (not all-inclusive)	4.4
Other anomalies of the face and neck	1.6
Muscuioskeietai system:	
Hip dislocation without central nervous system defects	27.0
Clubfoot without central nervous system defects	24.5
Polydactyly (extra fingers or toes)	20.5
Skull and facial bone anomaly	12.8
Syndactyly (webbing between fingers or toes)	6,7
Arm anomaly N. E.C.[a]	5.0
Reduction deformity (absence of a portion or all of a body part, especially limbs)	3.5
Other congenital anomalies of the limbs (not all-inclusive)	92.8
Other musculoskeletal anomalies (not all-inclusive)	23.7
Other seiected birth defects:	
Hemangioma of skin (birthmarks formed by bundles of blood vessels)	25.7
Anomalies of abdominal wall	7.0
Breast anomalies	2.6

aN E C,—N,t elsewhere classified

SOURCE. Birth Defects Monitoring Program

Figure A.5.–Percentage of United States Live Births in the Birth Defects Monitoring Program (BDMP), by United States Census Region, 1980



SOURCE: U.S. Department of Health and Human Services, Centers for Disease Control, Congenital Malformations Surveillance, 1982

and personal habits often contribute to the risk of being adversely affected by a given agent. Such confounding variables must be considered when attempting to isolate potential workplace hazards (134). In addition, the same agent may have different effects, depending on the extent and timing of embryo/fetal exposure. For example, structural abnormalities are most likely to be induced during the first 8 weeks of gestation (when many women do not yet know that they are pregnant), since this is when most differentiation and organogenesis takes place (see chapter 3). Later fetal stages may be equally sensitive to induction of certain other defects, such as carcinogenesis or behavioral, immunological, or endocrine abnormalities (111).

one study apportions the etiology of birth defects as follows (181):

- genetic transmission, 20 percent;
- chromosomal abnormalities, 5 percent;
- therapeutic radiation, 1 percent;
- . infection, 2 to 3 percerlt;
- maternal metabolic imbalance (e.g., diabetes), 3 to 5 percent;

c drugs and environmental chemicals, z to 3 percent.

The remaining 63 to 67 percent of birth defects are designated as of unknown origin.

This section re~'iews the causal factors for major birth defects that have been identified to date, some only tentatively. These causal factors are categorized as environmental, pathological, heritable, iatrogenic, nutritional, or sociobehavioral.

Ent~ironmental Factors.–v'arious environmental pollutants, such as the ubiquitous polychlorinated biphenyls (PCBS), which are synthetic, chlorinated hydrocarbons used for electrical insulation (1 12,185), and possibly dioxins (119), are thought to produce birth defects. Although PCBS iire transferred in greater amounts to the child postnatally through the mother's milk, prenatal transfer across the placenta may nonetheless have a significant impact on the embryo/fetus

due to: 1) the continuous exposure, 2) the relatively small size of the fetus, 3) increased vulnerability at certain stages of intrauterine development, and 4) the fact that the fetus lacks the protective barriers found postnatally, such as the blood-brain barrier that bars certain drugs and potentially harmful substances from reaching the brain (65, see chapter 4).

Animal experiments suggest that exposure of the embryo/fetus in utero and neonatally to polycyclic aromatic hydrocarbons (major pollutants also found in cigarette smoke), radioactive substances, and gamma rays may destroy substantial numbers of female egg-cell precursors. Although there is presently no direct evidence, the human embryo/fetus may also be vulnerable to these agents, especially during the last trimester, leading to egg-cell-precursor depletion and eventual premature menopause (30,31). In the case of ionizing radiation, there is evidence that a dose of less than 10 rads to the implanted embryo does not significantly increase the incidence of congenital malformations, growth retardation, or fetal death (15a).

A recent report on more than 5,000 newborns found a dose-related correlation between high lead levels in the umbilical cord blood and increased risk of minor congenital anomalies such as hemangioma, hydrocele, and undescended testes (118).

Exposure of the embryo to the pesticide DDT (see chapter 4) before implantation in the uterus, and thus before protective placental barriers develop, may retard intrauterine growth, according to animal studies (36). In the mid-1960s, neurological disorders resembling cerebral palsy were discovered in children after maternal ingestion of mercury-contaminated fish in the now well-known case of Minamata, Japan (97; see chapter 2).

Maternal exposure to some pesticides used in farm work has been associated with diverse birth defects in isolated reports (46,59). There may also be a link between the consumption of high-nitrate groundwater by pregnant women and teratogenesis (33). Glycol ethers, a chemical species contained in a wide variety of products (see chapter 4)—including paints, stains, varnishes, and solvents—have been shown to be teratogenic in animals. High levels of air pollution have been associated with reduced birth weight (180).

Pathological Factors.—The first teratogenic infectious agent discovered was the rubella virus. This virus produces a variety of birth defects, including congenital cataracts, brain damage, and growth retardation (140) (see chapter 4). The only other infectious agents that have been unequivocally proven to be teratogenic are cytomegalovirus, the virus most commonly affecting human fetuses (although only 10 percent of those infected develop symptoms) (51) (see chapter 4), and a parasite, *Toxoplasma gondii*, transmitted through improperly cooked mutton or pork. These three maternal infections are estimated to cause an aggregate 2 percent of all congenital malformations (71). The agent of syphilitic infections, *Treponema pallidum*, is likely to be teratogenic if the pregnant woman is not treated for the infection. Other viruses and bacteria suspected of being teratogenic include: herpes simplex virus (116,142), varicella and herpes zoster (32), Venezuelan equine encephalitis (177), and influenza viruses (80). Other viruses that are not necessarily teratogenic but may cause fetal disease are mumps, polio, and hepatitis.

Heritable Factors.—The incidence of malformations among offspring of epileptic parents is two to three times higher than that in the general population. These malformations include cleft lip, cleft palate, and skeletal and cardiac abnormalities (151). Impaired mental function and increased perinatal mortality have also been associated with offspring of epileptic women. The problem is compounded by the fact that the anticonvulsant medications used to treat epilepsy may contribute to teratogenesis.

Maternal, insulin-dependent diabetes is associated with congenital malformations involving multiple organ systems, particularly the cardiovascular and musculoskeletal systems. There is an estimated two- to threefold increase in malformations among the offspring of diabetic women, constituting a rate of 6 percent or more. This effect is probably not seen in women whose diabetes is controllable by diet or oral hypoglycemic agents (113). Greater variability in maternal blood glucose has been strongly linked to a higher risk of neonatal complications, including stillbirth and metabolic blood imbalances (7). In recent years, the proportion of infants with congenital malformations born to diabetic mothers has increased, perhaps because of better management of the disease during pregnancy that allows the fetus to survive to a viable stage (122).

Maternal, sickle-cell anemia, afflicting 1 in 625 U.S. blacks (144), is associated with low birth weight and high perinatal mortality (45). Maternal phenylketonuria (a metabolic disorder caused by a deficiency of an enzyme needed to metabolize the amino acid phenylalanine, a normal protein component) is relatively rare, afflicting 1 in 12,000 people in the United States (144), but is associated with some serious defects including small head-size, growth retardation, heart defects, and childhood neurologic problems (66). Offspring of women with congenital heart disease may also exhibit higher perinatal mortality (34). The offspring of women with Down syndrome who did not inherit the syndrome have been reported to show higher frequen-

cies of congenital malformations (135). A certain type of tumor causing secretion of hormones that induce hypertension in the mother can cause fetal death. Other rare tumors that cause maternal sex hormone imbalances may masculinize a female fetus (66).

Iatrogenic Factors. —Perhaps the most famous case of teratogenesis resulting from medical treatment involved thalidomide, a drug used widely in Europe during the early 1960s as a sedative (see chapters 2 and 3). The drug was relatively harmless to the mother but was belatedly found to produce severe limb deformities as well as anomalies of the heart, kidney, and gastrointestinal tract in the fetus tvhen taken early in pregnancy (83,103).

Isoretinoin (Accutane®, Roche Laboratories, Nutley, NJ) an orally administered acne medicine licensed in 1982, was recently found to cause spontaneous abortion and a variety of birth defects when taken during the first trimester of pregnancy. The defects include small or absent outer ear and ear canal, central nervous system anomalies including hydrocephalus and microcephaly (small headsize), and congenital heart defects. Through mid-1984, there were 17 reported cases of birth defects and 20 reported instances of spontaneous abortion in women who were receiving isoretinoin. However, there is still no accurate information on the number of normal births among women using isoretinoin (95,154).

Some seemingly innocuous over-the-counter (OTC) drugs may also be hazardous because they are often regarded as nonpharmacological agents and are taken indiscriminately. One study found that 9s percent of pregnant women surveyed used OTC drugs during pregnancy. Some minerals and vitamins, the most frequently consumed OTC drugs (65 percent of women surveyed), can be fetotoxic in excess amounts. Excess maternal ingestion of lfitamin D may result in vascular disorders, mental retardation, and hypercalcemia. Chronic intake of analgesics, the second most frequent type of drugs consumed (61 percent), have been tentatively associated with low birth weight and stillbirth. Certain cough medications (ranking sek~enth at 11 percent) ma, also be hazardous: chronic maternal use of such codeine-containing compounds can cause symptoms similar to narcotics withdra~va] in the newborn (61).

Other medicines now suspected, but not conclusively proven, to be teratogenic, include:

- **anticonvulsants,** used-to treat epilepsy (38,186);
- CNS **stimulants,** such as certain amphetamines, the antidepressive imipramine, and possibly lithium (I09,131);
- sex **hormones:** The synthetic estrogen diethylstilbestrol (DES), a drug used in the 1940s and 19 sos to prevent miscarriage, is now known to be both teratogenic (73) and a transplacental carcinogen (60) (see chapter 2). Danazol, a pharmacologic used to treat endometriosis and fibrocystic breast disease, may also cause masculinization of the female fetus when taken during pregnancy, especially after the 8th week when the embryo becomes sensitive to danazol's male-hormone activity (127);
- **beta adrenergic drugs,** used to treat hypertension and cardiovascular disease (89);
- **anticoagulants,** such as warfarin or dicumarol, given orally during early pregnancy, are teratogenic (28,170) and increase the rate of spontaneous abortion and stillbirth (49);
- **alkylating agents** for the treatment of cancer have been associated with a variety of malformations **(27,120),** and intrauterine growth retardation and death (36);
- **antibiotics,** such as penicillins, tetracycline) or chloramphenicol rna~' be teratogenic or fetotoxic (16,17,130). Streptomycin may cause hearing loss and cerebral damage (172);
- insulin and other ;mtidiabetic drugs (8);
- antinauseants, such as Bendectin® (Merrell-National Laboratories, Cayey, PR), and **antihistamines** (80); and
- **thyroid suppressants** (56).

Therapeutic X-rays at doses above 10 rads may harm the fetus; the risk at doses below this level becomes progressively minute (15b,15c). one hypothesis based on animal data suggests that chronic in-utero irradiation of the embryo/female fetus accumulating to above 20 rads may be associated with premature menopause in the offspring. Furthermore, there may be a period of particularly high sensitivity of the female fetal germ cells during the last trimester of gestation, during which comparable damage may be inflicted by a dose of about 7 rads (29). Exposure to radiation during the first 3 weeks of gestation is more likely to result in spontaneous abortion than other developmental effects (147).

Nutritional Factors .—Maternal malnutrition during pregnancy results in fetal growth retardation (182). The periods of famine during World War 11 were accompanied by increased rates of spontaneous abortion, stillbirth, neonatal death, and congenital malformation (5,136,137).

Although imbalances in t'arious nutrients have been suspected of causing congenital malformations, only zinc deficiency has occurred often enough in humans to provide solid evidence of teratogenicity (18). Certain cytotoxic drugs used to treat cancer, as well as chronic alcohol consumption, can cause folate defi -

ciency—a disorder related to CNS defects (140). Vitamin supplements taken soon after conception may help prevent CNS defects (141).

Sociobehavioral Factors.—Many recreational drugs (licit and illicit) are known to adversely affect the fetus. Alcohol is clearly teratogenic when consumed by the mother in large amounts (defined variably) and can result in "fetal alcohol syndrome," characterized by CNS dysfunction, mental retardation, growth deficiency, and facial deformities (72,151). Among neonates of alcoholic mothers, 83.3 percent had birth weights under the tenth percentile compared with 2.3 percent in a nonalcoholic sample (152). A prospective study of the relationship between birth weight and alcohol drinking during the first trimester of pregnancy in 31,604 pregnancies indicated that consuming at least 1 to 2 drinks daily was associated with a significantly increased risk of producing a growth-retarded infant. Conversely, consuming less than one drink daily had a minimal effect on intrauterine growth and birth weight. The authors note that "an occasional drink has only a trivial effect on intrauterine growth" (114).

Cigarette smoke and nicotine are also harmful, carrying an increased risk of: 1) prematurity, 2) low birth weight, due partly to fetal malnutrition resulting from depression of uterine circulation or maternal appetite, and 3) perinatal death (121,151). A pregnant woman who smokes two packs of cigarettes a day may reduce the oxygen supply to her fetus by 25 percent (4). Beginning in October 1985, new warning statements will be required (Public Law 98-474) on the packages and advertising of all cigarette brands sold in the United States (175). One of these statements calls specific attention to the hazards imposed by maternal smoking on the offspring:

> **SURGEON GENERAL'S WARNING:** Smoking by Pregnant Women May Result in Fetal Injury, Premature Birth, and Low Birth Weight.

Paternal smoking (35) and chronic alcohol consumption (84) are both associated with sperm abnormalities that may increase the risk of birth defects (66).

The regular use of marijuana has been linked to a shortened gestation period. A 1-week reduction in gestation length observed among heavy marijuana users is of questionable clinical significance in and of itself. However, the figure of 1 week is an average, and the reduction is more marked as the quantity consumed increases. The finding that marijuana usage can contribute to a shortened gestation length may take on clinical significance in certain individuals who consume large amounts of the drug or in individuals whose lifestyle habits include the use of other drugs that may also reduce the length of gestation (39).

Although caffeine is suspected of being a teratogen (13), heavy maternal coffee drinking (seven or more cups per day) is associated with increased risk of low birth weight offspring (62). Finally, narcotics can cause prematurity, retarded intrauterine growth, and neonatal addiction (151).

Advanced maternal age is considered a risk factor for a variety of birth defects, particularly for Down syndrome (87): the risk of bearing an affected child at age 45 is 1 in 32, more than 11 times greater than at age 35 (123). Since an estimated 25 percent of children with Down syndrome received their extra chromosome from their fathers (123), paternal risk factors should be further investigated. The incidence of Down syndrome may rise in the future due to the increasing popularity of delayed childbearing since the early 1970s. The first-birth rate in the 30 to 39 age group has risen markedly compared with younger age groups. The rate among women aged 30 to 34 doubled between 1972 and 1981 (159).

In contrast to infant mortality and low birth weight, birth defects are more common overall among white than black babies (165). Further, male babies and babies from plural deliveries (i.e., twins, triplets) are more likely to have birth defects. Finally, the incidence of birth defects is generally higher among babies born to women with less than a high school education (165).

Appendix A References

1. Abramson, F.D., "Spontaneous Fetal Death in Man," *Social Biology* 20(4):375-403, 1973.
2. Aitken, J., "The Zona-Free Hamster Egg Penetration Test," *Male Infertility*, T.B. Hargreave (ed.) (Heidelberg: Springer-Verlag, 1983), pp. 75-86.
3. Alexander, N.J., "Antibodies to Human Spermatozoa Impede Sperm Penetration of Cervical Mucus or Hamster Eggs," *Fert. Steril.* 41(3): 433-439, 1984.
4. American Lung Association, Cigarette Smoking, Published by American Lung Association, 1982.
5. Antonov, A.N., "Children Born During the Siege of Leningrad in 1942," *J. Ped.* 30:250, 1942.
6. Aral, S.O., and Cates, W., "The Increasing Concern With Infertility: Why Now?" *J. Am. Med. Assoc.* 250(7):2327-2331, 1983.
7. Artal, R., et al., "The Effect of Plasma Glucose Variability on Neonatal Outcome in the Pregnant Diabetic Patient," *Am. J. Obstet. Gynecol.* 147(5): 537-541, 1983.
8. Babson, S.G., and Benson, R.C., *Management of*

High-Risk Pregnancy and Intensive Care of the Neonate (St. Louis, MO: C.V. Mosby, 1971).
9. Bachmann, G.A., and Kemmann, E., "Prevalence of Oligomenorrhea and Amenorrhea in a College Population," *Am. J. Obstet. Gynecol.* 144 (1):98-102, 1982.
10. Bell, J.S., "Psychological Aspects," *Male Infertility,* T.B. Hargreave (ed.) (Heidelberg: Springer-Verlag, 1983), pp. 46-55.
11. Berthelsen, J.G., "Sperm Counts and Serum Follicle-Stimulating Hormone Levels Before and After Radiotherapy and Chemotherapy in Men With Testicular Germ Cell Cancer," *Fert. Steril.* 41(2):281-286, 1984.
12. Bloom, A.D., *Guidelines for Studies of Human Populations Exposed to Mutagenic and Reproductive Hazards* (White Plains, NY: March of Dimes Birth Defects Foundation, 1981).
13. Borlee, R., et al., "LeCafe, Facteur de Risque Pendant La Grossesse?" *Louvain Med.* 97:279-284, 1978.
14. Bostofte, E., Serup, J., and Rebbe, A., "Interrelations Among the Characteristics of Human Semen and a New System for Classification of Male Infertility," *Fert. Steril.* 41(1):95-105, 1984.
15a. Brent, R.L., "The Effects of Embryonic and Fetal Exposure to X-Ray, Microwaves, and Ultrasound," *Clin. Obstet. Gynecol.* 26: 484-510, 1983.
15b. Brent, R.L., "Environmental Factors," *Prevention of Embryonic, Fetal, and Prenatal Disease,* R.L. Brent and M.R. Harris (eds.), vol. 3 (Bethesda, MD: U.S. Department of Health, Education, and Welfare, 1976), p. 182.
15c. Brent, R.L., "Radiation and Other Physical Agents," *Handbook of Teratology, Vol. I, General Principles and Etiology,* J.G. Wilson, F.C. Fraser (eds.) (New York: Plenum Press, 1977), pp. 153-223.
16. Carter, M.P., and Wilson, R., "Antibodies in Early Pregnancy and Congenital Malformations," *Dev. Med. Child. Neurol.* 7:353, 1965.
17. Carter, M.P., discussion of a paper by B.C.S. Slater, in J.M. Robson, et al. (eds.), *Embryopathic Activity of Drugs* (Boston, MA: Little, Brown, 1965), p. 253.
18. Cavdar, A.O., et al., "Zinc Deficiency and Anencephaly in Turkey," *Teratology* 22:141, 1980.
19. Chandley, A., "Chromosomes," *Male Infertility,* T.B. Hargreave (ed.) (Heidelberg: Springer-Verlag, 1983), pp. 144-159.
20. Chapman, R.M., "Gonadal Injury Resulting From Chemotherapy," *Reproductive Toxicology,* D.R. Mattison (ed.) (New York: Alan R. Liss, Inc., 1983), pp. 149-162.
21. Collins, J.A., Wrixon, W., Janes, L.B., and Wilson, E.H., "Treatment-Independent Pregnancy Among Infertile Couples," *N. Eng. J. Med.* 309 (20):1201-1206, 1983.
22. Cramer, D.W., et al., "Tubal Infertility and the Intrauterine Device," *N. Eng. J. Med.* 312:941-947, 1985.
23. Cumming, D.C., and Rebar, R.W., "Exercise and Reproductive Function in Women," *Reproductive Toxicology,* D.R. Mattison (ed.) (New York: Alan R. Liss, Inc., 1983), pp. 113-126.
24. Curran, J.W., "Economic Consequences of Pelvic Inflammatory Disease in the United States," *Am. J. Obstet. Gynecol.* 138:848, 1980.
25. Daling, J.R., et al., "Primary Tubal Infertility in Relation to the Use of an Intrauterine Device," *N. Eng. J. Med.* 312:937-941, 1985.
26. de Kretser, D.M., "Endocrinology of Male Infertility," *Br. Med. Bull.* 35:187-192, 1979.
27. Diamond, R., et al., "Transplacental Transmission of Busulfan (myleran) in a Mother With Leukemia: Production of Fetal Malformations and Cytomegaly," *Pediatr.* (Spirnafield), 25:85, 1960.
28. DiSaia, P.J., "Pregnancy and Delivery of a Patient With a Stan-Edwards Mitral Valve Prosthesis: Report of a Case," *Obstet. Gynecol.* 28:469-472, 1966.
29. Dobson, R.L., and Felton, J.S., "Female Germ Cell Loss From Radiation and Chemical Exposures," *Am. J. Indust. Med.* 4:175-190, 1983.
30. Dobson, R.L., et al., "Diminished Lifetime Reproductive Capacity in the Female Following Early Radiation Exposure," Lawrence Livermore National Laboratory. Paper prepared for submittal to 22d Hanford Life Sciences Symposium, September 1983.
31. Dobson, R.L., et al., "Vulnerability of Female Germ Cells in Developing Mice and Monkeys to Tritium, Gamma Rays, and Polycyclic Aromatic Hydrocarbons," *Developmental Toxicology of Energy-Related Pollutants,* D.D. Mahlum, et al. (ed.) DOE Symposium Series 47, CONF.-771017, 1978.
32. Dodion-Fransen, J., et al., "Congenital Varicella-zoster Infection Related to Maternal Disease in Early Pregnancy," *Scand. J. Infect. Dis.* 5:149, 1973.
33. Dorsch, M.M., et al., "Congenital Malformations and Maternal Drinking Water Supply in Rural South Australia: A Case-Control Study," *Am. J. Epi.* 119:473-486, 1984.
34. Elias, S., and Yanagi, R.M., "Cardiovascular Defects," *Genetic Diseases in Pregnancy,* J.D. Schulman and J.L. Simpson (eds.) (New York: Academic Press, 1981), pp. 197-227.
35. Evans, H.J., et al., "Sperm Abnormalities and Cigarette Smoking," *Lancet* 1:627-629, 1981.
36. Fabro, S., McLachlan, J.A., and Dames, N.M.,

"Chemical Exposure of Embryos During the Preimplantation Stages of Pregnancy: Mortality Rate and Intrauterine Development," *Am. J. Obstet. Gynecol.* 148(7):929-936, 1984.
37. Felton, J.S., et al., "Genetic Differences in Polycyclic Aromatic Hydrocarbon Metabolism and Their Effects on Oocyte Killing in Developing Mice," in D.D. Mahlum, et al. (eds.), *Developmental Toxicology of Energy-Related Pollutants*, DOE Symposium series 47, pp. 1526-1532, 1978.
38. Finell, R.H., "Phenytoin Induced Teratogenesis: A Mouse Model," *Science* 211:483-484, 1981.
39. Fried, P.A., Watkinson, B., and Willan, A., "Marijuana Use During Pregnancy and Decreased Length of Gestation," *Am. J. Obstet. Gynecol.* 150: 23-27, 1984.
40. Fries, H.S., et al., "Epidemiology of Secondary Amenorrhea II. A Retrospective Evaluation With Special Regard to Psychogenic Factors and Weight Loss," *Am. J. Obstet. Gynecol.* 118:473-479, 1974.
41. Frisch, R.E., "Body Fat, Puberty, and Fertility," *Biol. Rev.* 59:161-188, 1984.
42. Frisch, R.E., and McArthur, J.W., "Menstrual Cycles: Fatness as a Determinant of Minimum Weight for Height Necessary for Their Maintenance or Onset," *Science* 185:949-951, 1974.
43. Ginsburg, J., Bowes, L., and Osgood, V., "Pregnancy in Infertile Couples," *N. Eng. J. Med.* 310 (20):1335, 1984.
44. Glick, B.J., Welsh, A.K., and Jason, C.J., "The Geographical Distribution of Unexplained Low Birth Weight," *Am. J. Epidemiol.* in press, 1985.
45. Golbus, M.S., and Laros, R.K., Jr., "Hemoglobinopathies and Hemolytic Anemias," *Genetic Diseases in Pregnancy*, J. D. Schulman and J.L. Simpson (eds.) (New York: Academic Press, 1981), pp. 89-122.
46 Gordon, J.E., and Shy, C.M., "Agricultural Chemical Use and Congenital Cleft Lip and/or Palate, *Arch. Environ. Health* 36:213-221, 1981.
47 Graves, C., et al., "The Effect of Maternal Alcohol and Cigarette Use on Infant Birthweight," Presented at the 14th Annual Medical Scientific Conference of the National Alcoholism Forum. National Council on Alcoholism and Research Society on Alcoholism, Apr. 14-17, 1983, in Houston, TX, summarized in *Alcohol Health and Research World* 8:39-40, fall 1983.
48 Hafez, E.S.E., "Reproductive Senescence," *Aging and Reproductive Physiology*, E.S.E. Hafez (ed.) (Ann Arbor, MI: Ann Arbor Science, 1976), pp. 1-19.
49. Hall, J.G., Pauli, R.M., and Wilson, K.M., "Maternal and Fetal Sequelae of Anticoagulation During Pregnancy," *Am. J. Med.* 68:122-140, 1980.
50. Hamerton, J.L., "Cytogenetic Disorders," *N. Eng. J. Med.* 310(5):314-316, 1984.
51. Hanshaw, J.B., "Congenital Cytomegalovirus Infection," *Intrauterine Infections*, K. Elliott, J. Knight (eds.), Ciba Foundation Symposium No. 10 (London: Associated Scientific Publishers, 1973), pp. 23-32.
52. Hargreave, T.B., "History and Examination," *Male Infertility*, T.B. Hargreave (ed.) (Heidelberg: Springer-Verlag, 1983), pp. 9-45.
53. Hargreave, T.B., "Incidence of Serum Agglutinating and Immobilizing Sperm Antibodies in Infertile Couples," *Int. J. Fertil.* 27(2):90-94, 1982.
54. Hargreave, T.B., and Nilsson, S., "Seminology," *Male Infertility*, T.B. Hargreave (ed.) (Heidelberg: Springer-Verlag, 1983), pp. 56-74.
55. Hargreave, T.B., Pryor, J.P., Jequier, A.M., and Crich, J.P., "Erectile and Ejaculatory Problems in Infertility," *Male Infertility*, T.B. Hargreave (ed.) (Heidelberg: Springer-Verlag, 1983), pp. 246-260.
56. Heinonen, O.P, Slone, D., and Shapiro, S., *Birth Defects and Drugs in Pregnancy* (Littleton, MA.: Publishing Sciences Group, Inc., 1977).
57. Heinrichs, W.L., and Gellert, R.J., "DDT Administered to Neonatal Rats Induces Persistent Estrus Syndrome," *Science* 173:642-643, 1971.
58. Hembree, W.C., et al., "Marijuana Effects on Human Gonadal Function," *Marijuana: Chemistry, Biochemistry, and Cellular Effects*, G. Nahas, et al. (eds.) (New York: Springer-Verlag, 1976), pp. 521-532.
59. Hemminki, K., et al., "Congenital Malformations by the Parental Occupation in Finland," *Int. Arch. Occup. Environ. Health* 46:93-98, 1980.
60. Herbst, A.L., et al., "Age-Incidence and Risk of Diethylstilbesterol-Related Clear Cell Adenocarcinoma of the Vagina and Cervix," *Am. J. Obst. Gyn.* 128:43, 1977.
61. Hill, R.M., et al., "Utilization of Over-The-Counter-Drugs During Pregnancy," *Clin. Obstet. Gynec.* 20(2):381-394, 1977.
62. Hogue, C.J.R., "The Effect of Common Exposures on Reproductive Outcomes," *Teratogen. Carcinogen. Mutagen.* 4:45-57, 1984.
63. Holmes, K.K., "The Chlamydia Epidemic," *J. Am. Med. Assoc.* 245(17):1718-1723, 1981.
64. International System for Cytogenetic Nomenclature, "An International System for Human Cytogenetic Nomenclature," *Birth Defects* 14:8, 1978.

65< Jacobson, J.L., et al., "The Transfer of Polychlorinated Biphenyls (PCBs) and Polybrominated Biphenyls (PBBs) Across the Human Placenta and Into Maternal Milk," *Am. J. Pub. Health* 74(4): 378-379, 1984.
66. Janerich, D.T., and Polednak, A.P., "Epidemiology of Birth Defects," *Epidemiological Reviews* 5:16-37, 1983.
67. Jansen, R.P.S., "Spontaneous Abortion Incidence in the Treatment of Infertility," *Am. J. Obst. Gyn.* 143(4):451-473, 1982.
68. Johnson, L., Petty, C.S., and Neaves, W.B., "Influence of Age on Sperm Production and Testicular Weights in Men," *J. Reprod. Fert.* 70:211-218, 1984.
69. Johnston, D.E., et al., "Inhibition of Testosterone Synthesis by Ethanol and Acetaldehyde," *Biochem. Pharmacol.* 30:1827-1831, 1981.
70. Jull, J.W., "Ovarian Tumorigenesis: Methods," *Cancer Res.* 7:131-186, 1973.
71. Kalter, H., and Warkany, J., "Congenital Malformations: Etiologic Factor and Their Role in Prevention" (first of two parts), *N. Eng. J. Med.* 308(8):424-430, 1983.
72. Kalter, H., and Warkany, J., "Congenital Malformations: Etiologic Factor and Their Role in Prevention" (second of two parts), *N. Eng. J. Med.* 308(9):491-497, 1983.
73 Kaufman, R.H., et al., "Upper Genital Tract Changes Associated With Exposure in Utero to Diethylstilbesterol," *Am. J. Obst. Gyn.* 128:51-59, 1977.
74 Kessel, S.S., Berendes, H.W., and Nugent, R.P., "The Changing Pattern of Low Birth Weight in the United States: 1970 to 1980," *J. Am. Med. Assoc.* 251(15):1978-1982, 1984.
75 Khoury, M.J., Erickson, J.D., and James, L.M., "Etiologic Heterogeneity of Neural Tube Defects: Clues From Epidemiology," *Am. J. Epid.* 115(4): 538-548, 1982.
76. Kley, H.K., et al., "The Effect of Methadone on Hypophyseal and Peripheral Glandular Hormones During Withdrawal," *Horm. Metals. Res.* 9:484-488, 1977.
77. Kliger, B.E., "Evaluation, Therapy and Outcome in 493 Infertile Couples," *Fert. Steril.* 41(1):40-46, 1984.
78. Kline, J., et al., "Drinking During Pregnancy and Spontaneous Abortion," *Lancet* —:176-180, 1980.
79. Kline, J., et al., "Smoking: A Risk Factor for Spontaneous Abortion," *N. Eng. J. Med.* 297:793, 1977.
80. Klingberg, M.A., Papier, C.M., and Hart, J., "Birth Defects Monitoring," *Reproductive Toxicology*, D.R. Mattison (ed.) (New York: Alan R. Liss, Inc., 1983), pp. 309-328.
81. Lamb, E.J., "Prognosis for the Infertile Couple," *Fertil. Steril.* 23:320, 1972.
82. Laxova, R., Ridler, M.A.C., Bowen-Bravey, M., "An Etiological Survey of the Severely Retarded Hertfordshire Children Who Were Born Between January 1965 and December 31, 1967, *Am. J. Med. Genet.* 1:75-86, 1977.
83 Lenz, W.V., "Die Thalidomide-Embryopathic," *Dtsch. Med. Wschr.* 86:2555, 1961.
84< Lester, R., and Van Thiel, D. H., "Gonadal Function in Chronic Alcoholic Men," *Adv. Exp. Med. Biol.* 85a:399-414, 1977.
85. Leto, S., and Frensilli, F.J., "Changing Parameters of Donor Semen," *Fert. Steril.* 36(6):766-770, 1981.
86. Levine, R.J., et al., "Superiority of Reproductive Histories to Sperm Counts in Detecting Infertility at a Dibromochloropropane Manufacturing Plant," *J. Occup. Med.* 25(8):591-597, 1983.
87. Lilienfield, A.M., *Epidemiology of Mongolism* (Baltimore, MD: The Johns Hopkins University Press, 1969), ch. 4.
88. Limm, S., et al., "Delay in Conception for Former Pill Users," *J. Am. Med. Assoc.* 247:629-632, 1982.
89. Loser, H., et al., "Kardiotoxische Wirking des Toskolytikoma Fenoterol," *Munch. Med. Worchr.* 123(2):49-52, 1971.
90. Lundberg, C., "Effects of Long-term Exposure to DDT on the Oestrus Cycle and the Frequency of Implanted Ova in the Mouse," *Envir. Physiol. Brochem.* 3:127:131 1973.
91. Mackenzie, K.M., and Angevine, D.M., "Infertility in Mice Exposed in Utero to Benzo(a) Pyrene," *Biol. Reprod.* 24:183-191, 1981.
92. Macleod, J., "Semen Quality in 1,000 Men of Known Infertility and in 800 Cases of Infertile Marriage," *Fertil. Steril.* 2:115-139, 1951.
93. Madanes, A.E., "Pregnancy in Infertile Couples," *N. Eng. J. Med.* 310(20):1334-1335, 1984.
94. March of Dimes, *Facts/1984* (White Plains, NY: March of Dimes Birth Defects Foundation, 1984).
95. Marwick, C., "More Cautionary Labeling Appears on Isoretinoin," *J. Am. Med. Assoc.* 251 (24):3208-3209, 1984.
96. Mathen, S., et al., "Sperm Motility on Post Coital Testing Correlates With Male Autoimmunity to Sperm, *Fert. Steril.* 41(1):81-87, 1984.
97. Matsumoto, H.G., et al., "Fetal Minamata Disease: A Neuropathological Study of Two Cases of Intrauterine Intoxication by a Methylmercury Com-

pound," *J. Neuropath. Exp. Neur.* 24:563-574, 1965.
98. Mattison, D.R., "The Effects of Smoking and Reproduction From Gametogenesis to Implantation," *Environ. Res.* 28:410-433, 1982.
99. Mattison, D.R., Shiromizu, K., and Nightingale, M.S., "Oocyte Destruction by Polycyclic Aromatic Hydrocarbons," *Reproductive Toxicology*, D.R. Mattison (ed.) (New York: Alan R. Liss, Inc., 1983), pp. 191-202.
100. Mattison, D.R., et al., "The Effect of Benzo(a)pyrene on Fertility, Primordial Oocyte Number and Ovarian Response to Pregnant Mares Serum Gonadotropin," *Pediatr. Pharmacol.* 1:143-151, 1980.
101. Mattison, D.R., and Thorgeirsson, S.S., "Ovarian Aryl Hydrocarbon Hydroxylase Activity and Primordial Oocyte Toxicity of Polycyclic Aromatic Hydrocarbons in Mice," *Cancer Res.* 39: 3471-3475, 1979.
102. Mattison, D.R., and Thorgeirsson, S.S., "Gonadal Aryl Hydrocarbon Hydroxylase in Rats and Mice," *Cancer Res.* 38:1368-1373, 1978.
103. McBride, W.G., "Thalidomide and Congenital Abnormalities," *Lancet* 2:1358, 1961.
104. Mehan, D.J., "Clinical Applications of Meiotic Preparations in the Infertile Male," paper presented at the 32d Annual Meeting of the American Fertility Society, Las Vegas, April 1976.
105. Meistrich, M.L., and Brown, C.C., "Estimation of the Increased Risk of Human Infertility From Alterations in Semen Characteristics," *Fert. Steril.* 40(2):220-230, 1983.
106. Mendelson, J.H., et al., "Effects of Acute Alcohol Intake on Pituitary-Gonadal Hormones in Normal Human Males," *J. Pharmacol. Exp. Ther.* 202:676-682, 1977.
107. Mendelson, J.H., and Mello, N.K., "Plasma Testosterone Levels During Chronic Heroin Use and Protracted Abstinence: A Study of Hong Kong Addicts," *Clin. Pharmacol. Ther.* 17:529-533, 1975.
108. Menge, A.C., et al., "The Incidence and Influence of Antisperm Antibodies in Infertile Human Couples on Sperm-Cervical Mucus Interactions and Subsequent Fertility," *Fert. Steril.* 38(4):439-446, 1982.
109. Mignot, G., et al., "Lithium of Grossesse," *J. Gyn. Obst. Biol. Reprod.* (Paris) 7:1303-1317, 1978.
110. Miller, J.F., Williamson, E., Glue, J., Gordon, Y.B., Grudzinskas, J.G., and Sykes, A., "Fetal Loss After Implantation: A Prospective Study," *Lancet* Sept. 13, 1980, pp. 554-556.
111. Miller, R.K., "Perinatal Toxicology: Its Recognition and Fundamentals," *Reproductive Toxicology*, D.R. Mattison (ed.) (New York: Alan R. Liss, Inc., 1983), pp. 205-244.
112. Miller, R.W., "Coca-colored Babies, Chlorobiphenyl Poisoning in Japan," *Teratology* 4:211-212, 1971.
113. Mills, J.L., "Malformations in Infants of Diabetic Mothers," *Teratology* 25:385-394, 1982.
114. Mills, J.L., Graubard, B.I., Harley, E.E., Rhoads, G.G., and Berendes, H.W., "Maternal Alcohol Consumption and Birth Weight: How Much Drinking During Pregnancy Is Safe?" *J. Am. Med. Assoc.* 252(14):1875-1879, 1984.
115. Milner, P.F., Jones, B.R., Dobler, J., "Outcome of Pregnancy in Sickle Cell Anemia and Sickle Cell Hemoglobin C Disease," *Am. J. Obst. Gyn.* 138:239-245, 1980.
116. Montgomery, J.R., et al., "Congenital Anomalies and Herpes Virus Infection," *Am. J. Dis. Child.* 126:364, 1973.
117. Mosher, W.D., "Fecundity and Infertility in the United States, 1965-1982," National Center for Health Statistics, paper presented at the Annual Meeting of the Population Association of America, Minneapolis, MN, May 3-5, 1984. Submitted for publication, *Demography*.
117a. Mosher, W.D., "Infertility Trends Among U.S. Couples: 1965-1976," *Family Planning Perspectives* 14(1):22-27, 1982.
118. Needleman, H.L., Rabinowitz, M., Leviton, A., Linn, S., and Schoenbaum, S., "The Relationship Between Prenatal Exposure to Lead and Congenital Anomalies," *J. Am. Med. Assoc.* 251(22): 2956-2959, 1984.
119. Neubert, D., et al., "Survey of the Embryotoxic Effects of TCDD in Mammalian Species," *Environ. Health Persp.* 5:67-79, 1973.
120. Nicholson, H.O., "Cytotoxic Drugs in Pregnancy," *J. Obst. Gyn. for Commonw.* 75:307, 1968.
121. Nilsen, S.T., et al., "Smoking, Hemoglobin Levels, and Birth Weight in Normal Pregnancies," *Am. J. Obst. Gyn.* 148(6):752-758, 1984.
122. Nitzan, M., "Diabetes Mellitus," *Genetics Diseases in Pregnancy*, J.D. Schulman and J.L. Simpson (eds.) (New York: Academic Press, 1981), pp. 339-365.
123. Oakley, G.P., "Incidence and Epidemiology of Birth Defects, *Genetic Issues in Pediatric and Obstetric Practice*, M.M. Kaback (ed.) (Chicago: Year Book Medical Publishers, Inc., 1981), pp. 25-43.
124. Poland, B.J., Miller, J.R., Jones, D.C., and Trimble, B.K., "Reproductive Counseling in Patients Who Have Had a Spontaneous Abortion," *Am. J. Obstet. Gynecol.* 127:685-689, 1977.

125. Prager, K., Malin, H., Spiegler, D., et al., "Smoking and Drinking Behavior Before and During Pregnancy of Married Mothers of Live-born Infants and Still-born Infants," *Pub. Hlth. Reports* 99(2):117-127, 1984.
126. Pusey, J., et al., "Outcome and Effect of Medical Intervention in Women Experiencing Infertility Following Removal of an Ectopic Pregnancy," *Am. J. Obst. Gyn.* 148(5):524-527, 1984.
127. Rosa, F.W., "Virilization of the Female Fetus With Maternal Danazol Exposure," *Am. J. Obst. Gyn.* 149(1):99-100, 1984.
128. Ryder, N.B., and Westoff, C.F., *Reproduction in the United States, 1965* (Princton, NJ: Princeton University Press, 1971).
129. Santodonato, J., Howard, P.H., and Basu, D.K., "Health and Ecological Assessment of Polynuclear Aromatic Hydrocarbons," *J. Environ. Pathol. Toxicol.* 5:1-364, 1981.
130 Saxen, P., "Associations Between Oral Clefts and Drugs Taken During Pregnancy," *In. J. Epidemiol.* 14:37-44, 1975.
131 Schou, M., et al., "Lithium and Pregnancy: A Report From the Register of Lithium Babies," *Br. Med. J.* 2:135-136, 1973.
132 Schreiber, J.R., and Rebar, R.W., "Endocrine Aspects of Genetic Disorders in Pregnancy (Excluding Diabetes Mellitus)," *Genetic Diseases in Pregnancy*, J.D. Schulman and J.L. Simpson (eds.) (New York: Academic Press, 1981), pp. 367-412.
133. Sciarra, J.J, and Steer, C.M., *Am. J. Obstet. Gynecol.* 82:612-615, 1961.
134. Shilling, S., and Lalich, N.R., "Maternal Occupation and Industry and the Pregnancy Outcome of U.S. Married Women, 1980," *Public Health Reports* 99(2):152-161, 1984.
135. Simpson, J.L., "Pregnancies in Women With Chromosomal Abnormalities," *Genetic Diseases in Pregnancy*, J.D. Schulman and J.L. Simpson (eds.) (New York: Academic Press, 1981), pp. 367-412.
136. Smith, C.A., "Effects of Maternal Undernutrition Upon the Newborn Infant in Holland (1944-1945)," *J. Pediatr.* 30:229, 1947.
137. Smith, C.A., "The Effects of Wartime Starvation in Holland Upon Pregnancy and its Product," *Am. J. Obst. Gyn.* 53:599, 1946.
138. Smith, C.G., et al., "Effects of Marijuana on the Reproductive System," *Advances in Sex Hormone Research*, J.A. Thomas, and R. Singhal (eds.) (Baltimore-Munich: Urban and Schwarzenberg, 1980), vol. 7, pp. 273-294.
139. Smith, H.C., Sealey, J.P., and Posen, S., "Premature Ovarian Failure in a Triple X Female," *J. Obst. Gyn. Br. Commonw.* 81:405-409, 1974.
140. Smithells, R.W., "Vitamin Deficiencies and Neural Tube Defects," *Arch. Dis. Child.* 51:944-950, 1976.
141. Smithells, R.W., et al., "Possible Prevention of Neural Tube Defects by Periconceptual Vitamin Supplementation," *Lancet* :339-340, 1980.
142. South, M.A., et al., "Congenital Malformation of the Central Nervous System Associated With the Genital Type (type 2) Herpes Virus," *J. Pediatr.* 75:13, 1969.
143. Stager, J.M., Ritchie-Flanagan, B., and Robertshaw, D., "Reversibility of Amenorrhea in Athletes," *N. Eng. J. Med.* 310(1):51-52, 1984.
144, Stanbury, J.B., et al., "Inborn Errors of Metabolism in the 1980s," J.B. Stanbury, et al. (eds.), *The Metabolic Basis of Inherited Disease* (New York: McGraw Hill Book Co., 1983).
145. Stray-Peterson, B., and Stray-Peterson, S., "Etiologic Factors and Subsequent Reproductive Performance in 195 Couples With a Prior History of Habitual Abortion." *Am. J. Obst. Gynec.* 148(2): 140-146, 1984.
146. Suzuki, T., Kashimura, S., Umetsu, K., "Thinner Abuse and Aspermia," *Med. Sci. Law* 23(3):199-202, 1983.
147. Swartz, H.M., and Reichling, B.A., "Hazards of Radiation Exposure for Pregnant Women," *J. Am. Med. Assoc.* 239:1907-1908, 1978.
148. Task Force on Intrauterine Devices, "PID Associated With Fertility Regulating Agents," *Contraception* 30(1):1-21, 1984.
149. Tinga, D.J., et al., "Factors Relating to Semen Improvement and Fertility After Varicocele Operation," *Fert. Steril.* 41:404-410, 1984.
150. Treloar, A.E., et al., "Variation of the Human Menstrual Cycle Through Reproductive Life Part 2," *Int. J. Fertil.* 12:76, 1967.
151 Tuchmann-Duplessis, H., "The Teratogenic Risk," *Reproductive Toxicology*, D.R. Mattison (ed.) (New York: Alan R. Liss, Inc., 1983), pp. 245-258.
152 Ulleland, C.N., "The Offspring of Alcoholic Mothers," *Ann. N.Y. Acad. Sci.* 197:167-169, 1972.
153. U.S. Department of Health and Human Services, Centers for Disease Control, "Gonorrhea—United States, 1983," *Morbidity and Mortality Weekly Report* 33(25):361-363, June 29, 1984.
154. U.S. Department of Health and Human Services, Centers for Disease Control, "Isoretinoin—A Newly Recognized Human Teratogen," *Morbidity and Mortality Weekly Report* 33(13):171-173, Apr. 6, 1984.
155. U.S. Department of Health and Human Services, Centers for Disease Control, "Ectopic Pregnancies, United States, 1979-1980," *Morbidity and*

Mortality Weekly Report 33(15):201-202, Apr. 20, 1984.
156. U.S. Department of Health and Human Services, Centers for Disease Control, Congenital Malformations Surveillance, 1982.
157. U.S. Department of Health and Human Services, Centers for Disease Control, "Sexually Transmitted Disease (STD)," Statistical Letter No. 129, Atlanta, 1980.
158. U.S. Department of Health and Human Services, National Center for Health Statistics, "Annual Summary of Births, Deaths, Marriages, and Divorces: United States, 1983," Monthly Vital Statistics Report, vol. 32, No. 13, Sept. 21, 1984.
159. U.S. Department of Health and Human Services, National Center for Health Statistics, "Health and Prevention Profile, 1983," U.S. Department of Health and Human Services, Public Health Service, 1983.
160. U.S. Department of Health and Human Services, National Center for Health Statistics, "Annual Summary of Births, Deaths, Marriages, and Divorces: United States, 1982," Monthly Vital Statistics Report, vol. 31, No. 13, 1983.
161. U.S. Department of Health and Human Services, National Center for Health Statistics, "Advance Report of Final Natality Statistics, 1981," Monthly Vital Statistics Report, vol. 32, No. 9, Supplement, Dec. 29, 1983.
162. U.S. Department of Health and Human Services, National Center for Health Statistics, "A Study of Infant Mortality From Linked Records by Birth Weight, Period of Gestation, and Other Variables: United States," Vital and Health Statistics, Series 20, No. 12, 1982.
163. U.S. Department of Health and Human Services, National Center for Health Statistics, "National Surveys of Family Growth, Cycle II: Sample Design, Estimation Procedures, and Variance Estimation" by W.R. Grady, Vital and Health Statistics, NCHS Series 2, No. 87, 1981.
164. U.S. Department of Health and Human Services, National Center for Health Statistics, "Use of Family Planning and Infertility: United States," data From the National Survey of Family Growth Vital and Health Statistics, Series 23, No. 8., 1981.
165. U.S. Department of Health and Human Services, National Center for Health Statistics, "Congenital Anomalies and Birth Injuries Among Live Births, United States, 1973-1974," Vital and Health Statistics, Series 21, No. 31, 1978.
166. U.S. Department of Health and Human Services, National Center for Health Statistics, "Trends in Fertility in the United States," Vital and Health Statistics, Series 21, No. 28, 1977.
167. Van Zyl, J.A., et al., "Oligozoospermia: A Seven Year Survey of the Incidence of Chromosomal Observations, Treatment and Pregnancy Rate," *Int. J. Fertil.* 20:129-132, 1975.
168. Verkauf, B.S., "The Incidence and Outcome of Single-factor, Multifactorial, and Unexplained Infertility," *Am. J. Obst. Gyn.* 147:175-181, 1983.
169. Vermeulen, A., "Decline in Sexual Activity in Aging Men: Correlation With Sex Hormone Levels and Testicular Changes," *J. Biosoc. Sci.* 6:5-18, 1979.
170. Villasanta, U., "Thromboembolic Disease in Pregnancy," *Am. J. Obst. Gyn.* 93:142-160, 1965.
171. Ware, G.W., and Good, E.J., "Effects of Insecticides on Reproduction in the Laboratory Mouse," *Toxicol. Appl. Pharmacol.* 10:54-61, 1967.
172. Warkany, J., "Antituberculous Drugs," *Teratology* 20:133-138, 1979.
173. Warren, M.P., "The Effects of Exercise on Pubertal Progression and Reproductive Function in Girls," *J. Clin. Endocrinol. Metab.* 51:1150-1157, 1980.
174. Washington, A.E., Cates, W., and Zaidi, A., "Hospitalizations for Pelvic Inflammatory Disease," *J. Am. Med. Assoc.* 251(19):2529-2533, 1984.
175. Wehr, E., "House Passes Tough Cigarette Labeling Bill," *Congressional Quarterly Weekly Report* 42(37):2225-2288, Sept. 15, 1984.
176. Weiland, W.E., and Yunger, M., "Sexual Effects and Side Effects of Heroin and Methadone," *Proceedings Third National Conference on Methadone Treatment* (Washington, DC: U.S. Government Printing Office, 1970).
177. Wenger, F., "Necrosis Cerebral Masiva del Feto en Casos de Encefalitis Equina, Venezuelana," *Invest. Clin.* 21:13, 1967.
178. Whitehead, E., et al., "The Effects of Hodgkin's Disease and Combination Chemotherapy on Gonadal Function in the Adult Male," *Cancer* 49:418-422, 1982.
179. Wilcox, A.J., and Horney, L.F., "Accuracy of Spontaneous Abortion Recall," *Am. J. Epidemiol.* 120(5):727-733, 1984.
180. Williams, L.A., Spence, M.A., and Tideman, S., "Implications of the Effect of Air Pollution on Birth Weight," *Social Biology* 24:1-9, 1977.
181. Wilson, J.G., "Environmental Effects on Development—Teratology," *Pathophysiology of Gestation*, N.S. Assali (ed.) vol. 2 (New York: Academic Press, Inc., 1972), pp. 269-320.
182. Winick, M., "Fetal Malnutrition," *Clin. Obstr. Gyn.* 13:526, 1970.
183. Wu, F., "Endocrinology of Male Infertility and Fertility," *Male Infertility*, T.B. Hargreave (ed.) (Heidelberg: Springer-Verlag, 1983), pp. 87-111.

184. Wyrobek, A.J., et al., "An Evaluation of Human Sperm as Indicators of Chemically Induced Alterations of Spermatogenic Function," *Mutation Res.* 115:73-148, 1983.
185. Yamashita, F., "Clinical Features of Polychlorobiphenyls (PCB)-Induced Fetopathy," *Pediatr.* 6:20-27, 1977.
186. Yoshibumi, N., et al., "Multi-Institutional Study on the Teratogenicity and Fetal Toxicity of Antiepileptic Drugs: A Report of a Collaborative Study Group in Japan," *Epilepsia* 21:663-680, 1980.
187. Zelnik, M., and Kantner, J.R., "Sexual Activity, Contraceptive Use, and Pregnancy Among Metropolitan-Area Teenagers:1971-1979," *Fam. Plan. Persp.* 12:230-237, 1980.
188. Zuckerman, Z., et al., "Frequency Distribution of Sperm Counts in Fertile and Infertile Males," *Fert. Steril.* 28:1310, 1977.
189 Zurer, P.S., "Drugs in Sports," *Chem. Engin. News* Apr. 30, 1984, pp. 69-78.