International Trends in Rates of Hypospadias and Cryptorchidism

Leonard J. Paulozzi

National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA 30341-3724 USA

Researchers from seven European nations and the United States have published reports of increasing rates of hypospadias during the 1960s, 1970s, and 1980s. Reports of increasing rates of cryptorchidism have come primarily from England. In recent years, these reports have become one focus of the debate over endocrine disruption. This study examines more recent data from a larger number of countries participating in the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) to address the questions of whether such increases are worldwide and continuing and whether there are geographic patterns to any observed increases. The ICBDMS headquarters and individual systems provided the data. Systems were categorized into five groups based on gross domestic product in 1984. Hypospadias increases were most marked in two American systems and in Scandinavia and Japan. The increases leveled off in many systems after 1985. Increases were not seen in less affluent nations. Cryptorchidism rates were available for 10 systems. Clear increases in this anomaly were seen in two U.S. systems and in the South American system, but not elsewhere. Since 1985, rates declined in most systems. Numerous artifacts may contribute to or cause upward trends in hypospadias. Possible "real" causes include demographic changes and endocrine disruption, among others. *Key words*: abnormality, cryptorchidism, endocrine, genital, hypospadias, testicle. *Environ Health Perspect* 107:297–302 (1999). [Online 11 March 1999]
http://ehpnet1.niehs.nih.gov/docs/1999/107p297-302paulozzi/abstract.html

Within the past 5 years, researchers have hypothesized that some natural or manufactured agents are disrupting normal endocrine function in humans and animals, with particular emphasis on male reproductive effects (*1–8*). This hypothesis attempts to unify and explain worrisome trends in measures of male reproductive health as the effects of estrogenic or antiandrogenic chemicals.

Among the most frequently cited trends, along with trends in sperm count and testicular cancer, are increases in the male genital birth defects of hypospadias and cryptorchidism (*3–5*).

These defects represent mild degrees of femininization. Hypospadias occurs when the urethral opening is displaced toward the scrotum. Cryptorchidism is a condition in which one or both testicles do not descend into the scrotum.

Increasing rates of these two anomalies have been reported within the past 25 years by a number of authors (*9–19*) (see Table 1). The increases that have been cited in support of the endocrine disruption hypothesis occurred for the most part in the 1960s and 1970s. They also derive from a small number of countries in North America and Europe. I have compiled information on worldwide trends in these anomalies to provide more contemporary and complete information for the ongoing debate on endocrine disruption.

Table 1. English-language published reports of upward trends in the prevalence of hypospadias and cryptorchidism

Year	Location	Birth years covered	Reference
Hypospadias			
1975	Norway	1967–1973	Bjerkedal and Bakketeig (*9*)
1979	Sweden	1965–1977	Källén and Winberg (*10*)
1982	Sweden	1965–1979	Källén and Winberg (*11*)
1985	England and Wales	1964–1983	Matlai and Beral (*12*)
1985	Hungary	1971–1983	Czeizel (*13*)
1986	Denmark	1970–1981	Källén et al. (*14*)
1991	United States	1974–1988	ICBDMS (*15*)
1991	Strasbourg	1982–1988	ICBDMS (*15*)
1991	Italy	1981–1988	ICBDMS (*15*)
1997	United States	1970–1993	Paulozzi et al. (*16*)
1997	Atlanta	1968–1995	Paulozzi et al. (*16*)
Cryptorchidism			
1984	England and Wales	1952–1977	Chilvers et al. (*17*)
1985	England and Wales	1969–1983	Matlai and Beral (*12*)
1986	England (Oxford)	1950s vs. 1984–1985	JRHCSG (*18*)
1992	England (Oxford)	1950s vs. 1984–1988	JRHCSG (*19*)

Abbreviations: ICBDMS, International Clearinghouse for Birth Defects Monitoring Systems; JRHCSG, John Radcliffe Hospital Cryptorchidism Study Group.

Methods

The International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS), a nongovernmental organization of the World Health Organization, collects rates of selected birth defects from member programs. To be a part of the ICBDMS, member programs must be actively engaged in the systematic and continuous collection of birth defects cases. The ICBDMS does not accept data from programs that only passively receive and report health statistics data from administrative sources. The Appendix lists the size and base (population or hospital) of each program as of 1990 (*15*). Hospital-based systems calculated their rates based on all births occurring in participating hospitals. Population-based systems used all births in a given geographic area.

In late 1997, the ICBDMS headquarters in Rome provided the latest hypospadias and cryptorchidism birth prevalence rates per 10,000 total births from 29 birth defects registries in 21 countries for all years available. In many cases, I received information for additional years via personal communication with the registrars. Registrars also provided information useful in the interpretation of changes in their rates over time.

The ICBDMS has defined both hypospadias and cryptorchidism, but the extent of adherence to those definitions by participating programs is not known. Almost all countries included defects among stillbirths, but the definition of a stillbirth varied. Prenatal diagnoses that were followed by pregnancy termination were not counted in the rates. Both isolated defects and defects found as part of syndromes are included. The number of cases per year of hypospadias ranged from 12 in the Northern Netherlands system to nearly a thousand in England and Wales.

Address correspondence to L.J. Paulozzi, Division of Birth Defects and Pediatric Genetics, National Center for Environmental Health, Centers for Disease Control and Prevention, Mailstop F-45, 4770 Buford Highway NE, Atlanta, GA 30341-3724 USA.

I thank the ICBDMS scientists making individual contributions to the data and its interpretation: P. Lancaster, S.W. Wen, B. Sibbald, W. Yanqiao, Z. Jun, A. Sipek, K. Helweg-Larsen, B. Botting, A. Ritvanen, E. Robert, J. Goujard, C. Siffel, Z. Johnson, P. Merlog, G. Cocchi, P. Mastroiacovo, R. Tenconi, Y. Sumiyoshi, O. Mutchinick, B. Borman, M. Cornel, A. Daltveit, M. da Graça Dutra, M.L. Martinez-Frias, B. Källén, and C. Torfs.
Received 29 October 1998; accepted 29 December 1998.

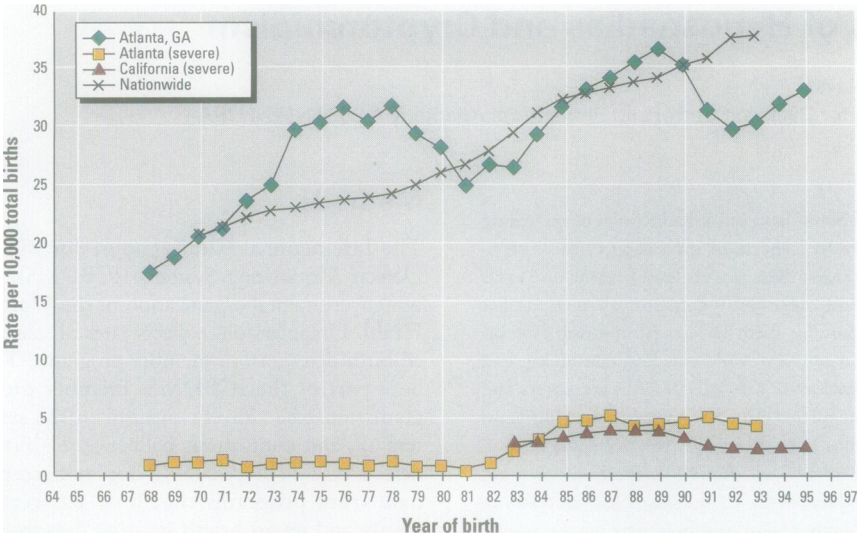

Figure 1. Hypospadias rates by system and year of birth (1968–1995), 3-year moving averages, United States group.

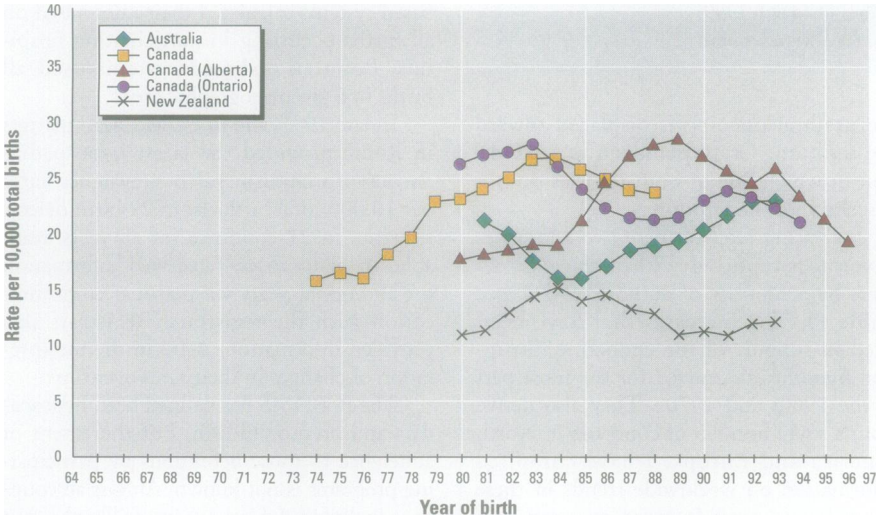

Figure 2. Hypospadias rates by system and year of birth (1974–1996), 3-year moving averages, Commonwealth group.

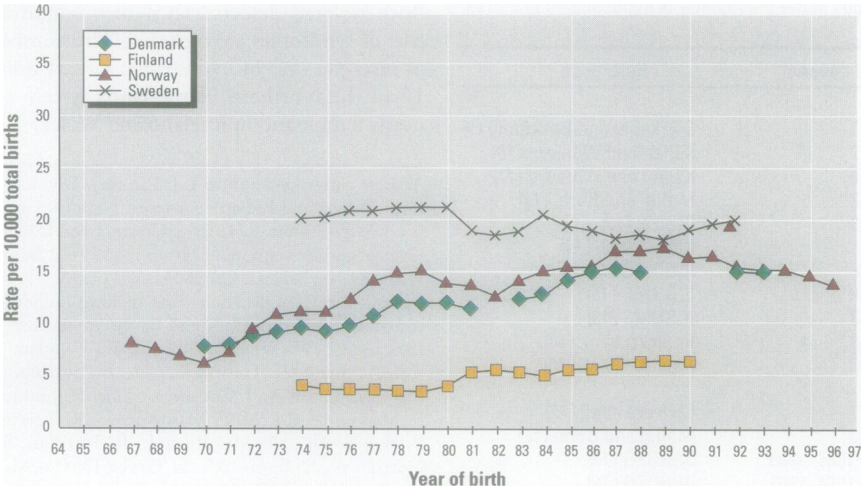

Figure 3. Hypospadias rates by system and year of birth (1967–1996), 3-year moving averages, Scandinavia group.

Three ICBDMS members, the California Birth Defects Monitoring Program, the Italy-Northeast registry, and the English registry (after 1989), collected data only on the more severe types of hypospadias (i.e., penile, scrotal, or perineal), sometimes known as second or third-degree hypospadias, wherein the meatal opening is proximal to the glans of the penis. These types of hypospadias will be referred to as "severe" hypospadias in this paper.

To determine whether trends depended on the degree of industrialization and to facilitate presentation, registries were grouped into categories loosely based on their country's gross domestic product (GDP) in 1984, chosen as the middle year of the bulk of the data. GDP was obtained from a University of Toronto online database (*20*). The U.S. group consisted of three American registries and had the highest GDP ($15,900 U.S.) in 1984. The Commonwealth group consisted of the most affluent nations from English-speaking countries (Australia, Canada, New Zealand), all of which had GDPs in excess of $12,000 U.S. The Scandinavian group included the four Scandinavian countries, whose GDPs were similar to those in the Commonwealth nations. The Northern Europe and Japan group (England, France, Japan, The Netherlands) had GDPs slightly lower than Scandinavia. The Mediterranean and Ireland group (Ireland, Israel, Italy, Spain) had yet lower GDPs, in the range of $5,500–8,000 U.S. The least affluent nations group (GDP less than $5,500 U.S.) included systems from two Eastern European nations, Hungary and Czechoslovakia, and the Chinese and Latin American systems.

I calculated 3-year moving averages to smooth the trends. An "increase" in a trend in this report is based only on visual inspection, and not on statistical testing.

Results

The highest and lowest rates reported by individual systems during the period under study sometimes varied by a factor of three or more for both hypospadias and cryptorchidism. However, few systems showed monotonic, unbroken upward or downward trends; trends typically reversed direction at least once during the period of years under study.

Hypospadias. Nationwide data from the Birth Defects Monitoring Program of the Centers for Disease Control and Prevention (CDC) showed an upward trend in hypospadias beginning in 1970 (Fig. 1). A more discontinuous upward trend began in 1968 in the CDC's Atlanta, Georgia, surveillance system. Severe hypospadias in the Atlanta system increased from 1982 to

1985 and then leveled off. Rates from the California Birth Defects Monitoring Program for severe hypospadias showed no upward trend.

In the Commonwealth group (Fig. 2), each system showed both short upward and short downward excursions and very little net change. Increases in the Australian and Canadian rates and rates in the Canadian province of Alberta were restricted to the late 1980s, whereas rates in the province of Ontario and in New Zealand were down or unchanged through the 1980s and early 1990s.

Scandinavian countries, with the exception of Sweden, show overall upward trends, with rates approximately doubling in Norway and Denmark during the 1970s and 1980s (Fig. 3). Norwegian rates declined somewhat in the 1990s. The Finnish registry reports that their increase was restricted to the mild form of hypospadias (first degree). In the northern Europe and Japan group (Fig. 4), all but the northern Netherlands registry showed some net increase. Rates dropped sharply in the northern Netherlands system during the 1980s.

The Mediterranean and Ireland systems (Fig. 5) include only one system with an increase, the Italian Multicentric Register of Congenital Malformations (IPIMC). The IPIMC suggests that its increase may have been secondary to a special case–control study of hypospadias launched during this interval. The Italy-northeast system, which records only severe hypospadias, showed a decrease. Rates in the Israeli system made wide upward and downward excursions.

Among the least affluent nations (Fig. 6), rates were generally stable since 1980, with the exception of the Czechoslovakian system, which registered an increase.

Cryptorchidism. Few countries in the ICBDMS had data on cryptorchidism. Among U.S. and Commonwealth systems combined (Fig. 7), the U.S. national rates increased during the 1970s and 1980s, whereas the U.S.-Atlanta system began to increase in 1970, rose sharply in 1985, and declined equally sharply by 1994. This peak corresponds to a 10-year period during which a more inclusive case definition was in effect in Atlanta. Rates in the Canadian national system increased until about 1980 and then stabilized. The Canadian provincial systems of Alberta and Ontario reported declines, at least since 1985.

The Norwegian system, the only Scandinavian system collecting cryptorchidism rates, shows no consistent trend between 1974 and 1996 (Fig. 8). The same can be said of the data from the France-Paris system (Fig. 9), whereas English rates dropped sharply around 1990, contemporaneous with the introduction of an "exclusion list." The Hungarian system rates have declined from an early peak, while the South American rates increased overall and since 1985 (Fig. 10).

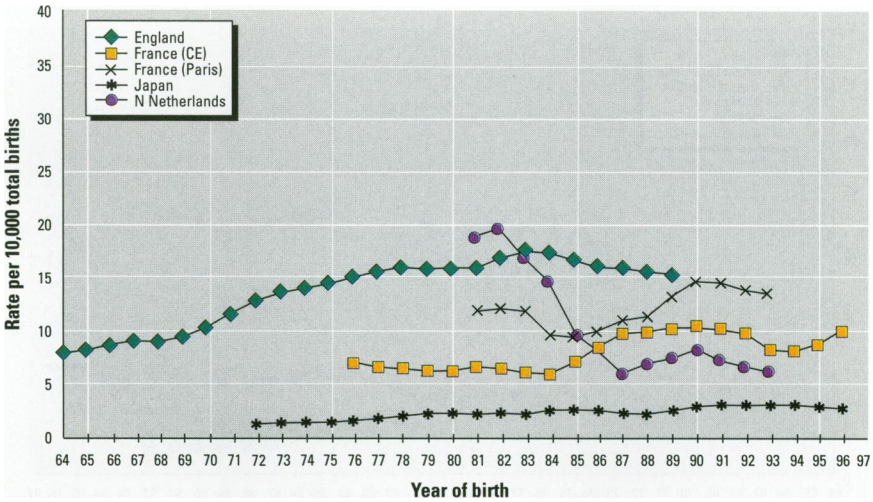

Figure 4. Hypospadias rates by system and year of birth (1964–1996), 3-year moving averages, Northern Europe and Japan group. Abbreviations: CE, central east; N, north.

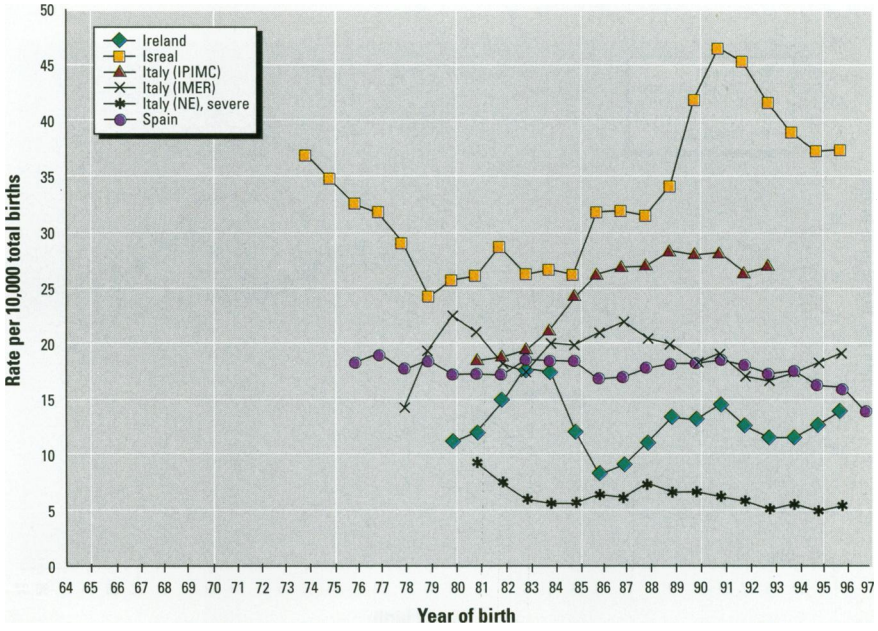

Figure 5. Hypospadias rates by system and year of birth (1974–1997), 3-year moving averages, Mediterranean and Ireland group. Abbreviations: IPIMC, Italian Multicentric Register of Congenital Malformations; IMER, Emilia-Romagna Registry of Congenital Malformations; NE, northeast.

Discussion

Review of data from 29 registries that monitor a total of 4 million births per year around the world reveals wide intercountry variation in rates of hypospadias and cryptorchidism. Given differences in registry methods, genetic variation, and other factors, the rates themselves are not directly comparable. The primary value of this data is what it shows about changes within systems in recent decades.

The data suggests an increase in reported rates of hypospadias during the 1970s and 1980s in two United States systems and in Scandinavia and Japan. Rates from other nations increased only in one Italian system (IPIMC), where an artifact is suspected, and in the Israeli system, which is the smallest system and the system showing the most unstable rates of hypospadias over time. The absence of an increase is perhaps most notable in Canada, whose society is similar to that of the United States. Among all systems showing an increase, rates tended to level off after 1985.

There is no indication of a generalized increase in cryptorchidism rates over time

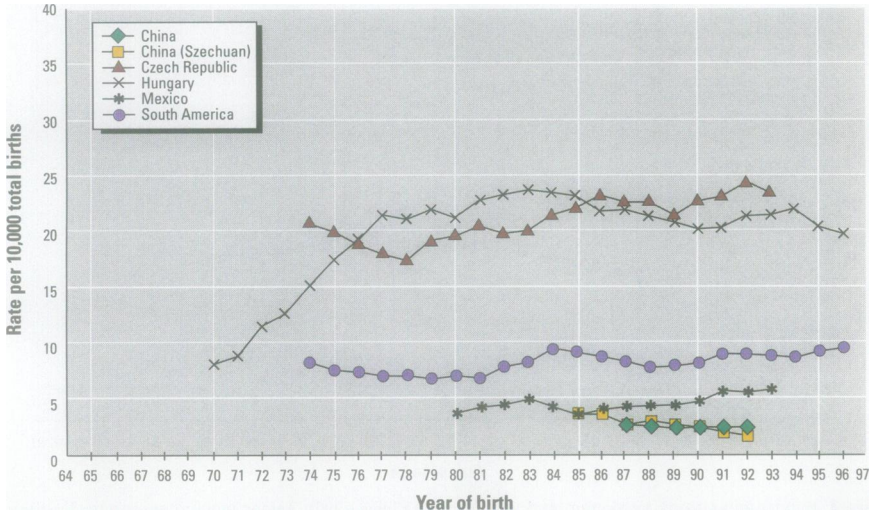

Figure 6. Hypospadias rates by system and year of birth (1970–1996), 3-year moving averages, least affluent nations group.

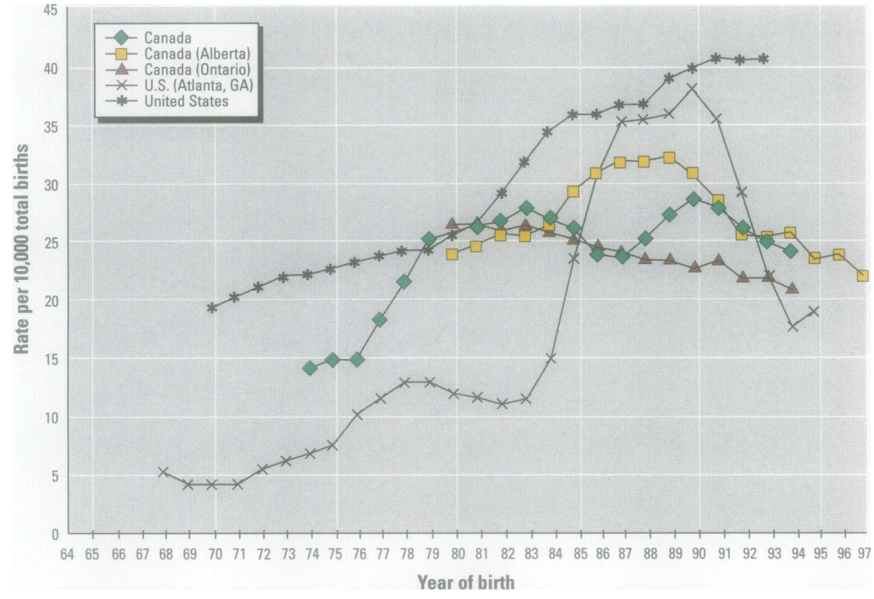

Figure 7. Cryptorchidism rates by system and year of birth (1968–1997), 3-year moving averages, United States and Commonwealth groups.

since 1970, although data on this defect is much more limited. Two U.S. systems show marked increases, but the data from the Atlanta system is difficult to interpret because of coding changes. Since 1985, rates in most systems have actually declined.

A number of factors may account for reported changes in these rates. Chief among them are artifacts. One possible explanation is that the definition of hypospadias may have changed over time to include more minor degrees of deviation from the normal position of the urethral opening on the tip of the penis. There is no anatomical marker that defines when normal variation stops and first-degree hypospadias begins. Slight degrees of deviation are much more common than more proximal meatal positions (*21*), and a subtle change in the case definition could have produced a large change in overall rates.

There is conflicting evidence on whether the case definition of hypospadias has indeed loosened to include more of the milder, first-degree cases. Previously published data from the Atlanta registry indicated that the percent of first-degree cases did not increase over time (*16*). In contrast, the Finnish registry communicated that the percent of more serious degrees of hypospadias declined as overall rates increased. Moreover, the California and the northeast Italy programs have shown no increase in rates of severe hypospadias. Severe hypospadias is much less likely to be affected by changes in definition because it has clearer anatomical boundaries.

Another possible explanation for the increase is gradual improvement over time in physician documentation of hypospadias. Because the foreskin is used in some surgical procedures to repair hypospadias and circumcision must be deferred if hypospadias is present, medicolegal considerations may increasingly cause physicians who perform circumcision to examine the penis carefully. They may therefore be referring more boys to urologists. Increasing numbers of such referrals may increase the number and/or prominence of diagnoses of hypospadias in medical records, thereby improving the chances of detection by a surveillance program.

The same artifacts could explain the increases in cryptorchidism rates noted in some of the systems. In particular, cryptorchidism may be sought more aggressively now because of the strong evidence accumulated over the past 20 years that undescended testicles are likely to become cancerous (*22*) and because of the standard practice of removing them early in life in hopes of reducing this risk. A second hospitalization for orchidopexy in infancy may double the chances of the anomaly being registered in a surveillance system.

For both hypospadias and cryptorchidism, it is also conceivable that rates after 1985 were affected by literature published during the 1980s describing increases in these anomalies. Perhaps criticism of the reports led to a tightening of case definitions in some systems. It is noteworthy that of the five registries publishing hypospadias increases by 1986 (Table 1), only Denmark reported any further increase in subsequent birth years.

Other, nonartifactual explanations have been proposed to explain the increasing hypospadias rates in Europe reported earlier. Initially, it was hypothesized that increasing use of steroid-containing medications by pregnant women might be responsible (*23*). However, the consensus now seems to be that the risk from such preparations is exaggerated, and the prevalence of their use is not great enough to account for the increase (*12,24,25*).

Alternatively, evidence of increased risk of hypospadias among couples of reduced fertility has produced speculation that an increasing proportion of such couples among all parents could account for an increasing trend in this anomaly (*25,26*). However, the magnitude of the risk for relatively infertile couples (*26*), combined with their low prevalence among the population of all parents, does not seem sufficient to account for the large observed increases in some registries.

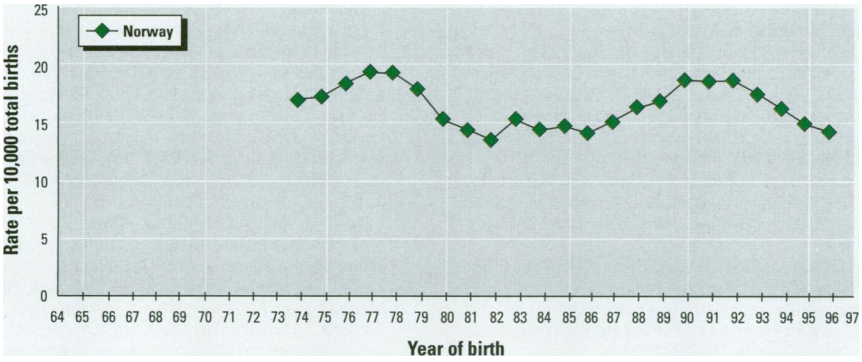

Figure 8. Cryptorchidism rates by year of birth (1974–1996), 3-year moving averages, Scandinavia group.

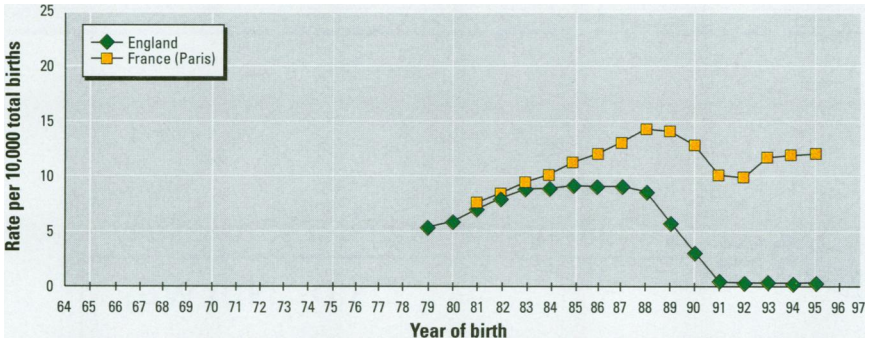

Figure 9. Cryptorchidism rates by system and year of birth (1979–1995), 3-year moving averages, northern Europe and Japan group.

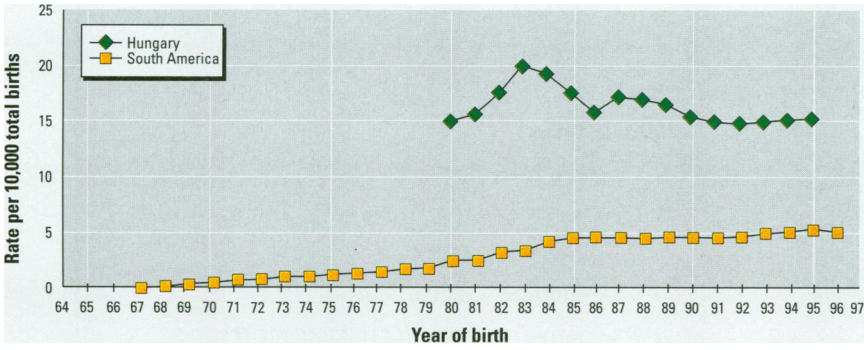

Figure 10. Cryptorchidism rates by system and year of birth (1967–1996), 3-year moving averages, least affluent nations group.

Conclusion

There is some evidence for an increase in hypospadias rates concentrated in more affluent nations. That increase may have ended in the mid-1980s. More registries that experienced increasing trends in hypospadias should report how their percentage of severe cases has changed over time. If an increase in all degrees of hypospadias is reported in more surveillance systems, more in-depth investigation will be warranted.

Assuming these upward trends are real and assuming exogenous agents are responsible, the relevant exposures may be more common in highly industrialized countries. Those exposures (or their body burdens) that may have stabilized since 1985 might also be the most logical ones to pursue among all potential environmental exposures.

Although it is important to examine these trends broadly, it is unlikely that further inspection of international trends alone will shed additional light on the question of endocrine disruption as a cause of birth defects. Such descriptive analysis is provocative, but more sophisticated study designs should be sought.

References and Notes

1. Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Declining semen quality and increasing incidence of testicular cancer: is there a common cause? Environ Health Perspect 103(suppl 7):137–139 (1995).
2. Sharpe R, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet 341:1392–1395 (1993).

Appendix

Characteristics of International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) included in this study as of 1990

ICBDMS program	Annual births (thousands)	Base
Australia	250	P
Canada	215	P
Canada (Alberta)	38	P
Canada (Ontario)	146	P
China	496	P
China (Szechuan)	65	H
Czech Republic	130	P
Denmark	60	P
England and Wales	700	P
Finland	64	P
France (central, east)	90	P
France (Paris)	40	P
Hungary	125	P
Ireland	19	P
Israel	18	H
Italy (IMER)	23	P
Italy (IPIMC)	140	H
Italy (northeast)	57	P
Japan	115	H
Mexico	50	H
Netherlands (north)	19	P
New Zealand	55	P
Norway	55	P
South America	215	H
Spain	60	H
Sweden	120	P
United States	575	H
United States (Atlanta, GA)	40	P
United States (California)	269	P
Total	4,249	

Abbreviations: H, hospital-based; P, population-based; IMER, Emilia-Romagna Registry of Congenital Malformations; IPIMC, Italian Multicentric Register of Congenital Malformations.

3. Giwercman A, Carlsen E, Keiding N, Skakkebaek NE. Evidence for increasing incidence of abnormalities of the human testis: a review. Environ Health Perspect 101(suppl 2):65–71 (1993).
4. Giwercman A. Declining semen quality and increasing incidence of abnormalities in male reproductive organs—fact or fiction? Hum Reprod 10(suppl 1):158–164 (1995).
5. Jensen TK, Toppari J, Keiding N, Skakkebaek NE. Do environmental estrogens contribute to the decline in male reproductive health? Clin Chem 41:1896–1901 (1995).
6. Guillette LJ Jr. Endocrine disrupting environmental contaminants and developmental abnormalities in embryos. Hum Ecol Risk Assess 1:25–36 (1995).
7. Guillette LJ Jr. Endocrine-disrupting environmental contaminants and reproduction: lessons from the study of wildlife. In: Women's Health Today: Perspectives on Current Research and Clinical Practice (Popkin DR, Peddle LJ, eds). New York: Parthenon Publishing Group, 1994;201–207.
8. Facemire CF, Gross TS, Guillette LJ Jr. Reproductive impairment in the Florida panther: nature or nurture? Environ Health Perspect 103(suppl 4):79–86 (1995).
9. Bjerkedal T, Bakketeig LS. Surveillance of congenital malformations and other conditions of the newborn. Int J Epidemiol 4:31–36 (1975).
10. Källén B, Winberg J. Dealing with suspicions of malformation frequency increase. Acta Paediatr Scand Suppl 275:66–74 (1979).
11. Källén B, Winberg J. An epidemiological study of hypospadias in Sweden. Acta Paediatr Scand Suppl 293:3–21 (1982).

12. Matlai P, Beral V. Trends in congenital malformations of external genitalia. Lancet 1:108 (1985).
13. Czeizel A. Increasing trends in congenital malformations of male external genitalia. Lancet 1:462–463 (1985).
14. Källén B, Bertollini E, Castilla A, Czeizel A, Knudsen ML, Martinez-Frias LM, Mastroiacovo P, Mutchinick O. A joint international study on the epidemiology of hypospadias. Acta Paediatr Scand Suppl 324:1–52 (1986).
15. Congenital malformations worldwide: a report from the International Clearinghouse for Birth Defects Monitoring Systems. New York:Elsevier Science Publishers, 1991.
16. Paulozzi LJ, Erickson JD, Jackson RJ. Hypospadias trends in two US surveillance systems. Pediatrics 100:831–834 (1997).
17. Chilvers C, Pike MC, Forman D, Fogelman K, Wadsworth MEJ. Apparent doubling of frequency of undescended testis in England and Wales in 1962–81. Lancet 1:330–333 (1984).
18. Cryptorchidism: an apparent substantial increase since 1960. John Radcliffe Hospital Cryptorchidism Study Group. Br Med J 293:1401–1404 (1986).
19. Chilvers CED. Cryptorchidism: a prospective study of 7,500 consecutive male births, 1984–8. Arch Dis Child 67:892–899 (1992).
20. CHASS Data Centre at the University of Toronto. Penn World Tables, Real GDP per capita. Available: http://datacentre.chass.utoronto.ca [cited 10 March 1998].
21. Fichtner J, Filipas D, Mottrie AM, Voges GE, Hohenfellner R. Analysis of meatal location in 500 men: wide variation questions need for meatal advancement in all pediatric anterior hypospadias cases. J Urol 154:833–834 (1995).
22. Schottenfeld D. Testicular cancer. In: Cancer Epidemiology and Prevention (Schottenfeld D, Fraumeni JF, eds). New York:Oxford University Press, 1996;1207–1219.
23. Aarskog D. Maternal progestins as a possible cause of hypospadias. N Engl J Med 300:75–78 (1979).
24. Källén B, Martinez-Frias ML, Castilla EE, Robert E, Lancaster PAL, Kringelbach M, Mutchinick OM, Mastroiacovo P. Hormone therapy during pregnancy and isolated hypospadias: an international case–control study. Int J Risk Safety Med 3:183–198 (1992).
25. Czeizel A, Toth J. Correlation between the birth prevalence of isolated hypospadias and parental subfertility. Teratology 41:167–172 (1990).
26. Källén B, Castilla EE, Kringelback M, Lancaster PAL, Martinez-Frias ML, Mastroiacovo P, Mutchinick O, Robert E. Parental fertility and infant hypospadias: an international case–control study. Teratology 44:629–634 (1991).