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An immunoreactive theory of selective male affliction

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Abstract: Males are selectively afflicted with the neurodevelopmental and psychiatric disorders of childhood, a broad and virtually ubiquitous phenomenon that has not received proper attention in the biological study of sex differences. The previous literature has alluded to psychosocial differences, genetic factors and elements pertaining to male "complexity" and relative immaturity, but these are not deemed an adequate explanation for selective male affliction. The structure of sex differences in neurodevelopmental disorders is hypothesized to contain these elements: (1) Males are more frequently afflicted, females more severely; (2) disorders arising in females are largely mediated by the genotype; in males, by a genotype by environment interaction; (3) complications of pregnancy and delivery occur more frequently with male births; such complications are decisive and influence subsequent development. We hypothesize that there is something about the male fetus that evokes an inhospitable uterine environment. This "evocative principle" is hypothesized to relate to the relative antigenicity of the male fetus, which may induce a state of maternal immunoreactivity, leading either directly or indirectly to fetal damage. The immunoreactive theory (IMRT) thus constructed is borrowed from studies of sex ratios and is the only explanation consistent with negative parity effects in the occurrence of pregnancy complications and certain neurodevelopmental disorders. Although the theory is necessarily speculative, it is heuristic and hypotheses derived from it are proposed; some are confirmed in the existing literature and by the authors' research.

Keywords: birth order; developmental disorder; embryology; immunology; parity effects; sex differences

Males are selectively afflicted with virtually every neurologic, psychiatric, and developmental disorder of childhood (see Table 1). There are conditions, of course, like anencephaly and dysraphism, which are commoner in females (Glucksmann 1978; Nakano 1973); but for the most important neurodevelopmental disorders – mental retardation, autism, hyperactivity, dyslexia, epilepsy, dysphasia, cerebral palsy, and conduct disorders – the sex differential works unequivocally to male disadvantage (Butler & Bonham 1963; Nichols & Chen 1981; Rutter 1970). This phenomenon is largely unexplained. Though the biology and psychology of sex differences has been an attractive area of recent scientific concern, the issue of selective male affliction seems to have generated neither broad interest nor systematic research.

In its ubiquity and breadth, the phenomenon compels an explanation that is couched, somehow, in the biology of sex differences. Although it is not unlikely that sex differences in parental handling or societal attitudes may have a role in the development or identification of at least some of the behavioral and emotional disorders of childhood (Rutter 1970), the role sex differences in adult perceptions of children, referral and labeling processes, and tolerance of deviant behaviors may actually play in the development of psychiatric disorders in children with normal brain development has yet to be determined. Boys are believed to be more vulnerable than girls to certain kinds of family disharmony (Rutter 1970) and other psychosocial stressors (Cadoret & Cain 1980), but the reason for this is not understood. However, psychosocial theories are hardly germane to the problem of selective male affliction with severe neurodevelopmental disorders like epilepsy, autism, and mental retardation.

It has been suggested that the genetic endowment of the male comprises sufficient cause for male "inferiority" (Childs 1965; Ounsted & Taylor 1972; Rutter 1970). The Y chromosome is considerably smaller than the X and also relatively inert, thus giving the female a "4–5% quantitative superiority in genetic material" (Childs 1965). This disparity means that the homogametic sex (female) is diploid with respect to many loci, whereas the heterogametic sex (male) must always be haploid. Because there are loci on the X chromosome that control functions apart from reproductive sex, males are necessarily the victims of whatever uncompensated dosage effects may exist (Childs 1965). X linkage has been proposed to account for greater male variability for virtually all biological traits, including mental functioning (Lehrke 1978). Untoward X-linked recessive genes will be expressed in males but not in heterozygous females, and the occurrence of X-linked disorders of development is not infrequent. However, they are not sufficiently frequent to account for the breadth and ubiquity of the phenomenon of selective affliction. Most of the conditions in Table 1 are not X linked, and the large majority do not show a pattern of inheritance that characterizes specific chromosomal abnormalities.

The effect of the Y-chromosome message has been

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Table 1. *Male–female differences in developmental neuropsychiatry and obstetrics*

Disorder	Sex ratio	Reference
A. *Pediatric psychiatry*		
Hyperkinetic syndrome	300	(Butler & Bonham 1963; Trites et al. 1979)
Conduct disorders	270	(Rutter 1970; Trites et al. 1979)
	200–900	(Zerssen & Weyerer 1982)
Childhood schizophrenia	170	(Kramer 1978)
Early onset schizophrenia	160	(Samuels 1979; Flor-Henry 1974)
Process schizophrenia	150	(Flor-Henry 1974; Allon 1971)
Suicide		(Schaffer & Fisher 1981)
Referrals to child psychiatry clinics	200	(Taylor & Ounsted 1972)
Admission to child psychiatric service	213	(Gualtieri 1983)
B. *Pediatric neurology*		
Seizure disorders		
All ages	120	(Taylor & Ounsted 1972)
Neonatal convulsions	116	(Taylor & Ounsted 1972)
Childhood seizures	140	(Taylor & Ounsted 1972)
Infantile spasms	210	(Taylor & Ounsted 1972)
Temporal lobe epilepsy	132	(Taylor & Ounsted 1972)
Febrile seizures	140	(Taylor & Ounsted 1972)
In mentally retarded children	170	(Corbett, Hannis & Robinson 1975)
Cerebral palsy	150–260	(Wing 1981; Taylor & Ounsted 1972)
Subacute schlerosing panencephalitis	220	(Taylor & Ounsted 1972)
Encephalitis (echo type 9)	220	(Sabin, Krombiegel & Wigand 1958)
Abnormal neurological exam at one year of age	114	(Singer et al. 1968)
C. *Developmental disorders*		
Severe mental retardation	130	(Abramowicz et al. 1975)
Down's syndrome	128–260	(Tsai & Beisler 1983; Burgio et al. 1981)
Speech and language disorders	260	(Ingram 1959)
Stuttering	400	(Reinisch et al. 1979)
Learning difficulties	219	(Nichols & Chen 1981)
Dyslexia	430	(McKinney & Feagans 1983)
Autism	400	(Ingram 1964)
D. *Obstetrics perinatal*		
Spontaneous abortion	120–140	(McMillen 1979)
Toxemia	109–171	(Toivanen & Hirvonen 1970)
Placenta praevia	120	(Ounsted 1972)
Abruptio placentae	206	(Ounsted 1972)
Anteparium hemmorhage	140–210	(Rhodes 1965)
Intra-partum anoxia	130	(Butler & Bonham 1963)
Pulmonary infection	250	(Butler & Bonham 1963)
Hyaline membrane disease	180	(Butler & Bonham 1963)
Pulmonary hemorrhage	210	(Butler & Bonham 1963)
Cerebral birth trauma	180	(Butler & Bonham 1963)
Apgar 6	130	(Singer et al. 1968)

The sex ratio is expressed, by convention, as the number of males divided by the number of females, multiplied by one hundred, or $(N_m/N_f)100$.

described by Ounsted and Taylor (1972, p. 257) as catalytic; that is, it serves to "modify any genome." Females express neither the fullest advantages nor the worst disadvantages of their genome. Their characteristics are said to be "less scattered," whereas males suffer the "extremes of viable disadvantage and the greatest advantage" (Ounsted & Taylor 1972, p. 258). Thus, male inferiority is said to be the consequence of greater genetic variability for "the majority of measurable characteristics" (Wing 1981).

According to Ounsted and Taylor, the increased variability expressed in males is at least in part a consequence of the function of the Y chromosome in regulating the pace of development. "Transcription of expressed genomic information in males occurs at a slower ontogenetic pace; the operation of the Y chromosome is to allow more genomic information to be transcribed" (Ounsted & Taylor 1972, p. 245). Whether or not the pace of development is regulated by the Y chromosome – there is, to the author's knowledge, no direct evidence that it is – it is an incontestable fact that development and maturation occurs more slowly in males (Taylor, 1969). At every developmental stage, the male is less mature than the female (D. C. Taylor 1969). A newborn girl is the physiological

equivalent of a 4-to-6-week old boy, and physiological maturity is achieved two years later in boys than in girls (Hutt 1972). In general, immature organisms are more susceptible to damage than mature ones (Rutter 1970), and the developing male is more susceptible to the information he extracts from his genome and the environment (Taylor & Ounsted 1972). Thus, relative immaturity means that males are more vulnerable to environmental factors for a longer period of time; these may be intrauterine, peri- or postnatal, psychosocial, or biologic. The classical and often cited example of the untoward clinical sequelae of prolonged immaturity was reported by Taylor and Ounsted (1971). The interval of susceptibility to convulsive seizures originating in the temporal lobe as a consequence of cerebral injury is considerably longer in the male infant.

The complement to prolonged maturation is increased complexity; the male human is said to be a more complex organism than the female and his brain is a more complex organ. The male brain is more completely lateralized (McGlone 1980), it is heavier (Dekaban & Sadowsky 1978), its oxygen requirements are higher (Hutt 1972), and it is an androgenized female brain (Reinisch, Gandelman & Spiegel 1979). If male brain development is more complicated and prolonged, "there are likely to be more opportunities for errors to occur" (Reinisch et al. 1979, p. 221). However, it is not explicit precisely how these errors come about, or precisely what they are, at least on a physiologic basis. By the same token, the immaturity hypothesis fails to describe any specifics about the information the developing child extracts from his genome or his environment, or how this process unfolds.

Male vulnerability is, of course, hardly limited to congenital disorders, and no review of the topic can afford to overlook the general pattern of male vulnerability at every age to accident and disease. (The notable exceptions are the autoimmune diseases and, of course, diseases of the female reproductive organs [Rutter 1970; Vessey 1972].) The higher mortality of males is reflected in the sex ratio ((male/females) × 100). Although the primary sex ratio (i.e. at conception) is probably around 120 (estimated range 110 – 170), male fetuses are more prone to spontaneous abortion and stillbirth, and by the end of gestation the (secondary) sex ratio falls to about 105 (McMillen 1979). By the end of childhood, the sex ratio drops to unity, a consequence of increased male mortality from accidents and childhood diseases (Reinisch et al. 1979). The relative vulnerability of males is a lifelong phenomenon, and overall the population of the United States is 51% female (Reinisch et al. 1979).

It is not likely, however, that this general, lifelong pattern of male vulnerability can be molded to accommodate a single, parsimonious, and unifying theory, or at least one that would make sense or generate testable hypotheses. The range of problems to which males succumb is simply too broad; each is probably the consequence of a host of different intervening variables. The specific area of concern here, the neurodevelopmental disorders of childhood, also encompasses a broad and diverse range of problems, but the topic is more tractable, and one that may well be open to intelligent theory.

It is fair to say that most of the foregoing ideas about selective male affliction may succeed as explanations or as seminal ideas, but they fail as theories; their capacity to generate testable hypotheses seems to have been extremely limited. Like Butler, we conclude that "the explanation for most of these striking [sex] differences is not understood" (Butler & Bonham 1963, p. 268). Many of the ideas have merit and are incorporated into the theory that is developed herein. However, by themselves, they leave an "unexplained residue . . . of staggering proportions" (Medawar 1963, p. 321).

The structure of sex differences

> In general, the morbific processes, mild and grave, attack the females with greater intensity than the males (Ciocco 1940, p. 204)

While females are less prone to affliction with neurodevelopmental problems, when such conditions do arise in the female, a severer form is usually manifest (Taylor & Ounsted 1972). This principle appears to hold for most of the pathologic conditions in which it has been tested. For example, although males are more frequently found to be mentally retarded, at the lowest levels of IQ the proportion of females is relatively higher (Taylor & Ounsted 1972). Autistic children are more commonly males, but at the lowest IQ levels the number of autistic females is proportionately higher (Lord, Schopler, & Revicki 1982; Lotter 1974; Tsai & Beisler 1983; Tsai, Stewart, & August 1981; Wing 1981). The mortality rate of institutionalized retardates (Forssman & Akesson 1970) and of Down's children (Fabia & Drolette 1970) is higher in females and the mortality rate of females with cerebral palsy is also higher (Ingram 1964; Schlesinger, Alaway & Peltin 1959). Females are less prone to epilepsy, but they are more prone to the morbid sequelae of febrile seizures (Taylor & Ounsted 1972) and to the development of epileptic psychosis (Flor-Henry 1969; Slater, Beard & Glithero 1963; D. C. Taylor 1969; Taylor & Ounsted 1972). In order to understand why this is important, it is essential to consider the structure of male–female differences as they relate to the disorders in question, and especially as they relate to the occurrence of perinatal problems.

In the neurodevelopmental disorders, sex differences cause a dissociation between the elements of frequency, or incidence, and intensity, or severity. As a general rule, males are more frequently afflicted and females more severely impaired when they are afflicted. An additional sex-based dissociation is that the occurrence of neurodevelopmental disorders in females seems to be mediated primarily through genetic channels, and that their disorders may be, as a consequence, more specific, whereas in males, the disorders are mediated largely through the occurrence of perinatal problems, and are less specific and more diverse in their manifestation. There is strong evidence suggesting this.

The occurrence of pure type dyslexia is more frequent in girls (Pennington & Smith 1983) and it is possible to fit a genetic model to learning disabilities in girls but not boys (Lewitter, DeFries & Elston 1980). The clinical picture of autistic children with positive family histories of developmental dysfunction is more homogeneous than that of those with negative family histories (August, Stewart & Tsai 1981). The range of IQ in autistic males is wider

(Wing 1981). Autistic girls are more likely than boys to have family histories of cognitive and language dysfunction (Tsai & Beisler 1983) and members of the families of dyslexic girls (Decker & DeFries 1980) and of girls with conduct disorders (Robins 1966) are more frequently afflicted. The clinical presentation of a disorder that is largely mediated by the genotype is likely to be more specific, whereas the behavioral and developmental sequelae of early brain damage are known to be relatively nonspecific (Graham & Rutter 1968).

The same pattern is suggested by studies of the genetics of schizophrenia. For example, the concordance for schizophrenia in monozygous (MZ) twins is higher for females than males (Rosenthal 1962). Schizophrenic mothers of children who become schizophrenic tend themselves to have had an earlier onset of the disorder than mothers of children who do not become schizophrenic (Mednick 1970), and the births of their children are characterized by relative difficulty (Mednick 1970; Mednick, Mura, Schulsinger & Mednick 1971). However, severity of the maternal illness is associated with the level of schizophrenia only in high-risk daughters and not in sons (Gardner 1967; Sobel 1961); perinatal complications, on the other hand, are more likely in high risk sons than in daughters (Mednick, Schulsinger, Teasdale, Schulsinger, Venables & Rock 1978). There is a significant relation between perinatal complications and the later development of schizophrenia in high-risk boys but not in girls (Mednick, Schulsinger, Teasdale, Schulsinger, Venables & Rock, 1977). The daughters of schizophrenic mothers are likely to be schizophrenic if they have any disorder at all, whereas the sons exhibit a more diverse range of psychopathology, especially sociopathy and criminal behavior (Mednick et al. 1978). What this suggests is that "schizophrenia in females is more genetically determined and that schizophrenia in males has a heavier environmental weight" (Mednick et al. 1977, p. 181). When the high risk daughters of schizophrenic mothers develop schizophrenia, it is largely (though not entirely) determined by their genotype; the sons develop schizophrenia or other severe psychiatric disorders, and this is mediated by a genotype by environment interaction. The environmental effect is keenly felt by male fetuses during pregnancy and parturition.

Schizophrenia is not properly counted among the neurodevelopmental disorders, although a cogent case could probably be made that it ought to be, especially the form of schizophrenia with early onset, which occurs more commonly in males, responds poorly to treatment, is often associated with demonstrable neuropathic changes, and follows a dementing course (Weinberger, Cannon-Spoor, Potkin & Wyatt 1980).

We have recently described a similar structure in the sex differences that occur in developmentally handicapped children (Hicks & Gualtieri 1984). In a retrospective review of 223 developmentally handicapped children referred for evaluation at the University of North Carolina within a given year, the majority of patients were, as expected, male (78%). In terms of IQ and SQ (social quotient), however, females were more severely impaired (Table 2A). For both males and females, there was found to be a positive linear relationship between the occurrence of newborn problems (e.g., hypoxia, jaundice) and IQ (F_{linear} [1,166] = 5.255, P = .025) and SQ (F_{linear} [1,185] = 4.715, P = .025), and between the occurrence of neurological problems in the first year of life (e.g., seizures, dystonia) and IQ (F_{linear} [1,168] = 11.907, P = .001) and SQ (F_{linear} [1,188] = 10.713, P = .001). Newborn problems and first-year neurological problems were associated (Pearson χ^2 = 24.295, P = .0001). There was a positive relationship between newborn problems and low birthweight (F_{linear} [1,204] = 8.087, P = .005) as well as with delivery complications (Pearson χ^2 = 21.7, P = .0002). Both newborn problems (F_{linear} [1,172] = 8.521, P < .01) and neurological problems were associated with pregnancy complications (F_{linear} [1,174] = 15.147, P < .001). However, pregnancy complications were significantly more common with male fetuses (Table 2B). On the other hand, a family history of neurodevelopmental disorders was more frequent in females (Table 2C). The severity of affliction was worse for females, and their genetic background was loaded. Male fetuses were more frequently afflicted, they experienced a higher rate of pregnancy complications, and their genetic background was less decisive (Hicks & Gualtieri 1984).

Table 2. *The structure of sex differences*

A. Females are more severely impaired than males

		Males	*Females*
IQ	Mean	55.3	41.2
	S.D.	+23.7	+21.5
	N	139	35

$F(1,172) = 10.18$, $P = .002$

		Males	*Females*
SQ	Mean	63.0	52.9
	S.D.	+24.2	±18.9
	N	154	40

$F(1,192) = 6.0$, $P = .015$

B. Proportion of each sex classified by number of problems in pregnancy

	Pregnancy problems			
	None	*One*	*More than one*	*N*
Boys	.058	.234	.708	171
Girls	.283	.130	.587	46
				217

Pearson $\chi^2 = 19.785$, $P = .0001$

C. Proportion of each sex classified by family history of neurodevelopmental disorders

	Relatives affected	*Relatives not affected*	
Male proband	21	146	167
Female proband	11	31	42
	32	177	209

Pearson $\chi^2 = 4.798$, $P = .05$

The structure of sex differences occurring in the neurodevelopmental disorders of childhood consists of four elements: Males are more commonly afflicted. When females are afflicted, the manifestation of the condition is more severe. In females, such disorders are largely influenced by the genotype and as a consequence, the manifestation is more specific. In males, the occurrence of neurodevelopmental disorders is mediated by a genotype by environment interaction; pre- and perinatal problems

play a more important role and their manifestation is more diverse.

Such a pattern is consistent with a model that posits a spectrum or a continuum of liability. Liability to a neurodevelopmental disorder is a function of a number of genes acting in concert, and these polygenes are presumed to be normally distributed within the population (Carter 1965). The essential part of this model is a differential threshold for expression of the phenotype for males and females. For females, a substantial genetic load is required for expression; for males a lower quantity of untoward genes is required. This threshold of liability model was originally proposed by Carter to account for sex differences in the occurrence of certain congenital malformations (Carter 1965) and the model has also been advanced with respect to dyslexia (Lewitter, DeFries & Elston 1980) conduct disorder and sociopathy (Cloninger, Christiansen, Reich & Gottesman 1978), stuttering (Garside & Kay 1964), left handedness (Hicks & Kinsbourne 1981), autism (Tsai & Beisler 1983), pyloric stenosis (Carter 1965), and cleft lip and palate (Woolf 1971).

The threshold for expression of neurodevelopmental problems in males may be lower by virtue of their proclivity to encounter serious and damaging pre- and perinatal difficulties. It is not necessary to postulate an increased level of vulnerability to such difficulties for males, although this may be the case, simply because the very occurrence of pregnancy complications in male fetuses is substantially more frequent (Butler & Bonham 1963; Nichols & Chen 1981; Singer, Westphal & Niswander 1968). The male fetus is much more likely to encounter intrauterine difficulties like toxemia (Toivanen & Hirvonen 1970b), abruptio placentae (Rhodes 1965), placenta praevia (Ounsted 1972), prematurity (Niswander & Gordon 1972), and miscarriage (McMillen 1979). It is well known that severe pre- and perinatal problems may cause or aggravate developmental problems, and that less severe gestational events like occasional bleeding are significantly associated with subsequent neurological, behavioral, and developmental problems (Nichols & Chen 1981). The increased frequency with which males encounter an inhospitable uterine environment or a difficult passage compromises brain development and lowers their threshold of liability to neurodevelopmental problems.

The natural question here is why male fetuses are more prone to pre- and perinatal difficulties. Males are heavier in utero and at birth (Butler & Bonham 1963), and larger fetuses are more prone to certain kinds of obstetrical and perinatal problems, but when birth weight is controlled, such problems are still more common in males (Singer et al. 1968). There seems to be something about the male fetus that evokes an untoward uterine environment.

Maternal insufficiency and negative parity effects

Selective male affliction is hypothesized to arise as a consequence of a lower threshold for expression of a deviant phenotype, and the threshold is lowered through the mediation of complications during pregnancy and delivery. These occur more frequently with male fetuses, and "the female conceptus is better adapted to survive in the maternal uterine environment than the male" (Loke 1978, p. 164). An evocative principle is called for: What is it about the male fetus that causes such trouble? Fetal size is not a suitable answer, but what may be?

There are two plausible alternatives: an endocrine effect or an antigenic effect. The former is a compelling idea, because a male fetus causes intermittent elevation of maternal levels of testicular androgens (Mizuno, Lobotsky, Lloyd, Kobayashi & Murasawa 1968), and the balance among androgenic, progestational, and estrogenic hormones is known to affect fetal brain development (Maccoby, Doering, Jacklin & Kraemer 1979) and the gestational health of the mother (Siiteri, Febres, Clemens, Chang, Gondos & Stites 1977). The endocrine aspects of pregnancy and fetal brain development, however, are extraordinarily complex, even ambiguous, and the state of the science is not amenable, in our opinion, to a ready explanation of the phenomenon of selective affliction. In addition, immediately below, we describe data that are incompatible, in our opinion, with an endocrinologic viewpoint.

The idea of male antigenicity is also interesting and is considered at greater length below. It is necessary, first, to turn to two additional areas of study that have important bearing on the occurrence of perinatal complications; these are the issues of maternal insufficiency, and the existence of parity effects in disorders of development. Together, they suggest that successive pregnancies are not independent events, but that there exists a kind of "memory" in the phenomenon of reproduction. The fate of one pregnancy influences, even predicts, the outcome of the next.

The terms "maternal insufficiency" (Costeff, Cohen, Weller & Kleckner 1981), "uterine inadequacy" (Ahern & Johnson 1973), and "reduced optimality" (Gillberg & Gillberg 1983) refer to the tendency of some mothers to experience an unusual degree of pre- and perinatal complications, including bleeding, toxemia, prematurity, difficult delivery, miscarriage, and perinatal death. As described above, the adequacy of a child's intrauterine environment exercises a substantial long-term influence on his neurological and cognitive development (Joffe 1969). Maternal insufficiency is an important risk factor in developmental disorders like autism (Aarkrog 1968; Gillberg & Gillberg 1983; Tsai & Beisler 1983; Tsai et al. 1981), mental retardation, mild and severe (Costeff, Cohen & Weller 1983; Drillien 1968; Hagberg, Hagberg, Lewerth & Linberg 1981; Lilienfield & Pasamanick 1956), minimal brain dysfunction (MBD) (Nichols & Chen 1981; Gillberg & Rasmussen 1982), and childhood psychoses (Funderburk, Carter, Tanguay, Freeman & Westlake 1983), among others. There may be a dosage effect because signs of uterine inadequacy occur more frequently and in greater number in severer disorders like autism than in MBD. It is also interesting that the signs of uterine inadequacy associated with certain disorders such as autism are not necessarily those that directly induce cerebral hypoxia (Gillberg & Gillberg 1983).

Central to the concept of maternal insufficiency is the idea of tendency. Although any woman can have an isolated bad pregnancy, there are some who are unusually prone to bad pregnancies. This tendency is at least in part genetically determined; for example, the tendency to give birth prematurely is familial (Keller

1981), there is a maternal genetic effect on the birth weight of cousins (Robson 1955), and the aunts and sisters of mentally retarded children have more mental retardation, miscarriage, stillbirth and neonatal death in their families than the uncles and brothers of mentally retarded children have in theirs (Ahern & Johnson 1973). Daughters from toxemic pregnancies are affected themselves with toxemia more often than those from control groups (Chesley, Annito & Cosgrove 1968).

Because of familial uterine inadequacy, a troubled pregnancy does not occur as an independent event. The nature of one pregnancy is capable of predicting the nature of another. The low birth weight of the first child is the most powerful predictor of low birth weight in the second (Bakketeig 1977), the percentage of premature infants increases with the previous number of premature births (Placek 1977), previous fetal, peri- or neonatal deaths predict similar deaths in subsequent pregnancies (Niswander & Gordon 1972). And there is, again, an element of nonspecificity, since previous fetal loss predicts prematurity, and previous prematurity predicts fetal loss (Niswander & Gordon 1972; Placek 1977). The first factor that operates here is the mother's constitutional insufficiency, which is genetic and probably speaks to a common underlying mechanism; the second factor is pre- or perinatal damage, and the effects of this on the fetus are nonspecific.

A demonstration of how reproductive inefficiency of mothers of developmentally impaired children may be related to fetal antigenicity is provided by Costeff, Cohen, Weller, and Kleckner (1981) who compare the incidence of complications of pregnancy, labor, and infancy in 87 mentally retarded children ("undifferentiated phenotype") of consanguinous matings with 161 (idiopathic) mentally retarded children of nonconsanguinous matings. Complications were significantly more common in the latter group. Consanguinous matings, in which antigenic differences are minimized, were not associated with obstetrical or perinatal complications. The authors speculated that "maternal [reproductive] inefficiency [i.e., obstetrical difficulties] may well reflect some so far unidentified factor [which also causes] fetal brain damage" (Costeff et al. 1981, p. 489).

Beyond the genetic memory of inherited uterine inadequacy is another kind of memory that is expressed in the parity effect. The parity effect refers to systematic change in some measurable characteristic of offspring with increasing birth order or pregnancy order. Here again, there is a common pattern: the incidence of the complications of pregnancy and delivery, prematurity, miscarriage, fetal and neonatal deaths increases with birth order; later born are at greater risk (Niswander & Gordon 1972). Parity effects are also observed in at least some of the neurodevelopmental disorders, for example, mental retardation (Belmont, Stein & Wittes 1976), MBD (Badian 1984; Nichols & Chen 1981; Schrag 1973) and autism (see below, "The primiparity effect"). A retarded, hyperactive, or learning disabled child is more frequently later born.

Maternal insufficiency has a predictable negative effect on pregnancies occurring within an extended family. The effects of maternal insufficiency within a family seem to be mediated however, by the parity effect, with an increasingly negative impact on successive pregnancies. This incremental phenomenon is a form of nongenetic memory. It suggests an immunologic aspect; some kind of sensitisation process is at work. What could be inherited as maternal insufficiency is, in fact, a genetic proclivity to react immunologically to fetal antigen. The ensuing maternal immune attack against the fetus would appear to the clinician as a complication of pregnancy and as a sign of an inadequate uterine environment.

Selective male affliction, or at least a portion of it, is mediated through complications of pregnancy and childbirth, which occur more frequently in male offspring. An evocative principle was postulated to characterize the male fetus and to render the occurrence of such complications more likely. The phenomenon of maternal insufficiency suggests a genetic element at play on the mother's side. The existence of negative parity effects is compatible with an antigenic but not an endocrine explanation of the phenomenon on the fetal side. The evocative principle, therefore, is deduced to be the unique antigenic character of the male fetus.

The existence of an evocative principle: The antigenic character of the male fetus

The identification of a male-specific antigen, termed H-Y, was originally made in connection with the Eichwald–Silmser effect (see below, "The primiparity effect"). The expression of H-Y antigen probably derives from a monomorphic gene locus (Ohno 1979). The original hypothesis was that H-Y antigen is specified by a gene located on the Y chromosome (Goodfellow & Andrews 1982), but Wolf (1981) presented evidence to suggest that the structural gene for H-Y antigen is autosomal and that its expression is regulated by an X-linked repressor and a Y-linked inducer. Whatever the genetic origin of H-Y antigen, there is no disagreement over issues of ubiquity or specificity. H-Y antigen has been shown to be conserved to the extreme throughout vertebrate evolution (Ohno 1979). Having performed an extensive series of H-Y antibody absorption tests, Wachtel, Koo, and Boyse (1975) demonstrated that male cells of all mammalian species tested, including man, absorbed out the male-specific cytotoxicity of H-Y antibody, whereas no cross reacting materials were found on female cells. H-Y antigen is ubiquitously expressed in every somatic cell type of the mammalian male (Ohno 1979). It is first expressed in preimplantation male embryos at the eight cell stage (Krco & Goldberg 1976). An exact and invariant function seems to have been assigned by evolution to H-Y antigen, and as far as mammals are concerned, it is believed to lie in the determination of primary (gonodal) sex; H-Y is an absolute prerequisite, though it is not necessarily sufficient, for testicular organization (Ohno 1979).

Although H-Y is the prime candidate to account for the hypothesized antigenicity of the male fetus, it is a minor histocompatibility antigen, and its effects may be exercised in clinically important ways only through a cummulative effect with other antigens, including those of the ABO (Toivanen & Hirvonen 1970a), Rh (Renkonen & Timonen 1967; Scott & Beer 1973) and human lymphocytotoxic antigen (HLA) systems (Goulmy, Termijtelen, Bradley & van Rood 1977; Johansen, Festenstein & Burke 1974; Loke, 1978). Alternatively, maternal–fetal

immunoreactivity could be mediated in males whose mothers are sensitized to other antigens but not to H-Y, or in females, who do not express H-Y antigen, by virtue of an X-linked antigenic system (e.g. H-X, Xg^a) (Berryman & Silvers 1979; Loke 1978) that may have clinical importance.

Sex differences in antigenicity were first described in the so called Eichwald–Silmser effect: male skin grafts survive less well in female animals than do male-to-male, female-to-male, or female-to-female allografts (Eichwald & Silmser 1955). Trophoblast grafts from female concepti survive longer than male trophoblasts (Borland, Loke & Oldersnaw 1970); most choriocarcinomas arise from female concepti (Scott 1976) and those which arise from male concepti are notably less aggressive (Loke 1978).

There is clinical evidence that male fetuses are more antigenic than females. Immune complexes are found more frequently in the cord blood of male newborns (Farber, Cambiaso & Masson 1981); runt disease and Rh disease occur more commonly in males (Beer & Billingham 1973; Scott & Beer 1966); toxemia, which is probably an autoimmune disorder, is more common when the fetus is male, and the sex ratio increases proportionately with the severity of the disease (Toivanen & Hirvonen 1970b) (see Figure 1).

Antigenic differences between zygote and mother are thought to confer an implantation advantage (Kirby, McWhirter, Teitelbaum & Darlington 1967). Trophoblastic invasion of the uterine decidua may be more extensive if the fetus is antigenically dissimilar to the mother, a mechanism that seems to promote genetic diversity. The male zygote, by virtue of its greater antigenic dissimilarity, is the beneficiary of this putative implantation advantage (Brent 1971). Thus, the special antigenic character of the male fetus was first studied in connection with studies of the sex ratio. The secondary sex ratio, or sex ratio at birth, favors males in every human society that has been studied; the mean value for the United States is about 105 (Novitski 1977). The primary sex ratio, that is the sex ratio at conception, although difficult to measure, is even more

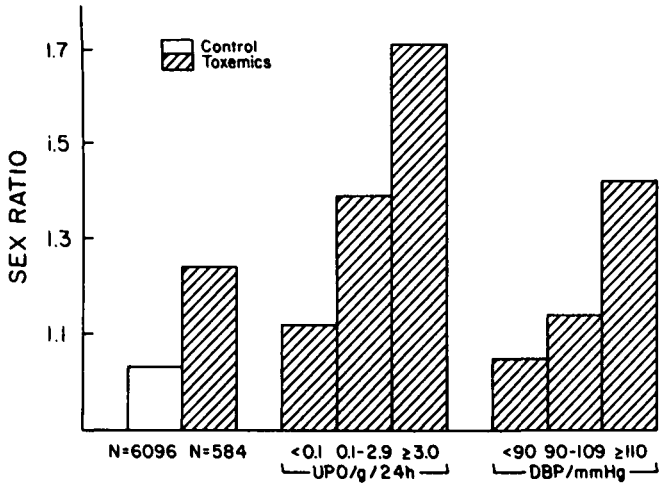

Figure 1. Preponderance of males in toxemia of pregnancy, from Toivanen & Hirvonen (1970b). UPO refers to urinary protein output; DBP to diastolic blood pressure; both are measures of the severity of toxemia, which increases with the sex ratio, on the ordinate.

favorable: around 120 (McMillen 1979). As if to compensate for selective male affliction, nature has produced an excess of boys to begin with. The implantation advantage of antigenic dissimilarity has been proposed to account for this initial male advantage. Thus, the advantage enjoyed by males in the primary and secondary sex ratio has been attributed to their unique possession of H-Y antigen.

Sex differences in antigenicity may confer a growth advantage as well as an implantation advantage (Clarke & Kirby 1966; Ounsted & Ounsted 1970). Fetuses which are antigenically dissimilar to their mothers are likely to be larger (Clarke & Kirby 1966), and the greater the antigenic dissimilarity, the greater the fetal growth rate (Ounsted & Ounsted 1970). Male embryos, of course, grow faster than females; a baby boy is about 150 grams heavier than a girl at term. The sex ratio of large-for-dates infants is 150 whereas that of small-for-dates infants is 63 (Ounsted 1972).

Placental weight is correlated with birth weight (Sedlis, Berendes, Kim, Stone, Weiss, Deutschberger & Jackson 1967), and mammalian placentation also seems to be under some sort of immunologic control (Jones 1968). In animal studies, antigenic dissimilarity is often found to promote placental growth (D. A. James 1965). The placental size of male fetuses is larger (Ounsted 1972). Interesting also in light of the presumed autoimmune origin of the disorder is the fact that increased placental size is associated with the development of toxemia (Gleicher & Siegel 1980).

Just as understanding the structure of sex differences influences one's appreciation of how males and females come to be afflicted by different pathways, so the sex ratio itself may influence one's respect for antigenicity as a causative agent in males, for at least some neurodevelopmental disorders. A telling example is the fact that the sex ratio decreases with parity; with increasing birth order, fewer boys are born (Novitski & Sandler 1956). There is a parallel between the sex ratio and selective affliction because in both there is a male preponderance, and in both parity effects are observed, and in both an argument in favor of male antigenicity and maternal immunoreactivity is raised.

An antigenic explanation for the secondary sex ratio, implantation, placentation, and fetal growth suggests that maternal sensitization to male antigens occurs and affects subsequent pregnancies. The sex ratio decreases with parity, whereas birth weight and placental size increase (Niswander & Gordon 1972; Novitski & Sandler 1956; Vernier 1975; Warburton & Naylor 1971). There is a nice balance here: the original implantation advantage enjoyed by the male zygote may be offset in subsequent pregnancies by the development of humoral antibodies or cell-mediated immune response in the mother. HLA antibodies, for example, develop in some mothers in response to pregnancy; with successive pregnancies, the number of HLA positive mothers increases (a ceiling seems to be reached at parity three or four) (Burke & Johansen 1974; Doughty & Gelsthorpe 1976). The sex ratio declines with parity in HLA positive mothers; in mothers who fail to develop HLA titres, the sex ratio actually increases with parity (Johansen & Burke 1974). (See Figure 2.) The model has a certain elegance: an early positive effect of immunoreactivity, which serves to promote genetic diversity, is balanced by a later negative

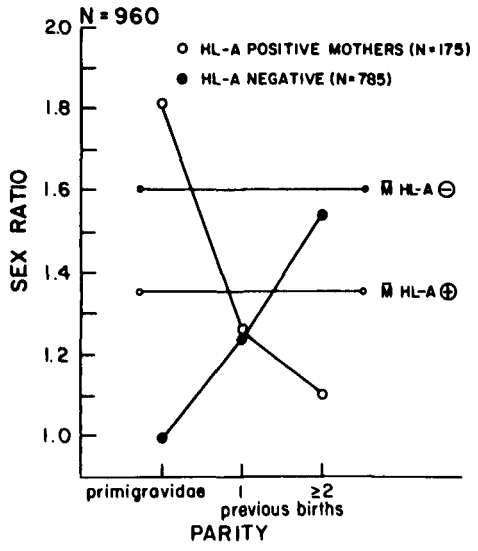

Figure 2. Sex ratio and maternal HLA antibodies, from Johansen, Festenstein & Burke (1974). In mothers who develop HLA antibodies, the sex ratio declines with parity; the opposite is true of HLA negative mothers. The mean ($\bar{M}$) sex ratio of HLA positive mothers is lower than that of HLA negative mothers (horizontal lines).

effect which seems to favor in large sibships the birth of the less expensive (female) sex.

If male fetuses are more antigenic, they should be more likely to sensitize mothers, and the impact of this should be felt in subsequent pregnancies in changes in placentation and the sex ratio. In fact, predictions based on the antecedent brother effect seem to hold up. Placental size increases with parity in all male sibships but not in all female sibships; mixed sibships fall in between (Vernier 1975). The sex ratio declines with parity if all antecedent siblings are male; it increases if all antecedent siblings are all female (Gualtieri, Hicks & Mayo 1984b; Renkonen, Mäkelä & Lehtovaara 1962) (See Figure 3).

It appears the parity effect on the sex ratio is mediated through an antecedent brother effect. This effect has also been observed with respect to the occurrence of pregnancy complications in the past history of autistic children.

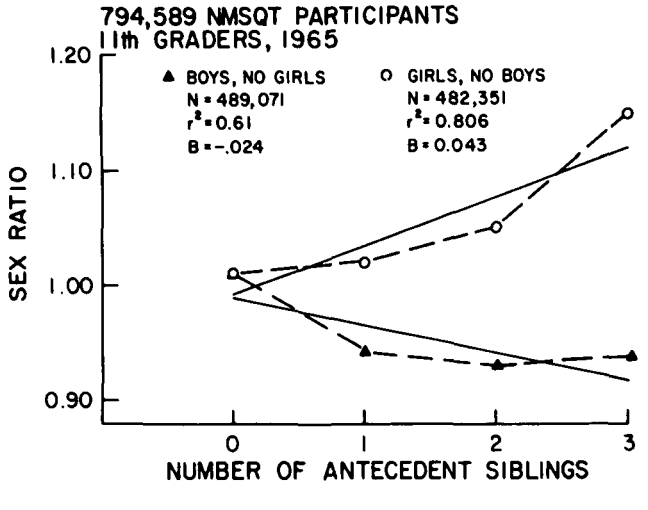

Figure 3. Sex ratio by sex of antecedent siblings, from Gualtieri, Hicks & Mayo's (1984b) reanalysis of Breland's (1974) data.

Table 3. *Antecedent brother effect on complications of pregnancy, 167 autistic boys*

		Antecedent brothers		
		None	One	
Complications of pregnancy	none	12	2	14
	one	31	8	39
	more than one	71	43	114
		114	53	167

χ^2 for linear trend = 5.815, P = .015

		Antecedent sisters		
		None	One	
Complications of pregnancy	none	8	6	14
	one	32	7	39
	more than one	79	35	114
		119	48	167

χ^2 for linear trend = 0.005, N.S.

We have reviewed the medical records of 209 autistic children evaluated at the Medical School at the University of North Carolina. In 167 autistic boys, there was a significant relationship between the occurrence of pregnancy complications and the antecedent birth of brothers but not of sisters (see Table 3). Pregnancy complications were more common in autistic boys who had older brothers, but not in autistic boys who had older sisters. The number of autistic girls was too small to permit a complementary analysis, however.

Maternal immune attack

> The concurrent evolution of viviparity and the ability to render an immunologic response to foreign antigens raised certain problems for the fetus. (Medawar 1963, p. 324)

> Pregnancy is associated with the development of circulating maternal antibodies directed against the histocompatability antigens of the fetus simultaneously with the specific inhibition of immune reactivity against the fetus as a graft. (Simmons 1971, p. 407)

The mechanisms by which the fetus is protected against the circulating antibodies and effector lymphocytes of the mother have been of considerable interest to transplantation biologists, oncologists, and other scientists, who have reviewed the topic (Bernard 1977; Billingham 1964; Simmons 1971). It is sufficient here to say that the mechanisms by which the fetus as an allograft is protected from maternal immune attack are still imperfectly understood (Simmons 1971); when they are, someday, they will doubtless prove to be marvels of biology. But they do not always work. The system, whatever it is, can break down. Fetal antigens and cells enter the maternal circulation and maternal antibodies and effector lymphocytes enter the fetal circulation (Adinolfi 1976; Adinolfi, Beck, Haddad & Seller 1976; Barnes & Tuffrey 1971). A cell-mediated immune response can develop in mothers during pregnancy; it may increase in intensity with gestation and increase even more so with succeeding pregnancies (Burke & Johansen 1974; Doughty & Gelsthorpe 1976; Johansen & Burke 1974; Terasaki, Mickey, Yamazaki & Vredevoe 1970).

For HLA, maternal lymphocytotoxic antibody production increases with the first three or four pregnancies and then levels off (Doughty & Gelsthorpe 1976). It has been hypothesized that if certain kinds of cytotoxic antibodies reach critical levels in the maternal circulation, they will exceed the number of available binding sites on the placenta and enter the fetal circulation (Doughty & Gelsthorpe 1974). Other fetal antigens may also play a role; for example, the ABO system may also contribute to maternal immune sensitivity, and ABO incompatibility between mother and fetus is known to contribute to increased fetal wastage (Cohen & Mellitts 1971).

In the British Perinatal Study (Butler & Bonham 1963), perinatal mortality data relative to maternal ABO typing was available for 14,730 pregnancies. As predicted by the IMRT, perinatal mortality increased more sharply with parity in O type mothers, who are more likely to react to fetal red blood cell antigens than A, B, or AB mothers. The slope of the perinatal mortality–parity regression line was significantly steeper for O mothers: O = 16.9, A = 13.2, B = 12.7, AB = 12.9 (Gualtieri, Hicks & Mayo 1984a). (See Figure 4.) Thus, ABO antigens as well as sex-linked antigens may induce maternal immunoreactivity.

There appears to be substantial interindividual variation in the maternal immune response (Lawler, Ukaejoofo & Reeves 1975). In one study, only 15% of pregnancies were characterized by the development of maternal HLA antibodies (Doughty & Gelsthorpe 1974). Medawar has shown that antigenic incompatibility is necessary but not sufficent to cause Rh disease. Rh disease is also more likely to afflict males (Loke 1978; Medawar 1963); isoimmunization is necessary, but not sufficient, to produce hemolytic anemia in the newborn (Medawar 1963). Figure 5 captures the wide range of reactivity that may exist between maternal and fetal lymphocytes (Lawler et al. 1975). Maternal immunoreactivity is more likely in some women and it is more likely when the fetus is male. In light of the genetic nature of maternal insufficiency, it would be interesting to know whether maternal–fetal immunoreactivity follows a similar genetic pattern.

There are known pathologic consequences of maternal immune attack on the fetus, for example, Rh disease and

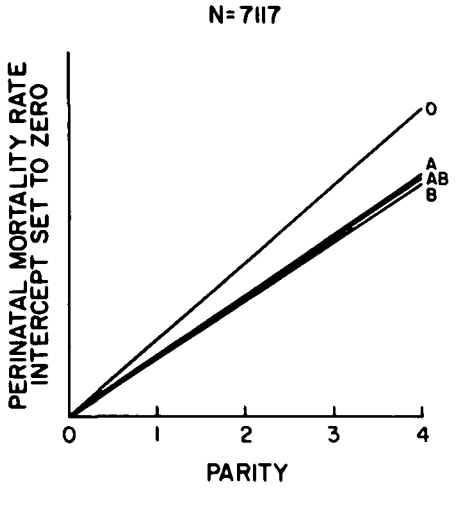

Figure 4. Perinatal mortality and maternal blood groups from Butler & Bonham (1963). See also Gualtieri, Hicks & Mayo (1984b).

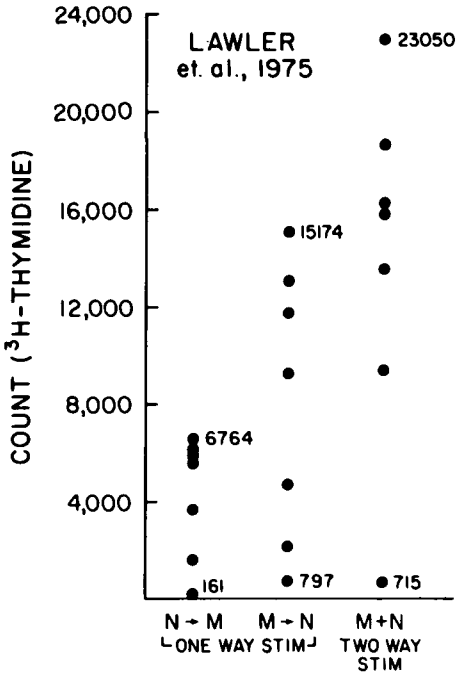

Figure 5. Maternal/neonatal cell interactions in mixed lymphocyte cultures, from Lawler, Ukaejoofo & Reeves (1975). One-way stimulation refers to live neonatal (N) cells admixed with killed maternal (M) cells, and vice-versa. Two-way stimulation (M + N) refers to two populations of live cells.

runt disease, as mentioned above. ABO incompatibility between mother and fetus is associated with an increased perinatal mortality (Cohen & Mellitts 1971). Other examples include autoimmune thrombocytopenia and autoimmune hemolytic anemia, myasthenia gravis, thyroiditis, and the lupus erythematosis (LE) phenomenon and cardiomyopathy in children of mothers with systemic lupus erythematosis (SLE) (Beer & Billingham 1973; Brent 1971; Bresnihan, Grigor, Oliver, Leiskomia & Hughes 1977; Kitzmiller 1978). In the latter condition, transplacental transfer of antinuclear antibody from mother to fetus occurs (Beck & Rowell 1963).

The autoimmune diseases are extremely interesting to consider in this context, because they are the only diseases to which both sexes are vulnerable that are more common in females; they are characteristically diseases of young women in their reproductive years (Kitzmiller 1978). Autoimmune disorders are also good examples of how maternal immunoreactivity can afflict the fetus. Some autoimmune disorders, like rheumatoid arthritis, tend to remit during pregnancy, while others, like SLE, often arise during pregnancy (Bresnihan et al. 1977; Kitzmiller 1978). In autoimmune hemolytic anemia, the disorder may remit post partum, only to arise again with a subsequent pregnancy (Kitzmiller 1978). Increased fetal loss through spontaneous abortion is seen in SLE, schleroderma, autoimmune hemolytic anemia, and autoimmune thrombocytopenic purpura. Fetal wastage is increased in SLE mothers even before the disease is clinically manifest (Kitzmiller 1978). Lymphocytotoxic antibody titres are higher in SLE mothers who have had spontaneous abortions than in mothers who had normal live births (Bresnihan et al. 1977). Toxemia is more common in mothers with SLE (Kitzmiller 1978). And,

based on our review of an admittedly sparse literature, more girls than boys are born to mothers with SLE.

Brain as the target of immune attack

The brain may be an immunologically privileged site in some respects, but immune attack on nervous tissue does occur in conditions like multiple sclerosis, polyneuropathy and spongiform encephalopathy (Abramsky, Lisalc, Silberger & Pleasure 1977; Dalakas & Engel 1981; Hauser, Dawson, Lehrich, Beal, Kevy, Propper, Mills & Weiner 1983; Sotelo, Gibbs & Gadjusek 1980). The heyday of taraxein is over (McPherson 1970), but neurobiologists continue to pursue the possibility of autoimmune mechanisms in the genesis of some forms of schizophrenia (Abramsky & Litvin 1978).

Brain tissue is antigenic (Foster & Archer 1979). It shares antigens with other tissues, including histocompatibility antigens, organ specific antigens, and antigens present on tissue cells (Foster & Archer 1979; Roszkowski, Plaut & Lichtenstein 1977). There are brain antigens specific to neurons and oligodendroglia (Poduslo, McFarland & McKahanon 1977); there are antigens specific to cells in functional groups (Williams & Schupf 1977) or anatomic areas (Blessing, Costa, Gefen & Rush 1977); there are antigens specific to subcellular components of neural tissue (Sotelo et al. 1980). Antibodies to brain antigens can act as teratogens when injected into pregnant animals (Brent 1971). Rats and guinea pigs immunized to nerve growth factor (NGF) develop anti-NGF antibodies which attack fetal nervous tissue in utero when the animals are bred (Johnson, Gorin, Brandeis & Pearson 1980). The immature blood–brain barrier is not capable of protecting the developing brain from damage by maternal antibodies or effector lymphocytes (Adinolfi 1976; Adinolfi et al 1976).

It is not our purpose to review the vast research areas having to do with the immunoprotection of pregnancy or the immunopathology of the brain. Nor can we describe the precise immunopathic mechanisms that mediate maternal attack and induce neuropathic changes in the fetus. Nor can we specify whether H-Y antigen alone is involved, or whether there are other important antigens in the male at particular points in time during gestation, nor whether incompatibility in other antigen systems, like HLA and ABO, may also play a role, and if so, whether the reaction that ensues is additive or multiplicative. These are grounds for speculation and basic research. Sufficient to guide the argument are these conclusions, which are fair and conservative: fetal immunoprotection is not invariant or complete; breakdowns in the system do occur, with occasional pathologic consequences to the fetus, occurring along a continuum of severity; the brain, especially the fetal brain, is not invulnerable to immune attack; and in laboratory animals at least, maternal antibodies can damage the developing nervous tissue of the fetus.

The idea that male antigenicity or maternal immunoreactivity may exert a negative influence on the neurological development of children has been suggested on previous occasions by Adinolfi (1976), Foster and Archer (1979), Loke (1978), Rubenstein (1982), and Singer, Westphal, and Niswander (1968). The hypothesis has usually been advanced on the basis of indirect evidence, to explain, for example, the prevalence of pregnancy complications in males (Singer et al. 1968) or the negative parity effect on IQ (Foster & Archer 1979). Adinolfi based his argument on the immaturity of the fetal blood–brain barrier (Adinolfi et al. 1976), the detection of maternal specific antibodies in the cerebro-spinal fluid (CSF) of infants tested during the first week of life (Thorley, Holmes, Kaplan, McCracken & Sanford 1975), and supporting data from preclinical experiments (Adinolfi 1976). There is additional direct evidence, but not much.

Bonner, Terasaki, Thompson, Holve, Wilson, Ebbin, and Slavkin, 1978 reported cytotoxic antibodies in the sera of 574 parous women; 25% had cytotoxins after their first pregnancy and 50% after the sixth. Children with congenital anomalies are more likely to be born to mothers who have developed cytotoxic antibodies. Harris and Lordon (1976) reported that mothers with lymphocytotoxic antibodies were more likely to show signs of maternal insufficiency (pre-eclampsia, fetal distress, carbohydrate intolerance, unexplained fetal death, intrauterine growth retardation, congenital anomaly and premature labor) than mothers with no lymphocytotoxic antibodies. Bardawil et al. (1962) reported that a group of 20 women with repeated miscarriage manifested rapid rejection of skin grafts from husbands four times more frequently than grafts that were made from unrelated donors (Loke 1978). In a mixed lymphocyte reaction paradigm, the percentage of transformed cells was discovered to be lower in normal fertile couples and higher in infertile couples; a dosage effect was observed in women who had had repeated miscarriage (Halbrecht & Komlos 1976; Omaha & Kadotani 1971). Finally, in two papers from the Soviet Union, it was reported that mothers with "antibrain antibodies" were more likely to give birth to children with developmental or neurological disorders (Burbaeva 1972; Kolyaskina, Boehme, Buravlev & Faktor 1977).

The immunoreactive theory

Selective male affliction with the neurodevelopmental disorders may be related to male vulnerability to environmental stressors, to the genetic endowment of the male, or to his complexity and relative immaturity. In our opinion, these hypotheses are strong and compelling but insufficient. They do not explain the male fetus's proclivity to encounter complications in pregnancy and childbirth. It is argued, with some support, that pregnancy complications mediate the occurrence of neurodevelopmental disorders more strongly in male offspring. The incidence of such complications in males leads to the postulation of an evocative principle, which may be hormonal or antigenic. The first alternative is extremely attractive but it is not consistent with the occurrence of parity effects in fetal loss and in at least some developmental disorders.

The antigenicity of the male fetus is consistent with the negative parity effect. The proposition that the male is especially antigenic and that some mothers are immunoreactors finds convincing support in the literature. The antigenicity of the male is probably related to the sex-linked H-Y antigen, although the contribution of other antigen systems cannot be discounted.

Maternal immune attack on the fetus is well known in a number of pathologic conditions and when it occurs, it is the male who is more severely afflicted. Brain tissue is antigenic, the immature blood–brain barrier affords only slight protection from maternal immune attack, and maternal antibodies are sometimes found in the infant's CSF. Congenital anomalies, infertility, and complications of pregnancy may occur in mothers with elevated antibody titres more frequently than in mothers with low or absent titres.

The argument is based on indirect evidence for the most part, although there is some direct supporting evidence. The relative paucity of direct support is not surprising. Although the theory of maternal–fetal immunoreactivity was first applied to studies of the sex ratio by Renkonen, Makela, and Lehtovaara in 1962, only a few scientists have even raised the question with respect to selective male affliction. Furthermore, the argument presented above relies heavily on the structure of sex differences in the occurrence of schizophrenia, and this dimorphic pattern has not been widely tested in clinical samples of developmentally handicapped children. When we did test the idea, it held up (see above, "Structure of sex differences"). Finally, it is unfortunate that most scientists who undertake studies of pregnancy complications and developmental disorders do not analyze their data taking sex of the proband into consideration.

The fundamental premise of the immunoreactive theory is that pregnancy is an immunological phenomenon characterized by a state of maternal tolerance. But fetal immunoprotection is relative, not absolute, and the system can break down. There is substantial interindividual variation in maternal–fetal immunoreactivity, but on the average, male fetuses are more antigenic than females, and maternal attack on the male embryo is more likely, especially if the mother has been sensitized by previous male pregnancies. Finally, maternal immunologic attack can be directed against fetal brain antigens.

Immunoreactivity is by no means a global explanation for all of the neuropathic disorders of childhood. The phenomenon may be robust but at the same time relatively weak and difficult to discern, especially in small clinical samples. Furthermore, the precise nature of the immunologic reaction cannot be described: whether it involves cell-mediated or humoral antibodies, whether a specific antigen, like H-Y, is responsible, or whether a number of fetal antigens or a combination thereof may be involved. Some fetal antigens may be short-lived and impossible to detect postnatally.

We are aware that there is disagreement surrounding at least some of the facts upon which the theory is based. Parity estimates can be inaccurate, for example, since early abortions are easily missed (Metrakos & Metrakos 1963). Not every investigator has agreed that placentation is promoted by antigenic similarity (Jones 1968), or that the sex ratio decreases with antecedent brothers (McLaren 1962), or that toxemia is an autoimmune disorder (Gleicher & Siegel 1980). H-Y antigen is a fascinating new development in the study of sexual differentiation, but it is very difficult to measure (Goodfellow & Andrews 1982); nor is there any direct evidence that H-Y antigen is present on neural cell membranes in humans (Johnson, Bailey & Mobraaten 1981). There are, not surprisingly, alternative (and occasionally credible) explanations for virtually every natural or clinical phenomenon that has been described thus far or is described below. Still, it is our opinion that the theory has an appeal, and perhaps also a certain usefulness.

Hypotheses engendered by the theory

The immunoreactive theory and the structure of sex differences on which it is based are particularly interesting in light of the hypotheses they engender. It is likely that many of the hypotheses presented below can be tested in existing data sets.

Parity effects. The immunoreactive theory is derived, in part, from the demonstration of negative parity effects in at least some of the developmental disorders. But it does not require, nor does it predict that parity effects will be found for all psychiatric, neurologic, and developmental disorders. The birth order–parity literature with respect to specific psychiatric and neurologic disorders (e.g. schizophrenia, epilepsy, alcoholism) is extensive but inconsistent, and there are serious methodological difficulties in executing a definitive parity study in clinical populations.

Because birth order effects are relatively slight, large numbers of subjects are required to detect them (Birtchnell 1971). Birth order studies rarely compare their findings to a general population control group, and the statistical analysis that is most often used, the Greenwood–Yule method, is not without its critics (McKeown & Record 1956). Birth order effects are sensitive to changes in the birth rate, numbers of marriages, and family size in the general population; a decrease in family size, for example, may lead to an overrepresentation of early birth ranks in small sibships and an increase in later birth ranks in large sibships (Price & Hare 1969). To consider sibling position irrespective of the size or composition of the sibship in which it occurs is probably unjustifiable (Birtchnell 1971). Additional sources of bias that can compromise the findings of a birth order study include the analysis of incomplete sibships, differential survival by birth rank, differential migration to sources of ascertainment of patients (i.e., places such as clinics where patients are identified) (Hare & Price 1969) and the fact that birth order is not necessarily the same as pregnancy order (Metrakos & Metrakos 1963). Parity studies of psychiatric disorders may be compromised by the fact that death, divorce, separation or other causes of early parental loss cannot prevent the conception of the last child in a family. Accordingly, the likelihood of parental deprivation having occurred during early childhood will always be greater for later born than for earlier born persons (Delint 1966).

The primiparity effect. The deleterious effects of primiparity may obscure a birth order effect. Primiparas are more prone to obstetrical complications, such as dystocia and toxemia. Subfertile women will be overrepresented among primiparas. A woman whose first child is defective has a number of strong reasons to limit the size of her family. Congenital rubella and infantile autism are examples of disorders in which relative risk is greatest for first

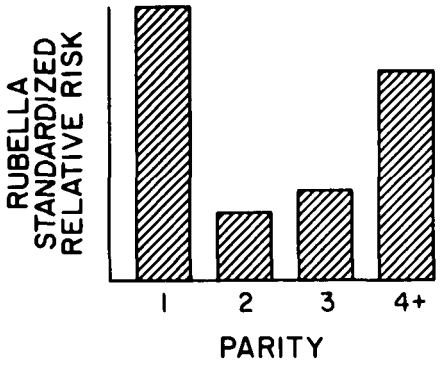

Figure 6. Rubella and parity effects, from Schoenbaum, Biano & Mack (1975).

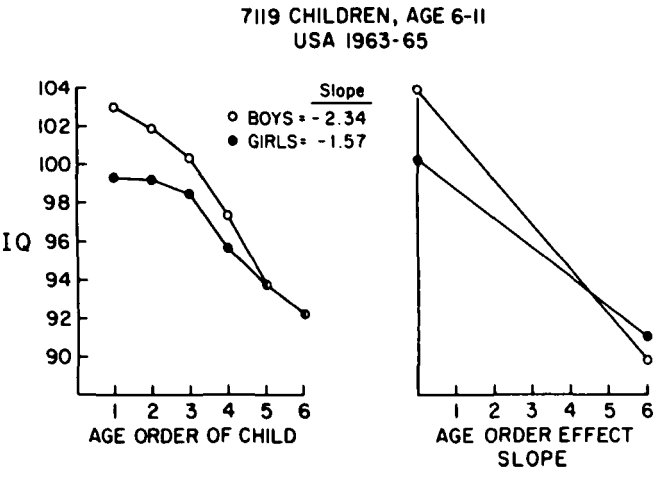

Figure 8. Parity effects on IQ by sex of proband, from the National Health Survey, USA, 1963–65.

borns (Deykin & MacMahon 1980; Schoenbaum, Biano & Mack 1975); thereafter, however, a parity effect appears to emerge. A U-shaped distribution of pathologic events with parity has also been described in association with fetal loss after 20 weeks gestation, stillbirths, and neonatal death (Ernst & Angst 1983).

In Figures 6 and 7, the relative risk of rubella and autism is plotted against birth order. First borns are at greatest risk, but for ensuing birth orders there is a clear parity effect. One way to measure the relationship between parity and risk for these disorders is orthogonal polynominal analysis of variance. When this method is applied to the data contained in Deykin & MacMahon (1980) and Schoenbaum et al. (1975), it is found that the quadratic relation (i.e. risk declines from birth order 1 to 2; increases thereafter) captures substantially more of the variance in the sample than the linear relation. (Rubella: r^2 [*linear*] = 0.04, F [1,106] = 143.5; r^2 [*quadratic*] = 0.93, F [1,106] = 1423.3; analysis of difference between slopes by Fischer's r to z transform, z = 13.04 [150]. Autism: r^2 [*linear*] = 0.05, F [1,455] = 45.86; r^2 [*quadratic*] = 0.46, F [1,455] = 417.3; difference, zRR = 4.07 [151].) The proper analysis of a birth order effect has to take this primiparity effect into consideration.

Sex differences in parity effects. Parity effects are more interesting to examine with an eye to specific hypotheses (Ernst & Angst 1983). If, for example, the question has to do with relative male vulnerability to a negative birth order effect, study of parity effects is enlightening. For example, the authors' reanalysis of data from the Second National Health Survey, 1963–65 (Roberts & Engel 1974), shows that males are more vulnerable to parity effects than females. The National Health Survey was an epidemiologically sophisticated population survey of 7,119 American children age 6–9 (Roberts & Engel 1974). One part of the survey was an IQ estimate derived from vocabulary and block design subtests of the Wechsler Intelligence Scale for Children. In this survey, clear parity effects on IQ were found; however, the parity effect was felt more sharply by boys than girls (see Figure 8). The slope of the regression line of IQ on birth orders is −2.34 for boys and −1.57 for girls. (Orthogonal polynomial regression analysis, sex × birth order [*linear*], F [1,7117] = 239.13, $p < .005$. After we had made this analysis, Steelman and Mercy published the same data set using multiple regression analysis, and demonstrated the same effect [Steelman & Mercy 1983].)

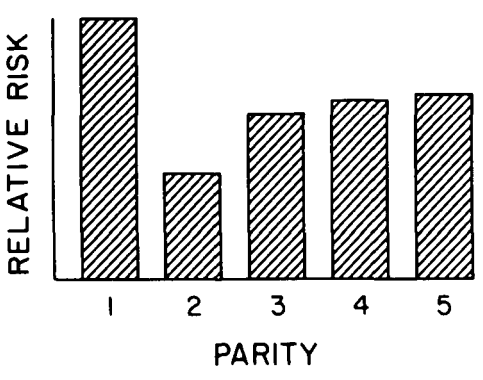

Figure 7. Autism and parity effects, from Deykin and MacMahon (1980).

Our reanalysis of IQ data published in two additional studies confirms the relative susceptibility of male offspring to negative birth order effects. In 1965, Reed and Reed published *Mental retardation. A family study*, an extraordinary and unique collection of pedigree analyses on 289 residents of an institution for the mentally retarded in Minnesota. Actual IQ scores were available for 258 probands, 118 boys and 140 girls. These were regressed against birth order. The correlation between IQ and birth order for boys was negative (r = −0.45, $p < .001$, *slope* = −1.5) whereas for girls the correlation was actually positive (r = 0.48, $p < .001$, *slope* = 1.4) (difference between slopes, F [1,256] = 37.075, $p < .0005$).

The data are even more striking in a more homogeneous group of mentally retarded children who had all been born prematurely. These data were reanalyzed from Moore's 1965 study of 137 mentally retarded residents of the Arizona Children's Colony. The correlation between birth order and degree of retardation was again negative for boys (N = 63, r = −0.85, p .001, slope = −0.74) and positive for girls (N = 71, r = 0.93, $p < .001$, slope +0.30) (F [1,126] = 11.22, $p < .001$).

It is clear that there is more to parity effects than a simple birth order analysis yields. The sex of the proband is a relevant variable, but it is not usually considered in

birth order studies of cognitive development or of neuropsychiatric disorders.

If parity effects are greater on the male fetus, one should expect to see the birth of developmentally handicapped boys earlier in the sibship. The data of Reed and Reed (1965) and of Moore (1965) provide at least some support for this prediction. The mean birth rank for 137 boys in Reed and Reed was 3.3 (±2.4) and for 152 girls, 3.7 (±2.5). In Moore, the mean birth rank for boys (N = 63) was 3.1 (±3.0) and for girls (N = 71) 3.3 (±2.5). Although neither result was significant at the 0.05 level, both were in the predicted direction.

Another way to look at parity effects is to examine the sex ratio–parity interaction in special populations. Sex ratio decreases with parity in the general population, but the decrement is very small (slope = −0.001 [Novitski & Sandler 1956]). The IMRT predicts that the sex ratio–parity regression line will be steeper in developmentally impaired populations because of increased occurrence of maternal immunoreactivity. A comparison of sex ratio–parity lines is given in Figure 9 for three populations: the general population from the 1946–52 U.S. vital statistics (Novitski & Sandler 1956), a sample of 496 patients with congenital cleft lip–palate (Woolf 1971), and 880 siblings and probands from Reed and Reed's MR study (1965). The regression lines are substantially steeper, by a factor of 30, in the two disordered samples.

Yet another way to analyze parity effects in light of the IMRT is to test the hypothesis that with increasing birth order, offspring should increasingly come to resemble their mothers. Having been sensitized by several previous pregnancies, mothers ought to "prefer" antigenically similar zygotes. This hypothesis is guided, of course, by the fact that the sex ratio decreases with parity; that is, relatively more girls are born later in the sibship. Judging from the very small sex-ratio effect, however, we think that only a very large data base will yield a proper answer to this question.

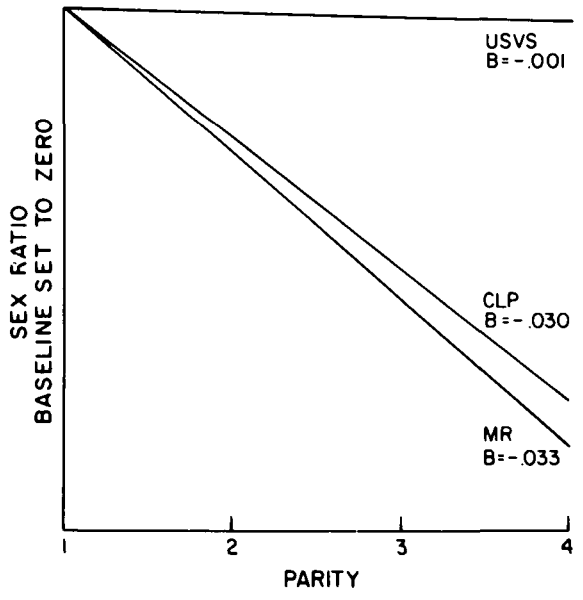

Figure 9. Sex ratio and parity, normal and handicapped populations from Novitski & Sandler (1956); Reed & Reed (1965); and Woolf (1971). USVS = United States Vital Statistics, i.e., census data. CLP = cleft lip and palate; MR = mentally retarded.

An atheoretical approach to parity effects in psychiatric illness or neurodevelopmental disorders, executed in relatively small and possibly biased samples, is not likely to yield useful information. Within the context of a specific hypothesis, however, such as relative male–female vulnerability or the IMRT, the study of birth order effects can be both interesting and enlightening.

Parity effects and IQ. In 1874 Francis Galton noted a disproportionate number of firstborn children among fellows of the Royal Society. Galton was the first modern scientist to suggest that primogeniture conferred a unique and selective advantage on intellectual development. The modern variant is found in studies of parity or birth order effects on intelligence. It is reasonably well established that IQ scores of first borns are higher, and that IQ decreases with birth order (Belmont & Marolla 1973), even when maternal age is controlled. This finding has usually been explained in psychosocial terms: parents spend more time with first-born children, they play with them more, they talk to them more, they expect more of them (Altus 1966; Galton 1874; Zajonc 1976). The family environment of later borns is necessarily shared and diminished. This is an intuitive explanation, and one that is given to empirical examination; however, attempts to confirm the hypothesis have not been notably successful (Ernst & Angst 1983; Grotevant, Scarr & Weinberg 1977). For example, socioeconomic advantage and early stimulation mitigates, but does not abolish parity effects on IQ (Zajonc 1983). The family–environment argument, or confluence model, (Zajonc 1976) predicts that closer spacing of siblings will compound the parity effect; in fact, spacing effects on intellectual development have not been found to exist in developed countries, where close spacing does not lead to maternal undernutrition (Belmont, Stein & Zybert 1978; Grotevant et al. 1977).

Negative parity effects are found not only for IQ and academic achievement, which may be amenable to psychosocial explanation, but also for specific learning disabilities (Badian 1984; Schrag 1973), mental retardation (Belmont, Stein & Wittes 1976), perinatal mortality (Niswander & Gordon 1972), and height (Belmont, Stein & Susser 1975) which clearly are not. Parity effects have even been observed in newborns (Waldrop & Bell 1966). The IMRT represents an alternative, biological explanation for negative parity effects in general, and it is particularly germane to parity effects on intellectual development.

The antecedent brother effect. The IMRT predicts that parity effects on later born boys will be greater if antecedent siblings are boys. In such cases, mothers may be sensitized to H-Y antigen, or to other sex-linked antigens. This sensitization can compromise the development of subsequent male fetuses. The idea is borrowed from studies of the sex ratio and of placentation relative to antecedent brothers. The antecedent brother hypothesis can be tested by comparing relative parity effects on any neurodevelopmental measure in males with antecedent brothers against males with antecedent sisters. Crossed comparisons can also be made with females who have antecedent brothers or sisters.

In a study of college entrance examination scores in 1013 students, secondborn males were found to score

lower than firstborn males, whereas secondborn females scored the same as or higher than firstborn females. Boys with older sisters scored higher than boys with older brothers. The data in this paper, however, were not sufficient to allow a statistical reanalysis (Rosenberg & Sutton-Smith 1969).

Additional statistical support for the antecedent brother hypothesis is available, however, in Breland's study of 794,589 eleventh grade students who took the National Merit Scholarship Qualifying Test in 1965 (Breland 1974). In our reanalysis of these data, four family configurations were compared: males with antecedent brothers, males with antecedent sisters, females with antecedent brothers, and females with antecedent sisters. Negative parity effects are seen for all four groups, but the sharpest negative parity effect is observed in boys with antecedent brothers (Gualtieri, Hicks & Mayo 1984b).

These two data sets contain selected populations, college bound high-school students and college freshmen, who are not representative of the population as a whole. The fact that these students were at least 16 years old means that psychosocial factors may have played a role in the development of younger children from same sexed sibships, but we are not aware of a convincing psychosocial explanation for such an effect.

The antecedent brother hypothesis could conceivably be tested in large populations relative to any intellectual, developmental, or neuropathic measure. It could also be tested in deviant populations: In mentally retarded children, for example, the hypothesis predicts that increased severity or retardation will occur in males who have antecedent brothers compared to males who have antecedent sisters. The antecedent brother effect may also play a role in some other hypotheses derived from the IMRT.

Subfertility. If maternal immunoreactivity is related to development disorders, one may expect to see relative infertility in the families of developmentally disabled children. Relative infertility can be measured indirectly by family size or directly by the length of time required for unprotected mothers to conceive. In fact, relative infertility has been found in mothers of children with mental retardation (Wallace 1974), Down's syndrome and cerebral palsy (Tips, Smith & Mayer 1964), epilepsy and congenital anomalies (Drillien 1968), learning problems (Nichols & Chen 1981), and low birth weight (Wilson, Parmelee & Huggins 1963). This effect is even more pronounced when the disordered child is male (Wallace 1974). There is, as a rule, a longer period of relative infertility after the birth of male children (Wyshak 1969).

The IMRT predicts not only that relative infertility should characterize mothers of developmentally disabled children, but also that the phenomenon should be more apparent when the disabled child is a male. This prediction is supported by at least one study of children with febrile seizures (Bernard 1977). A reanalysis of Reed and Reed (1965) reveals that mentally retarded males tend to come from smaller families (males, mean family size 6.1, females 7.0, $t = 2.12$, $P = 0.02$, one-tailed test). Maternal immunoreactivity may contribute to the birth of a fetus who is developmentally retarded and may also lower fertility thereafter.

Studies of maternal subfertility and reproductive inefficiency support the IMRT, but further studies with much larger samples ought to be done.

Additional hypotheses. The IMRT predicts that antigenic dissimilarity would increase the likelihood of maternal immune attack upon the fetus. When a developmentally handicapped child is born into a large sibship, it is hypothesized that he will be more likely to differ from his mother in measurable antigenic characteristics such as HLA or ABO. It is also predicted that there will be a tendency for later born sibs to resemble their mothers more closely in terms of the same antigenic characteristics. It is also proposed that antigenically dissimilar matings will be prone to produce female offspring. These hypotheses are based, of course, on the premise that H-Y and other antigen systems exercise an additive effect. They could conceivably be tested in the data banks that are maintained by tissue transplant services when typing records are maintained on families.

The IMRT is premised on the idea of an immunoreactive subgroup of mothers. It predicts that such immunoreactive mothers will exhibit an increased incidence of infertility and maternal insufficiency. It is possible that such women may be identified by the presence of allergic or autoimmune disorders. The occurrence of maternal insufficiency in women with autoimmune disease has been reviewed above. We propose that allergic and autoimmune disorders will occur more commonly in the mothers of developmentally handicapped children, in their families, and in the children themselves.

In fact, parents of developmentally disabled children frequently complain of their children's proneness to allergies. Although this has never received much attention from clinicians or researchers, recent studies have shown patterns of abnormal immunoresponsivity in children with infantile autism and Down's syndrome (Fialkow 1966; Stubbs 1976; Stubbs & Crawford 1977; Weizman, Weizman, Szekely, Wijsenbeek & Levni 1982). The IMRT predicts that mothers of such children would include a substantial number of immunoreactive individuals, and this factor could contribute to their children's disabilities. In support, abnormal levels of immunoreactivity have been reported in the families of children with Down's syndrome (Fialkow 1966). Geschwind's recent report of an increased occurrence of autoimmune disorders in left handers and their families is also consistent with this line of thinking, although in that study no distinction was made between familial and pathological sinistrals (Geschwind & Behan 1982). The latter would be expected to exhibit the trait more strongly. It is not unreasonable to suggest that a genetic disposition to autoimmune or allergic disorders might be associated with heightened maternal immunoreactivity, and non-right handedness may simply be one more clinical consequence thereof.

Clinicians who work with developmentally handicapped children occasionally come upon families who exhibit this pattern: the first child is normal, the second, learning disabled, and the third, retarded or autistic. Such families represent an ideal immunoreactive subgroup for further investigation. Mothers whose children follow such a pattern would be expected to be especially immunoreactive and might also be expected to have strong family histories of immunoreactive disorders. Hy-

potheses concerning specific kinds of immune activity connected with maternal–fetal attack would best be tested in such a subgroup.

Finally, a farfetched idea, but one which is intriguing and irresistible to us in light of the foregoing: there appears to be a unique and truly remarkable association between the sex of the fetus and schizophrenia occurring in pregnancy. In 1967, Shearer, Davidson, and Finch reported that only female children were born to women who conceived within one month before or after an acute schizophrenic episode. This finding was later confirmed by M. A. Taylor (1969) who also reported four stillbirths (all males), two perinatal deaths (both male) and six severe birth defects (five of six male) in mothers who became psychotic during the second or third month of pregnancy. It was suggested that there is a factor in acutely psychotic mothers that is especially toxic to the male embryo (Shearer et al. 1967). This element could be hormonal, but, in light of some recent autoimmune theories of schizophrenia, it could also be immunologic. Perhaps the element is the initiation of an acute hyperimmune state provoked by the fetus, leading to maternal attack not only against fetal tissue, but also against her own brain tissue. Of course there is no direct evidence to support the idea. But it is not outlandish to suggest that hypotheses germane to the IMRT might be profitably tested in schizophrenics, at least in schizophrenics with early onset or evidence of neuropathic damage.

Summary

The IMRT draws from a diverse array of sources to present a possible etiology for many cases of neurodevelopmental impairment. It is concerned with the problems of selective male affliction, maternal insufficiency, the structure of sex differences, and negative parity effects on intellectual development. The strongest appeal of the theory lies neither in its internal consistency nor in its success in bringing together obscure and seemingly unrelated findings, but in its ability to engender testable hypotheses. Many of these are affirmed in the literature or by preliminary investigations derived from existing data. The theory suggests two interesting routes for further investigation: the antecedent brother effect and the study of immunoreactive subgroups. We strongly suggest that studies of parity effects, pre- and perinatal complications, maternal insufficiency, and family genetic background relative to intellectual development take the following elements into considerations: the sex of the proband and of antecedent siblings, and the family proclivity to autoimmune and to allergic disorders.

If the theory were supported by research along the lines suggested above, hypotheses concerning specific immunologic mechanisms might be developed. Such research might yield strategies for the prevention of some of the neurodevelopmental disorders of childhood.

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Immunoselection and male diseases

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On the whole, I think it is unlikely that Gualtieri & Hicks (G & H) can convince a large number of readers that maternal immunoreactivity to fetal, male-specific antigens is responsible for the higher frequency and severity of diseases in males than in females. Although they cite a very long list of presumptive evidence to support their hypothesis, they provide little critical analysis of the data mentioned.

For example, much emphasis is given to the theory, first put forward by Kirby and collaborators (Kirby 1967; Kirby, McWhirter, Testelhaum & Darlington 1967) that antigenic differences between zygote and mother confer implantation advantages. Yet in 1975 McLaren reanalyzed these studies and concluded that "the experimental foundations on which the hypothesis was originally based are no longer secure and much evidence points to the opposite direction" (p. 270).

Again, when G & H attribute "the advantage enjoyed by males in the primary and secondary sex ratio . . . to their unique possession of the H-Y antigen," they do not cite the many studies showing that maternal H-Y antibodies do not induce an immunoselection against Y-bearing sperm or male blastocysts (Hoppe & Koo 1984; McLaren 1962).

G & H also often cite studies by Renkonen and collaborators (Renkonen, Mäkelä & Lehtovaara 1962; Renkonen & Timonen 1967). These suggest that in humans the sex ratio at birth becomes progressively lower with increasing parity and that this can be attributed to maternal immunization against male antigens. However, a careful analysis of the published data does not support an immunological interpretation, first because the variations of the sex ratios were only marginal, and second because the sex ratios of the fourth or fifth child after three or four previous male infants were not lower than those observed at the end of the first pregnancy.

When G & H, in order to support their theory, stress that "toxemia, which is probably an autoimmune disorder, is more common when the fetus is male," they overlook more recent investigations which have not confirmed a higher incidence of male than female conceptuses (Juberg, Gaar, Humphries, Cenac & Zambie 1976; Redman, Bodmer, Bodmer, Berlin & Bonnar 1978).

Readers actively working in the field of immunology of reproduction will also find it disturbing to see so many papers miscited. For example Loke (1978) is often mentioned in the text to imply that he supports certain findings and conclusions. Yet these findings are only cited critically in his book on the immunology and immunopathology of human fetal–maternal interaction. My own work is miscited, first, because I have not shown transfer of lymphocytes across the placenta – on the contrary, I maintain that there is little or no traffic of these cells between mother and fetus – and second because the references reported in the text deal with a different topic. In describing the results of the studies of Lawler, Ukaejoofo & Reeves (1975) on maternal–newborn cell interaction G & H imply that the maternal immunoreactivity was more likely when the fetus was male. Yet the entire investigation was performed using families with male infants.

The hypothesis reproposed by G & H is very interesting and it may explain why in certain disorders males are more severely affected than females, but in expounding and supporting a theory still surrounded by controversy, G & H should be presenting a more balanced account of the experimental data.

Testing the immunoreactive theory

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The principal attraction of the immunoreactive theory (IMRT) is the prospect that its central concept can unify hitherto unrelated findings concerning gender differences in a variety of neurological, psychiatric, pediatric, and behavioral disorders of childhood within a framework that can also encompass parity effects on the viability and cognitive development of normal males and females. Given the enormity of this goal it is not surprising that the empirical basis of support for the IMRT, at least at present, is less than secure. Furthermore, Gualtieri & Hicks (G & H) interpret some of their own data in a way we regard as overly enthusiastic. For example, consider the data reported in Table 2. Examination of IQ and SQ (social quotient) scores for developmentally disabled children indicates that, on average, males are less severely impaired than females, but there are roughly three times as many impaired males as females. Ostensibly these data support the view advanced by G & H that the occurrence of neurodevelopmental disorders in females is "largely influenced by the genotype" whereas in males "the occurrence of neurodevelopmental disorders is mediated by a genotype by environment interaction; pre- and perinatal problems play a more important role *and their manifestation is more diverse*" (emphasis added). In statistical terms this means that on any index of development the variability in the scores of handicapped males ought to be greater than the variability in the scores of handicapped females. Inspection of the standard deviations in Table 2 offers only modest support for this prediction.

To provide stronger support for the IMRT, data of the sort collected by Hicks and Gualtieri (1984) would have to reveal that: (1) The frequency of profoundly disturbed males is at least as great as the frequency of profoundly disturbed females. This follows from the assumption that the most devastating departures from normal development are primarily the results of genetic influences. If this is true for females, it must also be true for males. (Whether there should be an equal number of severely disturbed males or females or a slight preponderance of males depends on whether or not one assumes that the important genes are located only on autosomes or on autosomes and the X chromosome.) (2) There is a marked preponderance of moderately disturbed males because of the presumably greater tendency of antigens produced by the male fetus to provoke an immunological counterattack by its host-mother. As the data of Hicks and Gualtieri (1984) are presented, however, one cannot judge how well they fit the more precise predictions of the theory.

The major drawback of the immunoreactive theory is that there is simply no serological or pathological evidence to support an argument for an immunological attack on the child's central nervous system or the mother's uterus or placenta in any of the conditions listed by G & H. (It is also noteworthy that many of the "developmental disorders" listed in their Table 1 are not truly developmental; several are postinfectious, inflammatory, metabolic, vascular, or postanoxic.) Immunologically mediated conditions leave pathological calling cards which are clearly definable and reproducible in animal models. Serological abnormalities are also present in such conditions and are definable, reproducible, and even fluctuate measurably with disease activity. An immunoreactive theory not taking these aspects of basic clinical immunology into account is open to serious question and criticism. Even if this theory is statistically supported, one should remain skeptical as to whether a significant primary immunological mechanism is etiologic. It is obvious that "maleness" can affect a patient's response to a variety of insults without implicating an immunological process. The theory proposed reaches conclusions without having properly dealt with the potentially potent effects of other factors such as hormone levels.

Intellectually gifted students also suffer from immune disorders

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Gualtieri & Hicks (G & H) present an intriguing immunoreactive theory of selective male affliction. From this theory they predict that "allergic and autoimmune disorders will occur more commonly in the mothers of developmentally handicapped children, in their families, and in the children themselves." Geschwind and Behan (1982) and Behan (in press) have found such a relationship. Some new findings from my work with intellectually talented students also bear on this issue, but may be difficult to reconcile with the theory.

My study involved over 400 highly precocious students who had been tested earlier than usual with the Scholastic Aptitude Test (SAT) – Mathematics and Verbal – in a talent search and *before age 13* had scored at least 700 on SAT-M and/or 630 on SAT-V. Such students are estimated to represent at least the top 1 in 10,000 of their age group. Among such students I found a high frequency (over 50%) of allergies or other immune disorders (Benbow 1984). This was much higher than in the general population (10–20%) and in a much less able but gifted comparison group (35%). Moreover, the parents and siblings of these extremely precocious students were also more likely to suffer from such disorders (Benbow 1984). Although it seems plausible that maternal immunological attack against fetal brain antigens can cause learning disabilities or neurological impairment, it is not exactly clear to me how it can cause extreme intellectual giftedness. My training is not in this specific area, however.

There are well-documented sex differences favoring males in several specific abilities, such as high mathematical reasoning ability (Benbow & Stanley, 1980; 1983). Such differences may not be the sole result of environmental factors. It would be interesting if a theory dealing with selective male affliction could also account for selective male advantage. It is, of course, conceivable that they are independent.

In conclusion, I find the immunoreactive theory appealing and hope G & H can address the above concerns.

Male antigenicity and parity

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In their target article Gualtieri & Hicks (G & H) point out that many of the findings they refer to may have alternative explanations. Their theory, however, finds strong support in the overrepresentation of congenital disorders in males. This phenomenon had already been observed in the 1860s by Mitchell (1866), who found a sex ratio of 1.27 among 1,345 mentally retarded. W. H. James (1975) stated that the interval between a

male and a female (MF) pregnancy is longer than in MM and FF cases and that the average FM interval is especially short. Among early-born schizophrenics more men than women become hospitalized (Schooler 1964). One should not forget, however, that women are much more prone to affective psychoses. The findings of Juret, Couette, Delozier, Leplat, Mandard & Vernhes (1978) – that mothers who many years after the birth of a firstborn boy developed a breast cancer with axillary node involvement had a much better prognosis than mothers with a female first pregnancy ($\chi^2 = 11.08$, $p < .001$) – are highly suggestive of immunoreaction.

The occurrence of obstetrical complications in mentally retarded offspring or in boys who later develop autism (Table 3) is suggestive but should be compared with complications in pregnancies in which the offspring are not disturbed in order to clarify the connection between male sex and disorder. Parity, too, plays a marked role in Table 3. Provided there are no mixed cases (with two antecedent siblings), a combination of the two subtables into one 2 × 3 cell table leads to a χ^2 of 10.96, $p < .005$, clearly indicating that antecedent sisters contribute to the complications, a parity effect.

Control groups from the general population are crucial in all birth order studies. Cobb stressed this as early as 1914 in a criticism of the fallacious Greenwood–Yule model that later exerted a disastrous influence on birth order research for half a century. Weinberg (1913) had shown that sibship size must be taken into account before estimating any birth order effect; a trait that is more common in large sibships will elude a seeming overrepresentation of late ranks which are lacking in small sibships. The works of Hare and Price (1969) and of Birtchnell (1971) started a new era in international birth order research. Changes in birth cohort size, family size and length of intersibling interval produce an excess of late or early borns that is accessible to accurate calculation (Berglin 1981). It is now possible to predict the variation of birth ranks even in five-year cohorts of the general population fairly exactly (Berglin 1982).

In connection with G & H's reanalysis of the Reed and Reed (1965) study I find myself obliged to show (for the first time in literature, actually) how mean rank can be computed.

In a family of five, the sibling with rank III occupies the space from 2.00 to 2.99 around a mean point of 2.5. As the middle child, it occupies the middle position of its sibship: 2.5/5 = .5. A person with rank r among s siblings can be regarded as having the position $p = (r - \frac{1}{2})/s$.

If a sample is distributed with only children in one row, probands from two-child families in a second row, probands from three-child families in a third row, and so on, as in Table 1, we can record the number of probands in a certain row in an n-column so that Σn is the total number of probands. After dividing each n-value by its corresponding s-value we arrange a column of (n/s)-expressions. This column describes the relative distribution of families within $\Sigma(n/s)$ families in that population from which the probands were chosen. The mean size of such families is $\Sigma n/\Sigma(n/s)$, as Greenwood and Yule correctly demonstrated in 1914.

Now to the new formula, that of mean rank: The mean position of a sample is the sum of positions divided by the number of positions: $\bar{p} = \Sigma p/\Sigma n$. The mean point of any complete sibship is $.5 \times s$, for instance, $.5 \times 5 = 2.5$. The mean rank is registered half a space higher: $2.5 + \frac{1}{2}$ = rank III. With mean rank $\bar{r}$, mean size $\bar{s}$, and mean position $\bar{p}$, we have $\bar{p} = (\bar{r} - \frac{1}{2})/\bar{s}$, or $\bar{r} = \bar{p}\bar{s} + \frac{1}{2}$. The analysis above allows us to simplify: $\bar{r} = \Sigma p/\Sigma n \times \Sigma n/\Sigma(n/s) + \frac{1}{2}$, that is, mean rank of a sample: $\bar{r} = \Sigma p/\Sigma(n/s) + \frac{1}{2}$.

Table 1 is chosen for its simplicity and taken from the pedigree charts of Reed and Reed: 19 males in the primarily environmental category. A fourth column of ns-values has been added, giving the sum of all members of the probands' sibships. One cannot simply divide this sum by the sum of sibships represented ($\Sigma(ns)/\Sigma n$) in order to compute a sort of mean sibship size; that would be a coarse overestimation because large sibships are overrepresented. $\Sigma(ns)$ is needed for calculating the variance of $\bar{s}$: $\Sigma(ns)/\Sigma(n/s) - \bar{s}^2$. This variance divided by ($\Sigma(n/s) - 1$) gives the squared error of $\bar{s}$ (Berglin 1981, p. 57).

Table 1. (Berglin). *Arrangement of birth order data for calculating mean sibship size* $\bar{s}$, *mean sibling position* $\bar{p}$, *and mean sibling rank* $\bar{r}$.

	Birth order									
s	I	II	III	IV	V	VI	n	n/s	Σp	ns
1	1						1	1	.5	1
2	1						1	.5	.25	2
3		1	2				3	1	2.17	9
4	1	2		1			4	1	1.75	16
5	1			1			2	.4	.8	10
6							—	—	—	—
7		1		1		1	3	.43	1.5	21
8	1						1	.12	.06	8
9		1				1	2	.22	.78	18
10		1					1	.1	.15	10
⋮							⋮			
							1	.07	.32	14
14					1		19	4.84	8.28	109

Note: $\bar{s} = 19/4.84 = 3.92$; $\bar{p} = 8.28/19 = .44$; $\bar{r} = 8.28/4.84 + .5 = 2.21$; $\text{var}_{\bar{s}} = 109/4.84 - 3.92^2 = 7.15$; $\text{error}_{\bar{s}} = (7.15/3.84)^{\frac{1}{2}} = 1.36$.

If one treats the total male sample of Reed and Reed (136, not 137, boys, for case KMD 276 was wrongly described as a male) in this way, one arrives at a mean sibship size of 4.17 ± .54 and a mean rank of 2.4. The 153 females have a mean sibship size of 5.43 ± .56 and a mean rank of 3.0.

Most authors writing on birth order influences have until now made the same mistakes, but no doubt the new methods will slowly penetrate. Of course this formal flaw does not in the least detract from the interest evoked by G & H's stimulating synopsis and theory.

The sex ratio at conception: Male biased or 100?

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Gualtieri & Hicks's (G & H's) target article is a substantial heuristic contribution to both practice and theory. It should hasten our understanding of the effects of the interaction of birth (and pregnancy) order with the sex of the child. It will certainly stimulate prenatal sex differences research. It might even encourage those many investigators who study embryos without regard to sex to identify conceptuses as female or male. It has been obvious for some time that momentous physiological events early in gestation play a crucial role in sex differences in morphology and behavior. Nevertheless, much embryological research has ignored sex as a dimension.

G & H's reference to the strong male bias of sex ratios at conception is the focus of my comments. The primary sex ratio is central to any theory or analysis of selective male affliction. The immunoreactive theory (IMRT) is strengthened by the widely held belief that the conception ratio is 110 or higher (Daly & Wilson 1983; Kellokumpu-Lehtinen & Pelliniemi 1984; McMillen 1979; Ounsted & Taylor 1972; Yamamoto 1977). If,

however, those who have found evidence to support a sex ratio approaching 100 are right (Allan 1975; Mikamo 1969; Sasaki, Ikeuchi, Obara, Hayata, Mori & Kohno 1971) a theoretical adjustment to account for a disproportionate early loss of female embryos is essential.

I think we simply do not know enough to embrace either position at present. Kellokumpu-Lehtinen and Pelliniemi (1984) and Yamamoto (1977) appear to have developed more adequate methods of determining the sex of embryos and fetuses than the investigators who found a sex ratio approaching parity (also see Mikamo 1969 for additional discussion of the intricate problems associated with embryonic sex determination).

Yet there is provocative evidence that a ratio of 100 may be correct. Some other mammals approach parity at conception (Fechheimer & Beatty 1974; W. H. James 1982; Kaufman 1973). If parity is widespread at conception in mammals, it would be unlikely that our species would have evolved a different reproduction pattern (but see Clutton-Brock 1982 for a discussion of secondary sex ratio in a variety of species; also Spector 1956, Table 440). The sex difference, which is found in several disorders that probably develop during the embryonic period, also supports the belief that the ratio may be lower at conception. Anencephaly, spina bifida, cleft palate, and some congenital heart disorders are more common in female neonates (Hay 1971; Moore 1982). If – and it is a big if – these sex differences reflect a much greater female susceptibility to spontaneous malformation during the early and mid-embryonic period, it seems reasonable to assume that spontaneous female abortion would also be much more frequent during this period. Of course, it is possible that these afflictions are actually visited equally on the sexes and that affected males, faced with a less friendly intrauterine environment, are aborted in greater numbers.

Since the issue can be resolved only by examination of zygotes, animal studies are the essential first step. The human conceptuses available for determination of the early sex ratio are clinically aborted fetuses. Since many zygotes and embryos have been spontaneously aborted before these clinical specimens are obtained, no valid data regarding the sex ratio at conception can be collected. Definite conclusions about our species will have to await our developing relevant technology.

The sex ratio at conception is a theoretical issue which does not detract at all from the clinical significance of G & H's article. However, parity at conception would certainly prove heuristic for natural selection theory. What are the ramifications of a reproductive strategy – if it exists – that rapidly rejects atypical female embryos but follows a much more deliberate course with male conceptuses? Some evolutionists have speculated that, especially in polygamous species, a conservative reproductive "policy" is best suited to selection of female offspring but that the payoff from unique male progeny might produce a greater tolerance of diversity in that sex.

Undistributed middle term in the logic of Gualtieri & Hicks's immunoreactive model

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Does the immunoreactivity model generate testable hypotheses? Yes, but I question the specificity and stringency of those offered.

Concentration of complications in a subgroup should cause more concern than it seems to; are there not, for example, genetic reasons why some mothers develop HLA antibodies quickly, others never? Could allergy-proneness in affected children be due to the same immunoreactivity (IMR) genes?

Correlation may suggest, but can never imply, causation. Even the correlations discussed here have not been sufficiently questioned: Are mothers of neurodevelopmentally disabled (NDD) males indeed excessively immunoreactive compared to mothers of normal children or of NDD girls? This could be directly tested. Negative results would be evidence against any causal relationship between IMR and sex and NDD. If reproductive competence is really reduced in the affected families, can causes, and not just correlations, be found among immune functions?

Gualtieri and Hicks (G & H) consider parity and antecedent brother effects their best evidence against nonimmunological alternative interpretations. But isn't an NDD child more likely to be the last, especially if there is already a son? And wouldn't the likelihood of an affected child being last increase with the number of previous children? How can the reduced reproductive competence proposed for these families be reconciled with proposed parity effects?

The primiparity effect is said to be crucial, then averaged out of subsequent discussion. Least likely to have an immune basis, primiparity is a negative factor in reproductive competence, with known endocrine correlates. Wouldn't the NDD child be more of a problem for new parents, and more likely to reduce further reproduction? Aren't parity effects as likely to be mediated behaviorally as biologically?

Effects of maternal age have not been addressed. Increasing maternal age changes the hormonal dynamics of pregnancy, reduces reproductive competence, and alters immunoreproductive relationships (Holinka 1981). Aging of oocytes, directly, and as a result of coital frequency decreasing with age or parity, increases sex ratio and the probabilities of overripe gamete fertilization and abnormal development (Guerrero 1974; Guerrero & Rojas 1975; Harlap 1980; Lanman 1968; reviewed in Boklage, submitted). Potential for statistical confounding with parity effects is high indeed, and must be addressed.

The autism–parity results of Deykin and MacMahon (1980) are crucial to the argument, but do not make the stated point. If I include 20 autistic children left out because they had no sibs (the omission of which inflates all parities of two or more) and still reluctantly omit nine families with two autistic children each because their birth orders were not published, then all parities greater than one are deficient among the autistic children compared to their normal siblings. (In parity six plus, there are four cases instead of the expected three.) Compared to total live births (North Carolina Vital Statistics 1977), there are among these autistic children six cases more than the expected 21 of fourth and higher parities ($\chi^2 = 1.701$, 3 d.f.) This is far from significant and easily explained by sampling biased toward larger families. (Ideally, the comparison should be made with total live birth parities in the same races, cities and years.) According to Deykin and MacMahon themselves, their results, even without the above changes, "cannot be construed to indicate an excess risk for children who are the youngest of several siblings" (1980, p. 861). I have to agree.

Rubella results (Schoenbaum, Biano & Mack 1975) used by G & H to corroborate the autism results show only an excess of younger mothers among rubella cases compared to controls. Schoenbaum et al. state: "Not only is there no increased risk for multiparae, but there is clearly an excess of primiparae among the mothers with rubella" (p. 154). Table 2 of Schoenbaum et al. shows every parity but the first deficient among rubella cases compared to controls.

G & H's Figure 9 shows the male fraction of mental retardation declining as parity increases. If one imagines that the primary sex ratio is stable to parity and age, then the normal slight decline of the secondary sex ratio would mean reduced male survival to term (because of IMR?). Since the IMR hypothesis equates causes of male excess NDD with those of poor male survival, the fraction of males among retardates should rise with parity to satisfy the model. It falls. If instead, as it seems, the primary sex ratio and developmental anomalies increase with

gamete aging (due in part to coital frequency decreasing with age or parity), upward pressure would be even greater. Differential survival to term is a major unaddressed issue.

Sex differences are presumed by G & H to be mediated by histocompatibility differences, not necessarily limited to effects of minor antigens made in response to sex-determining genes on the Y chromosome. But sex affects the outcome of major sex-*in*dependent incompatibility (Scott & Beer 1973). We might therefore suppose that compatibility itself, regardless of the antigens in question, is of minor import. Antigenic maleness is present or absent, but for even the highest sex ratios in Table 1, 10–20% of those affected are female. There have to be other determinants, and interactions. Several X-linked genes, for example, affect control of the immune system or surface antigens (McKusick 1983: #30030, 30040, 30823–25, 31345–46, 31470, 31485, 31490).

Steroid hormones modify immunoreproductive relationships (Holinka 1981). The fertile female-preponderant expression of autoimmune disease can be hormonally altered (Smolen & Steinberg 1981). Prospects of endocrine bases for observed sex differences have been too readily dismissed, given known immunoendocrine interactions. Development of the thymus, as with most of the endocrine system, depends on neural crest derivatives (Bockman & Kirby 1984). Which is more sex-dependent?

Since sex differences have long been at issue in studies of usual and unusual brain laterality and NDDs represent anomalies of lateralization or lateralized function as well as of sex ratio, eventual resolution of these questions may be aided by adding laterality to the complexity of the present situation.

Parental nonrighthandedness (NRH) is associated with increased miscarriage and stillbirth and decreased family size (Fraser & Rex 1984). In Rife's (1940) data, families with either parent NRH averaged 15% fewer children, 72% as many sons, and 106% as many daughters, as families with both parents dextral ($\chi^2 = 5.78$, 1 d.f.). Nonrighthandedness is excessive in the parents of twins (Boklage 1981) and in the parents of children with neural tube defects, orofacial clefts, or congenital heart defects, raising prospects of shared genetic neural crest involvement (Boklage & Fraser 1984; Boklage & Fraser, in preparation; Fraser 1983). Autoimmune and allergic disorders are excessive in nonrighthandeders (Geschwind & Behan 1982; 1984) as well as among fertile females, and neuroendocrine relationships are lateralized (Gerendai 1984). A common feature of all these anomalies and relationships is the involvement of cell surface interactions.

An obvious component of sex differences lies in tissue specific growth rates. Genes on both X and Y are involved (Alvesalo & Portin 1980; Alvesalo & Tammisalo 1981; Alvesalo & Varrela 1980) as well as steroid hormones. Such sex and tissue-specific growth has been plausibly implicated in sex differences of both laterality and immune response (Geschwind & Behan 1984).

NDD children and male children have more birth problems. Some birth problems are caused by maternal IMR. It has not been shown that the excess of birth problems is greater in NDD males than in other males, it does not follow that maternal immunoreactivity causes either, and the proposed tests will not fill in the middle. Other tests might, with (in my opinion) a high likelihood of different conclusions.

Possible involvement of maternal alloreactivity in negative parity effects

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Gualtieri & Hicks (G & H) have advanced the idea of selective male affliction by maternal immunoreactivity. However, males are selectively afflicted not only in mammals with the XY male phenotype but also in nonmammalian vertebrates (for instance, male aves have phenotype XX), and even in dimorphic plants (Geodakjan 1983). During the past 20 years Geodakjan has elaborated on an attractive hypothesis concerning the role of sexual dimorphism during evolution (Geodakjan 1982). Sexual dualism may ensure two basic principles of any adaptive system. The female sex represents the conservative genetic aspect ensuring the transmission of the genetic pool from one generation to the other whereas the male sex performs a progressive ecological function by introducing new information from the environment into the system (Geodakjan 1982; 1983). This proposed sexual specialization localizes all advantages and failures in the male subsystem, whereas females ensure the selection of "male experiences" and the transmission of progressive trends into the genetic pool. Females are less phenotypically dispersed and more adaptive during ontogeny, but more stable during phylogeny; the evolutionary changes during ontogeny more easily afflict the male sex, which is depleted in adaptability but favored in variability (Geodakjan 1983).

Nevertheless, particularly in *Placentalia*, the contribution of maternal immunoreactivity to fetal development during intrauterine development cannot be overlooked, transmission of maternal immune influence is even possible during breast feeding (Beer & Billingham 1976; Freier & Eidelman 1980). Such maternal immunoreactivity could be either beneficial or deleterious to the fetus and infant. G & H have suggested that Rh isoimmunization, which is clearly of immunological origin and in which minimal risk of affliction to the first Rh+ proband can be expected in Rh− unsensitized mothers (Rote 1982), represents an analogy to negative parity effects on male affliction by maternal immunoreactivity and that the male brain is the most frequently afflicted tissue. Negative parity effects on IQ have been reported in all four possible groups of family configurations of students tested (also in females with antecedent sisters), but the sharpest negative parity effect is observed in boys with antecedent brothers; G & H find no convincing psychosocial explanation for such an effect. One concludes that there is some negative imprint of antecedent pregnancy on the subsequent progeny and that greater male affliction could be related either to higher male sensitivity to the same deleterious effect or to some antigenic substance present in the brain of male fetuses. Until the latter is tested it is difficult to decide between these possibilities. Unfortunately, the mechanisms responsible for selective male affliction by the maternal immune system have not been analyzed in more detail; nor are the mechanisms responsible for survival of fetal allografts yet understood.

If there is some negative effect of parity on brain development, it should be interesting to determine whether a brain organizational process is afflicted or whether it is the organized brain tissue itself which is the target of maternal immunoreactivity. Mental function starts to develop after birth, and in the newborn the brain hemispheres are unmyelinated (Lecours 1975; Yakovlev & Lecours 1967). The organizational process is most vulnerable during its most rapid stage; whereas during the initial stages recovery is possible, with no effect once organization is complete; damage of stable organized tissue can never be recovered from (Scott 1979). The cortex is histologically immature at birth compared to the nuclei of the central gray and brain stem (Trevarthen 1979). The speed of the organizational process may be related to incremental rates in DNA content in the human brain, which exhibit two peaks, one reflecting neuron multiplication in the midgestational period (20th week), and a second corresponding to glial multiplication associated with increased brain weight, dendrite development and synaptogenesis, and peaking in the 12th postnatal week (Dobbing 1971). The organizational process for sensorimotor function, which is already developed to some extent in the newborn, may be more vulnerable during intrauterine life, whereas the organizational process for higher mental function may still be highly

vulnerable during the first postnatal months. DNA incremental rates are lower before term and thus the organizational process may be less active, that is, less vulnerable during parturitional stress; nonetheless, the hitherto organized brain tissue can still be irreversibly afflicted by serious perinatal complications.

In view of the high vulnerability of the organizational process for mental function during the first postnatal months one may wonder how maternal immunoreactivity can postnatally affect subsequent progeny sharing the genetic background of their older sibships. Human colostrum and milk have been shown to possess immunoglobulins of which only low quantities can be absorbed a few days after birth (Ogra, Fishaut & Theodore 1980). There are, however, a considerable number of maternal immunocytes (macrophages, T-cells, B lymphocytes and plasma cells) and polymorphs, whose entry or nonentry into the breast-fed infant's tissues is still an open question. Nevertheless, studies of prolonged breast feeding by tuberculin positive mothers have suggested that there is transient transfer of tuberculin specific T-cell reactivity up to 10 to 12 weeks after birth (Ogra, Fishaut & Theodore 1980). The question can be raised whether or not the prolonged breast feeding of an infant having antecedent sibling can be correlated with lower IQ.

The mechanisms by which the maternal immunocytes may exert a deleterious effect on the developmental organization of the brain or on organized infant brain tissues are as yet highly speculative. We have recently suggested that there are specialized cellular mechanisms controlling cellular differentiation. The functional ability of most proliferating adult tissues may be dependent on a supply of committed Thy-1 glycoprotein released by specialized Thy-1+ cells; a role for Ia+ cells, macrophages, and lymphocyte subsets in the control of tissue growth has also been suggested (Bukovský & Presl 1984; Bukovský, Presl & Holub 1984). Some of these cells (macrophages, lymphocyte subsets) clearly belong to the immune system (IS) and it has been proposed that the IS plays a dual role in the tissues: the first, positive, stimulating cellular proliferation; the second, negative, eliminating superfluous or afunctional cells (Bukovský, Presl & Holub 1984). The other cells participating in the control of tissue growth (Thy-1+ dendritic cells associated with vessels, Ia+ cells of dendritic type) have been hypothesized to belong to a specialized tissue control system (TCS), cooperating with the immune, endocrine, and nervous system in the control of tissue function (Bukovský, Presl & Holub 1984). One of the most complex roles of IS and TCS may be to control the survival of an allogeneic fetus in the mammalian female (Bukovský & Presl 1984; 1985; Bukovský, Presl & Židovský 1984).

We agree that maternal lymphoid cells are unable to invade (allogeneic) fetal tissues during intrauterine life but, as mentioned above, they may enter the infant via breast feeding. The adult brain of various species (including man) has been found not to express class I MHC molecules (for data and review see Ponder, Wilkinson, Wood & Westwood 1983; Williams 1982). In our investigation of the brain development of 20-week-old human fetuses we have found that the maturation of brain cells proliferating from membrana limitants is associated with the interaction of the same control cells of the IS and TCS as described or expected within adult rat tissues, that is, macrophages, lymphocytes, Thy-1+ pericytes, and Ia+ dendritic cells (Bukovský & Presl, unpublished data). Moreover, the developing fetal neuronal cells bordering the "mature" Thy-1+ brain cells exhibit class I MHC molecules in addition to some differentiation antigen (DA) of lymphocytes on their surface, that is, leukocyte common antigen (Bukovský & Presl, unpublished data). Thus the maternal lymphoid cells entering the tissues of a breastfed infant could interfere with the organization of brain development for mental function, which perhaps peaks during the 12th postnatal week. Maternal lymphocytes may react by means of dual recognition (reviewed in Klein 1982), that is, against species-specific DA present on both maternal lymphocytes and fetal lymphoid cells and brain, and against sensitizing allogeneic class I MHC molecules of fetal lymphoid cells or a particular layer of developing neuronal brain cells. Such reactivity simulates the well-known mixed lymphocyte reaction in tissue cultures and is called DA restriction (Bukovský & Presl 1984; 1985). The infant's targets may also be its lymphoid cells participating in the organizational process for postnatal brain development, or the particulal layer of still-developing brain tissue. The resulting effect can be either transient interruption or definitive termination of development and the maturation of additional neuronal cells with subsequently lowered brain capacity. As an alternative to the transfer of maternal lymphoid cells from milk, large quantities could enter the fetal tissues via maternofetal "blood transfusions" due to insufficiencies of the fetal placental barrier associated with degenerative changes of the placenta during late stages of pregnancy. Moreover, maternal blood lymphoid cells have been reported to exhibit substantially higher reactivity than milk T-cells against alloantigens (reviewed in Ogra, Fishaut & Theodore 1980). Thus the absolute benefit of therapeutic intrafetal blood transfusions containing viable alloreactive lymphoid cells in Rh isoimmunizations is questionable. It is interesting that retarded, hyperactive, and learning disabled children more frequently tend to be later-born.

As to possible disadvantages of breast feeding, it has been reported of animals that milk can produce fatal graft-versus-host disease if the progeny of one inbred strain is nursed by the foster mother of another strain with different MHC specificity (Head & Beer 1979). This suggests that an infant should be breast fed only by his own mother. However, subsequent pregnancies could function as booster immunizations against the same father's genetic background, similar to enhanced anti-Rh reactivities in repeatedly sensitized mothers. Breast feeding is greatly beneficial to the infant, however, particularly because of the well-known induction of resistance to negative influences of the environment it produces. It is also tempting to speculate that the introduction of allogeneic MHC molecules into the infant's tissues via maternal milk lymphoid cells could enhance the antiallogeneic reactivity of the infant's IS, the phenomenon considered important in defense against cancer (Bukovský & Presl 1984; 1985).

In conclusion, we suggest that negative parity effects may be related to maternal alloreactivity increasing with birth order. The psychosocial effects among siblings could play an additional role in the mental development of an infant. The selective affliction of males could be in part related to the higher vulnerability of the male sex throughout evolution; possible involvement of male-specific antigen(s) cannot be rejected at present. The only way to minimize negative effects of parity is to avoid prolonging pregnancy or even to deliver shortly before term (38th week of pregnancy), particularly in later pregnancies. In view of the benefits of the biological mother's milk for the newborn, we suggest that the negative effects of longer-lasting breast feeding on the mental development of subsequent progeny with the same genetic background be viewed with suspicion.

Is the H-Y antigen a malefactor?

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Gualtieri & Hicks's (G & H's) immunoreactive theory contains one central, ambitious, and stimulating idea which, for its own good, should be isolated from the remainder of their essay: the proposition that maternal reactivity to the H-Y antigen damages some male fetuses and thus contributes to the surplus of males in

fetal wastage and in early-onset psychiatric, neurologic, and developmental disorders. Like any original thought, the theory's appeal is inseparable from the risk it runs. It is elegant, testable, and therefore unlikely to be confirmed. In my opinion there is no need to wed it to such postulated mechanisms as brain antibodies, ABO and HLA incompatibility, or maternal allergic and autoimmune disease, all of which fail to explain selective male vulnerability. In fact, to invoke brain antibodies is not only unnecessary but positively harmful. Should an H-Y stimulated maternal immune attack on the male fetus be confirmed, it could conceivably operate through nonneuroimmunologic mechanisms, explaining the male preponderance in nonneurologic, postnatal morbidity (Winter 1972). How brain antibodies could mediate these phenomena is difficult to imagine.

The hypotheses arising from this theory include the following:

1. In the population:
   a. Male intelligence will show a lower mean and a larger variance than female.
   b. Male intelligence will negatively correlate with numbers ($n \geq 1$) of elder brothers when social class is held constant, whereas female intelligence will not. Similar but weaker correlations will obtain with birth order and family size.
2. In brain-damaged groups:
   a. More complications of pregnancy will occur with male fetuses than with females. ("Complications" include a mother who tends to abort.)
   b. Proportion of male fetuses with complications of pregnancy will positively correlate with number of elder brothers, and less strongly with birth order and family size, when allowance is made for social class. Females will show no such phenomenon; pooled males and females will show it to an intermediate degree.

The population data so far adduced are equivocal. Birth order, when rendered independent of family size or social class, shows the expected effect on Raven scores of 19-year-old males in Holland (Belmont & Marolla 1973), but not on IQs of Scottish and French schoolchildren (Zajonc 1976). The expected birth-order effect is seen in all National Merit Scholarship Qualifying Test (NMSQT) scores among gifted American college applicants, but the same data show a male superiority, against expectations (Zajonc 1976). Since the theory attempts to explain a minority brain damage phenomenon, gifted groups may not be appropriate for testing the hypothesis. In that case, however, the observed American birth-order effect would not be relevant to the theory. At least one report (Altus 1966) suggests that in the U.S. this birth-order effect is indeed seen in bright college candidates but not in high-school graduates as a whole.

No brain-damaged populations have yet been analyzed to test the above hypotheses, with the exception of G & H's data on autistic children. After reading their target article I reviewed the raw data on Israeli mental retardates who were the subject of previous reports (Costeff, Cohen & Weller 1983a; 1983b). Among nonspecific retardates of nonconsanguineous parents the sex ratio was about 3 to 2 as in other series. Complications of pregnancy and delivery were seen in 58.2% of the males and 61.5% of the females. Fewer complications in males would suggest a genetic X-linked factor rather than immune attack. The difference is not significant, but even equality would go against the immune hypothesis.

Number of elder brothers and birth order are not readily available, but number of siblings at time of assessment is at hand. I analyzed the data separately for mildly and severely retarded probands and found the same trend in both. The overall association between family size, sex, and proportion of cases with complications of pregnancy and/or delivery is seen in Table 1. The trend, observed equally in both sexes, is for complications to be associated with smaller families, and presumably with lower birth order. The trend is statistically significant, and it is against the hypothesis. One possible explanation for this finding could be that an insidious maternal immune attack on the fetal brain is parity related and is not associated with bleeding, toxemia, or other complications. This would be consistent with Adinolfi's (1976) suggestions, but not with the immunoreactive theory as stated by G & H. Since the trend holds for both sexes, it also allows no significant role for the H-Y antigen.

Table 1 (Costeff). *Proportions of retardates with complications of pregnancy or delivery*

	Sibship size			
Sex	1–2	3–4	≥5	Total
Male	47/70	44/68	26/63	117/201
Female	32/38	23/47	28/50	83/135

Two other reported findings seem intuitively to conflict with the immunoreactive theory. One would expect an increasing preponderance of male fetal loss toward the end of pregnancy, but this seems not to occur (McMillen 1979; Ounsted 1972). Similarly, one would expect cases of congenital cerebral palsy to show a higher sex ratio than cases of postnatal cause, but they likewise do not (Stanley & Blair 1984).

These observations lessen the likelihood that the immunoreactive theory will be confirmed, but they do not completely refute it. In view of its attractiveness, the theory deserves further testing on its own terms. What this means is that sex and order of all pregnancies in the family have become relevant data for those of us who collect statistics on intelligence and on varieties of childhood brain dysfunction.

A possible role of sex steroid hormones in determining immune deficiency differences between the sexes

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Gualtieri & Hicks (G & H) offer strong support for a most reasonable theory that male fetal antigenicity may induce a state of maternal immunoreactivity. They also mention that endocrine effects may be a plausible alternative. Perhaps both an endocrine effect and an antigenic effect play a role. Not being an immunologist, I respect the authors' well documented proposal, but I offer some thoughts about a possible role of the sex steroid hormones in determining immune deficiency differences between the sexes.

My reasoning is as follows: Estrogen receptors are present in both the female and male rat cerebral cortex for about the first three weeks of life (MacLuskey, Chaptal & McEwen 1979). In the male at birth, the right hemisphere is significantly thicker than the left, although there are areas where this is not true. The female left cortex is in general thicker than the right, but not significantly so (Diamond, Dowling & Johnson 1981). We found that the addition of exogenous estrogen to the sexually mature female, which had been ovariectomized at birth, decreases her cortical thickness (Pappas, Diamond & Johnson 1979). After removing the gonads at birth and examining changes in asymmetrical patterns in the adult cortex, we also found that sex steroid hormones play a role in laterality (Diamond et al. 1981).

With this knowledge, Sandhu, Cook & Diamond (unpublished) from our laboratory have hypothesized that cortical

laterality may be induced by estrogen and that therefore the left cortex in the male would have more estrogen receptors during the early weeks of the animal's life. If this is true for the male, then the opposite is true for the female. With their recent data Sandhu et al. have shown that the male does indeed have more estrogen receptors in his left cortex during the first weeks of life and the female possesses the opposite. The estrogen receptors are no longer present after the first few weeks of life, as has been reported by others (MacLusky et al. 1979). The high levels of testosterone in the early stage of the male rodents' life may be responsible, when converted to estrogen, for determining the pattern of laterality.

The knowledge that male rats have a thinner left cortex and females in most cases a thinner right proved of value in the next series of experiments when we had learned that lesions in the left cortex of female mice reduced natural killer lymphocytes. Lesions in the right cortex did not (Renoux, Biziere, Renoux & Guillaumin 1980). Here was evidence that the left cerebral cortex could alter immune functions. We ask now a major question: is the left or right hemisphere associated with mediating immune responses in the male? We are presently measuring the cortical thickness in the male and female nude mouse and have found that in the female the frontal lobes and area 2 are significantly thinner than in a BALBc (mouse strain) control. The nude female mouse's area 18 in the left cortex is also significantly thinner than in the right. The measurements of the male are not as yet complete, although shortly we will have the answers from them as well. If the left cortex is thinner than the right in the male nude as well as in the BALBc control, then the evidence collected so far points to the left cortex as being related to immune functions in both males and females. These two experiments begin to shed light on factors which can control cortical laterality and may in turn relate to immune deficiency patterns between the sexes.

Short and sweet: The classic male life?

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That selective affliction of male *Homo sapiens* has a long evolutionary history is evidenced by the male-biased sex ratio at birth and the more rapid senescence of adult males. Indeed, numerous other mammals (elephant seals [LeBoeuf 1972; 1974]; Soay sheep [Grubb 1974]; deer [Robinette, Gashweiler, Low & Jones 1957]; and nonmammals (grackle [Selander 1966]) exhibit marked differential mortality of males. Such a widespread phenomenon demands a general explanation, but Gualtieri & Hicks's (G & H's) immunoreactive theory fails in this regard.

The most glaring problems arise when considering egg-laying species in which immunoreactivity between mother and offspring would not occur. Moreover, in birds the mechanism of sex determination is opposite that in mammals: males are homogametic (ZZ) and females heterogametic (ZW). Nevertheless in many species the mortality of males exceeds that of females, for example, the great-tailed grackle (Selander 1966). Even in freshwater crocodiles, whose sex is environmentally determined, there is differential mortality of eggs containing male and female embryos (Webb & Smith 1984). The common features of both invertebrate and vertebrate species exhibiting differential male affliction and mortality are polygynous breeding strategies and male competition for mating opportunities (Daly & Wilson 1983). It is among these features that we must search for the underlying causes of selective male affliction.

In man, as in many other animals, males compete with one another for the opportunity to inseminate females (who usually choose the mating partners). The intensive nurture that females bestow on offspring is a resource for which males pay a substantial competitive price; for the male who wins the right to inseminate a female also wins for his progeny a share of the female's parental investment. However, in many cases the very qualities that permit males to compete for mating opportunities also commit them to greater risks and resultant mortality. Darwin (1871) addressed such potentially maladaptive features in his theory of sexual selection and emphasized that sexual selection could, in principle, act in opposition to natural selection and so explain such burdensome characteristics as oversized antlers. These sexually selected features may expose males to higher mortalities not only through external factors such as risky behavior (Daly & Wilson 1983) but also through internal factors such as androgen secretion.

The most extreme case of increased male mortality due to internal factors is seen in marsupial mice of the genus *Antechinus* who exhibit a semelparous life history characterized by "big bang" or "kamikaze" reproduction (J. M. Diamond 1982; Lee, Bradley & Braithwaite 1977). In *A. stuartii* there is a brief mating season in the late Australian winter (August); pregnancy lasts about a month and all births in a population occur within a two-week period. The offspring never see their fathers, however, because within three weeks of the onset of mating all the males in the population die (J. M. Diamond 1982; Lee et al. 1977). In nature death is often caused by predation or fighting but even under controlled laboratory conditions male *A. stuartii* self-destruct with atrophy of the reproductive system, hepatic necrosis, anaemia, gastric and duodenal hemorrhages, hypertrophied adrenals, elevated corticosteroid levels, and suppression of the immune system (J. M. Diamond 1982; Lee et al. 1977). This physiological collapse is related to dramatic antecedent changes in behavior during the brief mating season including increased aggression, activity day and night, and repeated copulations of several hours duration. Even if captured prior to the mating season and isolated from cohorts, male *A. stuartii* still die. Although they sometimes survive for a few extra weeks, they never live to the next breeding season. Male *A. stuartii* is obligatorily semelparous, although a female may live for another two or three breeding seasons.

In man, androgens not only induce males to violent and risky behavior but probably also hasten degeneration and senescence. Hamilton and Mestler (1969) found that the mean age attained by a group of castrated males was 69.3 years whereas a comparable intact group averaged only 55.7 years. (Experimentally castrated cats also live longer [Hamilton, Hamilton & Mestler 1969].) One theory of senescence suggests that some attributes enhance fitness and hence by increasing reproductive success early in the life cycle are selected for, even though the same attributes have degenerative consequences later in life history (W. D. Hamilton 1966). It is not life span that selection maximizes but rather fitness (as measured by the number of offspring).

Such ideas may apply with equal vigor early in life. Given that females choose their mates and that males compete with each other for this prize, it is obvious that there is some advantage in having a higher degree of variation in males on which natural selection can operate. This greater degree of variation may reflect a higher mutation rate from whatever cause – transposed DNA segments, errors in controlling genes, and so forth. This in turn is likely to produce a higher degree of male affliction for a number of diseases and conditions. Such a mechanism would operate independent of whether the male was homogametic or heterogametic. An interesting common feature of homogametic, heterogametic, environmentally determined, oviparous or viviparous males is developmental rate during embryonic life. In general, males develop faster than females (Burdi & Silvey 1969a; 1969b; Ferguson & Joanen 1983; Mittwoch 1983; Mittwoch & Mahadevaiah 1980a; 1980b). A faster developmental rate, means that any upset (either environmental or genetic) is likely to have more serious sequelae, particularly relating to

the coordination of developmental events following compensatory growth (Snow & Tam 1979; Tam & Snow 1981). Such desychronization can lead to subtle behavioral and structural malformations of the central nervous and reproductive systems which do not manifest themselves until later life (Snow & Tam 1979; Tam & Snow 1981). These may contribute to selective male affliction.

Other factors influencing differential male affliction include circumstances in which individual parents might profit by biasing the sex of their offspring (Trivers & Willard 1973). Evidence for this comes from a study of the Florida packrat (McClure 1981). Well-fed females invested equal amounts of energy in sons and daughters, reared them in equal numbers, and weaned them at the same weight, whereas mothers who were food deprived during lactation channeled 68% of "transferred energy" into daughters and only 32% into sons. Thus many male pups died and those that survived grew more slowly and were weaned at lighter weights than their sisters. According to Trivers and Willard (1973), extra investment in a son of good quality may yield greater returns (in terms of numbers of future offspring) than comparable investment in a daughter of good quality. Thus a mother may prefer to produce sons when she has the resources necessary to give them a better than average competitive ability and daughters when she does not. Maternal physiology and nutrition may thus provide an alternative explanation for the "sex ratio according to birth order" data presented by G & H. However, if mothers could detect the nonpreferred sex (males when the maternal environment is poor) early and abort at low cost in time and energy then Trivers and Willard's (1973) theory would be in accord with the immunoreactive one. Clearly the multifactorial issue of selective male affliction is ripe for further investigation.

The Immunoreactive theory: One for all?

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The intriguing immunoreactive theory (IMRT) put forward by Gualtieri & Hicks (G & H) to account for selective male affliction in a vast number of neurodevelopmental disorders deserves very careful consideration. G & H's case seems to be strong enough and there is – as G & H point out – certainly considerable attractiveness in the theory's ability to generate testable hypotheses. Ever since Adinolfi's (1976) paper in which it was suggested that neurological abnormality in children might result from cross-placental transfer of maternal antibodies to the fetal central nervous system, the idea that certain kinds of brain dysfunction in childhood might result from mechanisms similar to those occurring in Rh-disease has been kept alive, albeit at a low level. The principal merit of G & H's target article resides in its forceful and rather comprehensive argument for reviving the Adinolfi idea.

However, I think some pros and cons should be highlighted. First, the main weakness of the argument, namely its failure to explain any of the great phenotypical variation in children with neurodevelopmental disorders, is toned down and assigned a very obscure and nonspecific statement to the effect that the IMRT is not "put forth as a global explanation for all neuropathic disorders of childhood." It would have been interesting to know G & H's opinion about how such clinically extremely different conditions as Down's syndrome and the autistic syndrome might result from unitary pathogenetic mechanisms. Not having discussed this variation at all, the whole IMRT argument risks the fate of claims for universal explanations for other well-known dichotomies, such as overweight versus underweight, namely that of being discarded at once because of its lack of general credibility.

I am not yet sure whether the IMRT can stand up to such criticism. There are, of course, different ways in which immunological attacks on the fetus might be achieved. G & H propose greater antigenic differences in male than in female fetuses when compared with the mother. Depending on the kind of differences and "the allergic state" of the mother, I suppose it is conceivable that different parts of the developing nervous system, or, for that matter, different chromosomes, may be injured.

However, in the case of Down's syndrome, for instance, is it not more probable that the chromosomal nondisjunction (trisomy 21) is primary, and not produced by a mother–fetus attack? By G & H's argument, Down's syndrome children, regardless of sex, might be more antigenic because of their different chromosomal makeup and therefore more prone to brain damage. Furthermore, boys would be more vulnerable than girls (IMRT prediction). Wouldn't this lead to either (1) an increased rate of abortion in Down's syndrome boys or (2) to brain damage and mental retardation being more severe in boys than in girls with Down's syndrome? Certainly it would not lead to an excess of live boys with Down's syndrome. Down's syndrome may be a bad example since experts differ in their views on sex ratios; for example Ratcliffe, Stewart, Melville & Jacobs (1970) state that males are equal to females. Nonetheless, G & H use Down's syndrome as an example in their first table; in any case my argument can be extended to include other chromosomal abnormalities with male excess.

The fragile-X syndrome in autism (Brown, Jenkins, Friedman, Brooks, Wisniewski, Raguthu & French 1982) represents another puzzling disorder in the realm of IMRT. Obviously, in the clearcut sex-linked cases, this chromosomal abnormality accounts for a substantial minority of the excess male cases with autistic syndromes. Possibly these cases too are more liable to additional brain damage than chromosomally normal children. There is in fact growing evidence that this may be the case (Gillberg & Wahlström 1984). There are, however, several autism–fragile-X cases that appear to be new mutations. Are these viewed by G & H as resulting from a maternal immunological attack?

Obviously, among such heterogeneous syndrome groups as "autism," and "stuttering," there are bound to be a variety of reasons accounting for male excess, and IMRT is able to explain only a fraction of them. Although it is theoretically attractive to hypothesize that the IMRT could account for a variety of developmental *abnormalities*, other theories, such as the immaturity model proposed by Ounsted and Taylor (1972), might be able to explain another fraction, namely some of the developmental delays (enuresis, language delays, some cases of dyslexia).

Another important and related point is that the IMRT may be relevant only in some of the neurodevelopmental disorders of childhood. G & H rely heavily on data from studies on autistic children, making generalization about other conditions hazardous.

In the case of autism, however, I think their argument is really suggestive. It would be most interesting to know, for instance, whether or not the antecedent brother effect has been observed in conditions like infantile spasms, the hyperkinetic syndrome, and the like. In preliminary analyses of a total population-based sample of children with minimal brain damage (MBD) (with perceptual, motor and attentional deficits) and controls, Gillberg, Rasmussen, Carlström, Svenson & Waldenström 1982) found no differences across the groups. However, in a population-based group of autistic children and controls (Gillberg 1984), autistic boys tended to have older brothers more often than controls (Table 1), even though the numbers involved were small, and statistical significance was not achieved. There was a clear trend toward boys (especially in the autistic group) with elder brothers having occasioned pregnancy

Table 1 (Gillberg). *Antecedent brother effect on complications of pregnancy. Results from a population-based study of 19 autistic boys* (A) *and 19 age-, sex-, and maternity-clinic-matched controls* (C).

	Antecedent brothers	
	None	One
	n	*n*
Complications of pregnancy	A,C	A,C
None	1,4	0,0
One	2,3	1,3
More than one	5,5	10,4
	Antecedent sisters	
	None	One
	n	*n*
Complications of pregnancy	A,C	A,C
None	1,0	0.4
One	2,4	1,2
More than one	13,9	2,0

complications more often than boys without elder brothers. On the other hand, there was no tendency toward an excess of firstborn males.

Studies indicative of links between high maternal age and neurodevelopmental disorders, like autism (Gillberg 1980), might, if analyzed in detail, provide additional support for the IMRT. Coleman and Gillberg (1984) and Funderburk, Carter, Tanguay, Freeman and Westlake (1983) have suggested that abortions are common in the preconception histories of autistic children.

Stubbs, Ritvo, and Mason-Brothers (1984) recently performed a very interesting study which might prove pertinent to the future elaboration of the IMRT. They examined 52 pairs of parents of autistic children and 83 pairs of parents of normal children and found that 77% of the former group shared at least one HLA antigen compared with 22% of the latter group ($p < .0001$). Studies on HLA in parents and children with autism comparing boys with girls might prove fruitful.

Inferential clues and suggestions for future scientific testing of the IMRT might also be provided by some data from another recent study. In a population-based study of infantile autism in Gothenburg, Sweden, 1 out of 40 boys (2.5%) and 2 out of 6 girls (33%) with infantile autism showed fragile sites on the sixth chromosome. The major histocompatibility complex, exercising control over susceptibility to autoimmunity and other immunological reactions, is located on the sixth chromosome.

Having read G & H's target article, I analyzed some more of my own data on children with MBD and children with left-handedness with a special view to finding evidence of autoimmune and allergic disorders in subgroups of these children. There was no excess of atopic disease (asthma, eczema or allergic rhinitis) in the population-based group of seven-year-olds with MBD (Rasmussen & Gillberg 1983). Among population-representative ten-year-olds with left-handedness (Gillberg, Waldenström & Rasmussen 1984), allergies were not more pronounced in cases with pathological left-handedness (i.e., those showing a very poor performance with the nonpreferred hand; Bishop 1980) from those with "normal" left-handedness. However, as in Geschwind's study (Geschwind & Behan 1982), allergies and autoimmune diseases tend to be common in the undifferentiated group of left-handers. To provide support for the IMRT, the pathological handers (i.e., those who are presumed to have sustained brain damage) would have to have the highest rate of allergies.

In summary I would say that the vast bulk of the scientific evidence reviewed by Gualtieri & Hicks does indeed favor the IMRT, but that the theorists would do well to refrain from overgeneral statements about the applicability of their model.

Does maternal–fetal incompatibility lead to neurodevelopmental impairment?

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The basic premise laid out in Gualtieri & Hicks's (G & H's) target article is a provocative one – namely that the underlying etiology in a significant number of cases of neurodevelopmental impairment is to be found in an immune response on the part of a subgroup of immunoreactive mothers directed against antigenic disparities encountered more frequently with a male fetus. G & H interpret the structure of the sex differences seen in neurodevelopmentally impaired offspring (in general, afflicted males outnumber females, though the female impairments tend to be more severe) as suggestive of a predominantly genotypic effect for females and a genotype-environmental interaction effect for males.

There is evidence that a maternal genetic principle or principles underlie the phenomenon of maternal insufficiency. In addition, G & H cite work suggesting that negative parity effects operate primarily against males as a result of genetic incompatibility (in part at last associated with an H-Y antigen). Both phenomena are consistent with G & H's hypothesis. Thus, for instance, the primary sex ratio (at fertilization) exceeds the secondary sex ratio (120:105). G & H report that implantation is favored by antigenic disparity between mother and fetus; placental size and birth size increase with parity, but predominantly only in male fetuses. Interestingly, the sex ratio decreases in mothers who develop an immune response to the fetus (characterized by HLA antibodies, see G & H's Figure 2) and in parous women with antecedent male children (Figure 3). The sex ratio actually increases if antecedents are female. It would be of interest to know the composition of anti-HLA$^+$ mothers in the data in Figure 3. The reader must be alert, as G & H indicate, to the myriad other incompatibilities that may contribute to these effects, ABO blood group disparities for instance (Figure 4).

In keeping with Popper's views on what constitutes a good theory, G & H are concerned to point out the falsifiability of their hypotheses. In their analysis of the data shown in Table 3, for instance, if the negative parity effect is indeed mediated by immunoreaction against antecedent males, there should be less correlation – or none – between pregnancy complications and antecedent brothers–sisters where autistic females (or females–males with other neurodevelopmental impairments) are studied. The number of autistic girls was unfortunately too small for this particular analysis. However, a more recent study cited (submitted in 1984c), using Breland's examiation of 794,589 eleventh grade students taking the National Merit Scholarship Qualifying Test in 1965, suggests that of the four family configurations possible the greatest negative parity effect was seen in boys with antecedent brothers. This is again in keeping with G & H's hypothesis.

The concept of a familial tendency towards immunoregulatory disorders in mothers of neurodevelopmentally impaired offspring is purely speculative. There are to my knowledge no data suggesting an increased frequency of impairments in males or females born to mothers exhibiting classical autoimmune-

type disorders. Moreover, there is good evidence for a psychoneuroendocrine axis in the latter disorders (Solomon 1983). Thus we must consider the likelihood that in these cases any hostile uterine environment may reflect a neuroendocrine effect and not one induced by fetal histoincompatibility antigens. Any additional bias in favor of greater frequency of impairment in the male fetus could presumably reflect alterations in fetal brain development as a result of changes in the balance of androgens, estrogens, and progestational hormones (caused even by elevation of androgens of fetal origin).

The effect of sex hormones on immune responsiveness per se is well established (e.g., the ability of castration to promote immunocompetence in male mice, particularly cellular immunity). Moreover, there are a number of reports that suggest that deliberate pertubation of hormonal balance during pregnancy may have long-term effects on subsequent offspring (Bakke, Lawrence, Bennett & Robinson 1975). G & H might be interested to note that a case has been made for an X-linked immunoregulatory gene contributing to the overall superior immunological performance of females (Purtilo & Sullivan 1979).

The evidence that in outbred matings, male antigens are more antigenic than female and thus more likely to evoke an immunological attack is not established. The first major evidence that maternal–fetal incompatibility might lead to fetal loss came from analyzing blood groups and not from minor histocompatibility, that is, H-Y antigens. Hirfeld and Zborowski reported a deficiency in the number of expected type A offspring born to matings of mothers of type O and fathers of type A. In contrast, they found the anticipated concordance of expected and observed frequencies when mothers were type A and fathers type O (Mourent, Kopec & Domaniewski-Sobczak 1978). This observation contributed to the later analysis of the etiology of hemolytic disease of the newborn.

In an outbred population the major antigenic disparity evoking immunological rejection phenomena are those of the major histocompatibility complex. Exactly how the fetus, a highly successful allograft, survives is as yet an unsolved problem. Attempts to explain the phenomena range from the notion of the trophoblast as a barrier to allograft rejection; to the now probably abandoned idea of diminished alloantigen expression on trophoblast tissue; to the concept of a role for active suppression of maternal antifetal immunity in fetal graft survival (Beer & Billingham 1976). It is worthy of note that the immunity developed by the mother to a fetal allograft is not typical of the response to an organ allograft in general. In particular, a state of hyporeactivity is the norm; "blocking" rather than "cytotoxic" antibodies are produced and there is general failure to evoke antigraft specific cytotoxic killer cells. Nor should it be forgotten that the fetus itself is a source of a great many agents known to have immunosuppresive potential, for example alpha-feto protein (which gains access to the maternal–fetal circulation), fetal suppressor cells, and the like.

That immune responses to H-Y antigen can occur in pregnancy has been established using inbred groups of experimental animals. In fact it was inferred from early studies by Eichwald and Silmser (1955) on skin grafting in mice. The natural biological function of the product of the H-Y locus on the cell surface, however, seems to be to provide the signal for testicular differentiation from an undifferentiated gonad. Indeed, Wachtel, Hall, Muller and Chaganti (1980) reported that the transformation of the freemartin gonad in bisexual twins in cattle is itself probably due to H-Y antigen secreted by the fetal bull, which passes into the common circulation. I know of no evidence that this particular antigenic system of the developing fetus is expressed to any significant degree in the developing neuronal tissue. This particular argument seems to be a prerequisite if one postulates that neuronal tissue is an important site of the immune system-mediated damage occurring as a result of maternal anti-H-Y immune activity.

What is in fact the evidence that immunoreaction on the part of the female is detrimental; particularly to the male conceptus in parous women? G & H cite older data from Bardawil (1962) suggesting that women with repeated miscarriages are more likely to reject grafts of their husband's skin than that of third-party donors. It is also known that over 20% of all spontaneous abortions are chromosomally normal. Similarly, mixed leukocyte reactivity is allegedly lower in fertile than in infertile couples. However, the relationship of the types of immune response measured in any of these studies to the critical reaction in monitoring in situ the maternal–fetal interaction is unknown. Judging from animal studies, I believe that a reaction of maternal cells to fetal antigens, especially as expressed on the trophoblast, is critical to survival and growth of the fetus, especially for a histoincompatible conceptus. That maternal reactivity produces increased vascularity at the site of implantation is a possible mechanism. Interestingly, there are reports that women with histories of abortion have demonstrable antipaternal, cell-mediated immunity, but lack serum "blocking" antibodies to counter this activity, unlike the serum of women with normal pregnancies. Finally, of note are claims that treating women with a history of spontaneous abortion and with low levels of incompatibility with paternal cellular antigens with a mixture of foreign lymphocytes leads to the birth of healthy children (Komlos & Halbrecht 1979; Taylor & Faulk 1981).

The subject G & H address is unquestionably very complex, dealing with little-understood immunological and neurodevelopmental problems. It has been noted that if all of the immunological factors of maternal antifetal type we can measure were of physiological significance, the mammalian world would not exist (Sio & Beer 1982). G & H's hypothesis certainly seems open to test. Unlike the authors, however, I would anticipate that the explanation for the paradoxical overrepresentation of males in neurodevelopmentally impaired children is not likely to be found in studies which view the female conceptus as "immunologically privileged," but may indeed reflect a complex interplay of neuroendocrine and immune phenomena. (Hirfeld & Zborowski is cited in Beer & Billingham 1976.]

Some implications of the immunoreactive theory for evolution and sex ratios

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Are the sex ratios in human mortality and morbidity always in the direction predicted by the immunoreactive theory? Is the greater "maternal attack" on male than on female an evolutionary accident, or can it serve some selective function? If birth order and H-Y antigen are important to the male-specific maternal attack, then similar sex ratios should be observed in lower species. Humans with greater H-Y antigen levels should have an even greater frequency of the male-typical childhood diseases listed by Gualtieri & Hicks (G & H). This commentary will address these implications along with some problems and alternative explanations.

Sex ratios in human morbidity and mortality. It is not always true that male children suffer more often from various childhood disorders and that when female children have the disorder, they often express a more severe form of that disorder. Throughout life, men typically suffer more often from the life-threatening disorders, whereas women more often suffer from chronically disabling disorders (Gove 1984; Hoyenga & Hoyenga 1979). Even during childhood, in some disorders such as sickle cell disease (Phebus, Gloninger & Maciak 1984) and retardation (Abramowicz & Richardson 1975; Clements, Van Arsdale & Hafer 1974; LaVeck & LaVeck 1977), boys are often more severely affected.

Females with a given disorder may not always have a more

disturbed environment and/or more genetic "load." In Cadoret's work on adoptive children (Cadoret & Cain 1980; Cadoret, Cunningham, Loftus & Edwards 1975; Cunningham, Cadoret, Loftus & Edwards 1975), psychiatric disorders among natural parents were found to be related to antisocial behaviors among boys and to physical disorders among girls. But during adolescence, the genetic load for antisocial behaviors showed no sex differences, and boys were more vulnerable to an unfavorable adoptive environment than girls were.

Dosage compensation more typically refers to X inactivation, which occurs early during fetal development in all mammalian females (Lyon 1972). So even though X-linked disorders appear more often in the genome of females, because of X-inactivation females will often express a less severe form of the disorder than will males who have only the one X (Berg 1979). Examples of this include color blindness (Born, Grützner & Hemminger 1976; Feig & Ropers 1978), disorders of myelination (Skoff & Montgomery 1981), and muscular dystrophy (Gomez, Engel, Dewald & Peterson 1977).

Because of sex differences in brain lateralization, which G & H suggest might be related to "maternal attack," the sexes are also differentially vulnerable to the effects of brain damage. However, contrary to what G & H imply, recent research has found that verbal ability in males is more severely affected by left- than by right-sided lesions, and spatial ability in males is more severely affected by right- than by left-sided lesions. Both types of ability in women are equally impaired by either left- or right-sided lesions (Inglis & Lawson 1981; 1982). Thus, males might be more severely affected in one area, but females might be more often affected by any type of brain damage.

Sex ratios in schizophrenia: Positive versus negative subtypes. Researchers have suggested that schizophrenia might be usefully divided into positive and negative subtypes based on types of symptoms, etiology, and prognosis (see Seidman 1983 for a review). G & H imply that males, having an earlier onset, would dominate the negative subtype, whereas females, with a later onset, would dominate the positive subtype. Males do tend to show not only an earlier onset, but also less affect, a more chronic course, and poorer premorbid functioning (Lewine 1981; Lewine, Burbach & Meltzer 1984). Female schizophrenics show a higher level of a dopamine metabolite in their cerebrospinal fluid (Bowers, Swigar & Jatlow 1983). However, when chronic schizophrenics were divided into positive and negative subtypes independent of gender, there were more males than females in the positive subtype (7 versus 3) and more females than males in the negative subtype (5 versus 3) (Opler, Kay, Rosado & Lindenmayer 1984).

Evolution and variation in sex ratios. Mammalian females may be able to regulate the strength of their maternal attack in order to vary the sex ratio of their offspring according to current conditions. Generally, females produce the most offspring of the gender which has the least competition among its siblings (Charnov 1982).

Did maternal attack evolve as a mechanism to adjust sex ratios? Birds also use H-Y antigen to control gonadal gender (the protein is expressed by females) (Wachtel, Wachtel, Nakamura & Gilmour 1983), and finches can vary the sex ratio of offspring in a clutch of eggs according to the "sexual attractiveness" of the mother and father. For example, attractive females had a greater proportion of female offspring than did unattractive females (Burley 1981). Among rats, stressing the male parent (by confinement prior to fertilization) reduces the sex ratio, whereas stressing the female increases it (Schuster & Schuster 1969). Can the degree of maternal attack be controlled to adjust sex ratios according to differential stress or attractiveness?

Sex ratios of morbidity and mortality in lower animals show some similarity to human sex ratios. The earliest research suggested that females often have a greater life expectancy than males do, though the sex difference was usually attributed to biological effects of sex hormones and to the reproductive roles of males versus females (e.g., intramale combat) (see review in Hoyenga & Hoyenga 1979). In more recent data, similar sex differences in mortality were seen in species as diverse as fruit flies and cats (Bronson 1981; Lints, Bourgois, Delalieuz, Stoll & Lints 1983). Among rats, the body weight of male fetuses is inversely related to the number of fetuses (and thus the number of males and the severity of the maternal attack?) in the ipsilateral uterine horn, but the body weight of females is not affected by the number of other fetuses present (Ward, Karp & Aceto 1977). However, animal data do not always parallel human sex ratios. Among monkeys, the sex ratio of the incidence of hyaline membrane disease is the reverse of the ratio among humans (Truog, Kessler, Palmer, Murphy, Woodrum & Hodson 1981).

Even more important, sex ratios at birth in cattle also show a male preponderance. Furthermore, the sex ratio varies with parity (Gray & Hurt 1979). Just as G & H note for humans, the sex ratio declines with birth order, at least up to the third parity (53.1, 51.42, 48.7). However, contrary to what G & H predict, the sex ratio then again increases for the fourth and fifth parities (54.5, 53.71).

Sex chromosome abnormalities. The level of H-Y antigen is increased over normal levels for the gender in various chromosome abnormalities such as in XYY males (Fraccaro, Mayerovó, Bühler, Gebauer, Gilgenkrantz, Lindsten, Curto, Lo & Ritzén 1982) and in Turner's females (XO mosaics) Müller, Mayerova, Fraccaro, Zuffardi, Mikkelsen & Prader 1983). If H-Y antigen is related to the severity of maternal attack, then XYY males and Turner's females should suffer more often from childhood diseases.

Several of the disorders listed in the target article are reported to have an increased frequency of occurrence in XYY and XO people. These include stuttering, immunological impairments, birth problems, learning disorders, hyperactivity, epilepsy, and schizophrenia (Haberman, Hollingsworth, Falek & Michael 1975; Hakola & Iivanainen 1978; Hier, Atkins & Perlo 1980; Nanko 1979; Ratcliffe, Axworthy & Ginsborg 1979; Ratcliffe, Tierney, Smith & Callan 1981; Robinson, Bender, Borelli, Puck & Salbenblatt 1983; Sørenson & Nielsen 1977). However, sometimes the elevated frequencies of disorders are shared with other chromosome abnormalities that have normal levels of H-Y antigen. For example, increased susceptibility to infection and asthma also occur in XXY males (Ratcliffe, Axworthy & Ginsborg 1979).

Alternative explanations and problems. G & H's support of their theory is marred by some logical problems. For example, when they suggest that "antigenic differences between zygote and mother are thought to confer an implantation advantage," the evidence cited in that paragraph has to do with sex ratios at conception and at birth. A very high sex ratio at conception has little to do with any implantation advantage of males, and the decline in the sex ratio from conception to birth does not suggest that males have any great advantage. G & H's hypothesis can explain why toxemia increases with parity, especially with prior males, but why are primiparas at the greatest risk? G & H rule out psychosocial explanations for negative parity effects by showing that traits such as height also show these effects – even though height is also sensitive to environmental variables.

A critical problem faced by G & H's theory is the greater frequency of immune disorders in females than in males. For example, systemic lupus erythematosis affects ten times as many females as males, and XXY males are more susceptible than are XY males; similar sex differences are seen among mice (Hoyenga & Hoyenga 1979; Siiteri, Jones, Roubinian & Talal 1980).

Factors other than maternal attack can affect sex ratios in childhood disorders. Maternal age, independent of parity, may affect sex ratios (Rostron & James 1977), and the incidence of breast feeding also covaries with parity (Broad & Duganzich 1983). Sex hormone levels at birth vary with parity (Maccoby,

Doering, Jacklin & Kraemer 1979), and at least some of the sex differences in childhood diseases have been attributed to sex differences in prenatal sex hormone levels (Arena & Smith 1978). Geschwind and Behan (1982) attribute the greater frequency of learning disorders, allergies, and autoimmune disorders in left- than in right-handed males to a higher level of fetal testosterone levels.

Thus, G & H's theory can explain some data not presented in their paper, but there are also some areas in which the theory does not successfully predict the observed sex ratios. Nevertheless, more research guided by the theory's predictions would certainly seem productive, regardless of the outcome.

The alleged antecedent brother effect in sex ratio

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Gualtieri & Hicks (G & H) write that their hypothesis is "borrowed from studies of the sex ratio." They frankly acknowledge that "there is disagreement surrounding at least some of the facts upon which the theory is based. . . . Not every investigator has agreed that . . . sex ratio decreases with antecedent brothers (McLaren 1962)."

In this commentary I urge that indeed the evidence points strongly in the opposite direction, that sex ratio (proportion of boys) *increases* with antecedent brothers (though not as an immediate consequence of them).

The literature. It must be noted that the types of variation to be discussed are small. So, bearing in mind the unanimity of the two largest samples (Ben-Porath & Welch 1976; Malinvaud 1955), nonsignificant data from small samples cannot be regarded as informative. Malinvaud's data (which have since been reprinted in [James 1975]) were on the sexes of nearly four million French births from 1946 to 1950, classified simultaneously by the numbers of prior brothers and prior sisters. Ben-Porath and Welch (1976) offered data from nearly 150,000 U.S. white women in the 1 in 100 Public Use Sample of the U.S. 1970 Census.

In both sets of data, the probability of a male child increases with the number of prior male children and decreases with the number of prior female children. The effect is greater in the U.S. data than in the French data, but the agreement between these studies is striking.

There are two points. First, G & H seem almost certainly wrong in their interpretation of the data here (although that does not necessarily falsify their hypothesis). Second, one wants to know the source of the variation shown in these two large samples.

The sorts of variation that could occur in principle are Poisson variation (variation within couples of p, the probability of a male child), Lexis variation (variation between couples of p), and Markov variation (influence of the sex of one pregnancy upon the sex[es] of subsequent one[s]) or any combination of these three types of variation [Edwards 1960]). Probably no final conclusion about the nature of the observed variation can be reached by statistical means in the absence of a very large sample of data giving the frequencies of sibships by the permutations of the sexes of their members (Crouchley, Davies & Pickles 1984; Pickles, Crouchley & Davies 1982).

However, if statistical manipulation cannot identify the nature of the variation in the data of Malinvaud and of Ben-Porath and Welch, other forms of argument might suggest it. In Western societies, it has usually been found that a large proportion of parents express a preference for families containing one or more representatives of each sex (Adelman & Rosenzweig 1978; Clare & Kiser 1951; Markle & Nam 1971; Sloane & Lee 1983). One effect of this is that parents with n existing children are rather more likely to have another child if the n existing children are all of the same sex than if they contain both sexes. This has the effect of diminishing the variance of the frequency distributions of small completed families of size n with 0, 2, 2 . . . n boys. However, the variance of such distributions is usually greater than binomial variance as, for example, in the data examined by Edwards (1958). Hence there is either Lexis variation or Markov variation, or both. Now the sort of Markov variation that could, in principle, be responsible would – from a biological standpoint – be rather odd. If a couple had a boy, that would make them more likely to have further boys; and if they had a girl, that would make them more likely to have further girls. Any tendency of this sort – if it exists – must be rather small; Greenberg and White (1967) could find no relationship between the sexes of consecutive sibs in more than 100,000 sibships. At any rate, if it is accepted that such variation is either nonexistent or minimal, the inference is that there is Lexis variation.

The point of this excursus may now become clear. I have noted that if maternal gonadotrophin levels at the time of conception were partially responsible for the sex of the infant (high levels being associated with females), then almost all of the observed variation in the human sex ratio (including the Lexis variation suggested above) would be explained (W. H. James 1980a). Moreover, pregnancies following ovulation induced by gonadotrophin or clomiphene do indeed contain a significantly high proportion of females (W. H. James 1980b). So it seems that hormones play a part in the determination of sex. Accordingly, one may wonder whether hormone imbalance – rather than antigenic action – is responsible for some of the selective male affliction addressed by the authors. The point is general because a large number of congenital malformations are also disproportionately associated with one sex or the other (Arena & Smith 1978); the possibility that hormone imbalance is responsible here too seems not implausible.

Breland's (1974) data. I now want to explain why I think the support given by the data of Breland (1974) to the antecedent brother hypothesis (in sex ratio) is illusory. G & H specify the sex ratio of nth children when their $(n - 1)$ predecessors were all of the same sex in families of exactly size n. Now as remarked above, there is good evidence that parents want families containing representatives of both sexes. So one would expect that if the first $(n - 1)$ children are all the same sex, then in families of exactly size n, the nth child would be of the sex opposite to that of its predecessors. This would reflect not a biological fact, but a sociological one, namely, that a family in which all the first n children were of the same sex is more likely to have another child (and thus eliminate itself from the category of family size n) than a family in which the first $(n - 1)$ children were of one sex and the nth child was of the other sex.

Accordingly, I suggest that if Breland's data were analysed without the restriction described above, they would show variation of the sort identified in the data of Malinvaud (1955) and Ben-Porath and Welch (1976).

Immunoreactive theory and the genetics of mental ability

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The variety of evidence presented by Gualtieri & Hicks (G & H) consistent with the immunoreactive theory (IMRT) is impressive and convincing, even if one acknowledges the many difficulties in ruling out possible alternative hypotheses that may accommodate many of the phenomena on which the IMRT

has been brought to bear. I suspect that G & H have exposed what may well turn out to be merely the tip of the iceberg of all of the implications and ramifications of the IMRT in general for the understanding of human variation, of which the sex difference in frequency of developmental disorders is only one aspect.

Implications of IMRT in general (not just the heightened antigenicity of the male fetus) for human behavioral genetics, and particularly for the genetics of mental development, seem worth investigating. Two problematic topics in the genetics of intelligence immediately come to mind: (1) the problem of accounting for all of the nongenetic variance in general mental ability, as indexed by IQ, and (2) the problem of the large differences between certain ethnic groups in the rate of what has been termed "reproductive casualty" and its associated developmental behavioral disorders, including mental retardation.

One of the problems in the study of the broad heritability (h^2) of intelligence is the difficulty in accounting for all of the nonerror variance in IQ. The best present estimates of h^2, based on various kinship correlations fitted to polygenic models, fall mostly in the range of .40 to .70, that is, some 40 to 70% of the IQ variance is attributable to genetic factors (Scarr & Carter-Saltzman 1982). Theoretically, then, the nongenetic, or environmental, variance should be $1 - h^2$, or between .30 and .60. But the commonly measured environmental variables – socioeconomic status, styles of child-rearing, and the like – repeatedly fail to account for even as much as 30% of the nongenetic variance. Much more telling is the fact that unrelated children reared together in adoptive homes show such very low correlations for IQ (see Scarr & Carter-Saltzman, Table 13.28) as to make it impossible to account for at most a small percentage – perhaps even less than 10% – of the total IQ variance in terms of differences in family environment. Yet the correlations between full siblings reared apart, and between other kinships, are of a magnitude such that the broad heritability (i.e., proportion of the total variance attributable to genetic factors) of IQ is not much more than about .50. In a review of recent studies on the heritability of intelligence, Plomin and DeFries (1980) state, "we know of no specific environmental influences nor combinations of them that account for as much as 10 percent of the variance in IQ" (p. 21). Yet Plomin and DeFries attribute only about 50% of the IQ variance to genetic factors. What, then, is the source of the remaining variance?

A closely related anomaly in this field is the fact that monozygotic twins reared apart show an IQ correlation of close to .70, which is a direct estimate of h^2, but it is a higher estimate of h^2 than the h^2 derived from other kinship correlations. The difference is not explainable in terms of the possibly correlated environments of the separated MZ twins, and the basis of the discrepancy has remained obscure.

The IMRT may provide at least a partial explanation of these phenomena – phenomena which so far have seemed puzzling. The usual answers, in terms of genetic theory, have invoked the mechanisms of epistasis (interactions between genes at different chromosomal loci) and genotype–environment interaction. But it has been difficult to get an empirical handle on these hypothesized effects. The IMRT may afford one handle, albeit a strictly biological one. Assuming the development of the brain is affected, varying degrees of antigen incompatibility between mother and fetus would tend to reduce the size of all kinship correlations except those of MZ twins, relative to the correlations expected on the basis of polygenic theory. Because MZ twins share exactly the same antigens, they would have the same degree of mother–fetus incompatibility. This effect should constitute, strictly speaking, an environmental enhancement of the degree of phenotypic similarity between MZ twins relative to the phenotypic similarity of other kinships.

Probably the most feasible test of this hypothesis could be made by studying a large number of sibships with respect to antigens such as the ABO, Rh, and HLA systems, as well as H-Y in male siblings. Sibling pairs would be categorized in terms of degree of similarity in a number of antigens and IQ correlations between siblings within each category would be compared. In addition, children's IQs would be looked at as a function of degree of mother–child antigenic compatibility and as a function of father–mother antigenic similarity. Statistically significant effects would definitely implicate the IMRT as an explanatory factor in this domain. Such information could ensure the IMRT explanation for the slight but significant negative effects of parity on mental development.

Another poorly understood phenomenon to which the IMRT would seem to be relevant is the quite different rates of "reproductive casualty" in black, white, and Asian Americans. The rates of fetal loss and of various developmental disabilities that affect mental development and scholastic performance are twice as high in the black American population as in the white and Asian populations, a difference that cannot be accounted for in terms of socioeconomic status. Blacks in general show higher rates for various types of reproductive casualty than the lower fifth of the white population in socioeconomic status. On the other hand, Jews and Asians living in poverty show lower rates than the middle-class white population (see Jensen 1973, chap. 19, for a review of evidence on ethnic differences in reproductive casualty). In addition, consider the following: (1) The sex ratio for live births is lowest in the black and highest in the Asian population, with the white population intermediate; these sex ratios have not changed in the U.S. in the past 50 years. (2) There is considerable evidence that the sex difference (favoring females) in mental abilities is greater among the black than among the white population (Jensen 1971). (3) The American black population is ethnically hybrid; on average, about 20% of the genes of black persons in America come from European–Caucasian ancestors (Reed 1969).

It is a plausible hypothesis that an ethnically hybrid population would be more heterogeneous with respect to antigens and would show a higher rate of mother–fetus antigenic incompatibility than would a more homogeneous population in which natural selection had minimized those specific antigenic factors which have the potential for producing the most deleterious developmental effects of antigenic incompatibility. Bresler (1970) has found that, even within the white population of the northeastern United States, the rate of fetal loss is directly related to the degree of ancestral heterogeneity of the fetus. Fetal loss was found to increase cumulatively by approximately 2.5 to 3% with each additional country of birth in the great-grandparental generation. Increased fetal loss was also found to be related to greater distances between the birth places of the mates within the grandparental generation. Conversely, low fetal loss is encountered with a small number of countries in the background and short distances between the birthplaces of the parents. There is no scientifically established explanation for these findings, but a hypothesis involving the IMRT obviously suggests itself and seems plausible in terms of genetic and evolutionary theory. The possible implications of the IMRT for understanding these various phenomena, after further theoretical consideration, may warrant empirical investigation.

A reproductive immunologist's view on the role of H-Y antigen in neurological disorders

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As a reproductive immunologist, I am very pleased to see that our subject has succeeded in attracting the interest of behavioral

scientists like Gualtieri & Hicks (G & H). Their immunoreactive theory, propounded to explain the selective male affliction with neuropathic disorders, is certainly most attractive, but I wonder whether it is somewhat premature on evidence presently available. The fundamental premise of the theory – that the male fetus, because of its additional H-Y antigen, is likely to be more immunogenic to the mother than an equivalent female fetus – is not in doubt. But it is debatable whether or not this is actually reflected in any discernible effects on human reproductive performance. G & H have amassed a great deal of evidence from studies on the sex ratio at birth which may be interpreted as indicating that the H-Y antigen, acting either alone or synergistically with some other stronger histocompatibility systems (that is ABO or HLA), can lead to a greater degree of maternal sensitization. However, as G & H have themselves admitted, there is a substantial degree of disagreement surrounding some of the observations on which their theory is based. Several investigators in this field do not believe that the H-Y antigen has any effects on the sex ratio at all. Indeed, some data may even point the other way, that is, that mothers become increasingly tolerant rather than sensitized to H-Y antigen with successive pregnancies. Thus, at the present moment it would be wise to admit that we do not know how the H-Y antigen behaves during mammalian reproduction.

Apart from the particular aspect of H-Y, the whole question of immunoregulation during pregnancy is in the process of reevaluation, so that G & H's concept that "pregnancy is an immunological phenomenon characterized by a state of maternal tolerance" can no longer be taken for granted. Analyses of the HLA phenotypes of women who are habitual aborters have yielded the paradoxical finding that they tend to share more HLA antigens with their husbands than women with normal pregnancies; this implies that too great a degree of histocompatibility rather than histoincompatibility between fetus and mother may be detrimental to fetal survival. Also, the discovery of "blocking" (nondestructive) antibodies in normal pregnancy sera but not in the sera of women with abortions has led to the hypothesis that the immune response of pregnant females is not simply lower or suppressed, rather, it is actually different from the response mounted by nonpregnant individuals, and this special response is in some way important for successful gestation. In other words, immunoregulation during pregnancy is not just a passive phenomenon geared towards producing a state of maternal nonreactivity but an active phenomenon, with the mother producing the kind of protective response mandatory for fetal survival against her allogeneic conceptus. This concept has a certain intellectual appeal in that it offers a possible mechanism whereby reproduction helps in maintaining a degree of antigenic diversity within the population. If this is indeed what happens during pregnancy, then it would be difficult to see how selection against H-Y can be fitted into this immunological framework.

Even if it were to be accepted that the H-Y antigen does lead to "selective male affliction," it is unclear how it could result in neuropathic disorders. G & H admit that "the precise nature of the immunologic reaction cannot be described," but it would be nice to have some kind of working hypothesis to strengthen their argument. I myself cannot offer any. It is easy to visualize the possible synergistic action between H-Y and another alloantigen like Rhesus to produce a distortion of the sex ratio in a disease such as erythroblastosis fetalis, but how incompatibility for H-Y can lead to selective destruction of the nervous system is more problematic. Perhaps the neuropathy is mediated by the deposition of immune complexes, in which case the patients with such disorders would also have other manifestations of this type of hypersensitivity.

In conclusion, I would like to stress that I am very much on the side of Gualtieri and Hicks in thinking that the H-Y antigen could theoretically have some effect on the fetal–maternal interaction. It is just that, with the evidence available at present, I am not at all certain what this effect is in practice. This may be because, as the authors have pointed out, "the phenomenon may be robust but at the same time relatively weak and difficult to discern." It remains to be seen whether or not the immunoreactive theory proves to be correct. It is such an elegant concept that it deserves to succeed.

Selective immunoreaction as an adaptive trait

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Gualtieri & Hicks (G & H) provide us with a most interesting data base aligned with a cogent, reasonable theory that, in turn, helps make sense of the patterns within that data base. Their efforts lend themselves congenially to complementary data and alternative theories from diverse disciplines.

Without delving into the fine points of G & H's work, let me attempt to fit the immunoreactive theory (IMRT) of selective male affliction into a phylogenetic or Darwinian perspective. First, two levels of analysis should be distinguished: one that G & H use and a second, presented here. The two levels of analysis are a "proximate causation" analysis and an "ultimate causation" analysis.

A proximate causation analysis attempts to isolate and understand the conditions and mechanisms of an organism's environment, whether internal or external, that trigger the responses of that organism (Immelmann, Barlow, Petrinovich & Main 1981; Wilson 1975). In other words, an analysis of proximate causation addresses the question of *how* – how did the behavior of an organism become organized and initiated. G & H's IMRT is an example of a proximate causation analysis.

A separate yet supplementary type of inquiry investigates the ultimate causation of a behavior pattern. An analysis of ultimate causation addresses the conditions or mechanisms in a species' history which render some behavioral traits adaptive and others nonadaptive (Immelmann et al. 1981; Wilson 1975). The adaptive traits become progressively overrepresented in the population and become characteristic or typical of the species. Framed differently, an ultimate causation analysis asks not *how* but *why*. Why do the behaviors in question exist to be emitted at all? I would like to look at the IMRT from this perspective. Why would the selective immunoreaction by gender exist at all?

Briefly, the IMRT suggests that humans have developed the following mosaic: There is a bias on the part of women, especially primiparous women, to conceive and to bear more sons than daughters. For subsequent births, sons rather than daughters are more at developmental risk and the sex ratio progressively decreases. In other words, there is an initial bias toward healthy, viable sons for firstborn and thereafter a progressive bias away from sons and towards daughters.

The data presented by G & H are diverse, and, given the intricacy of human biology, are fairly unambiguous. The question emerges: Why this pattern?

To help address this question, let us look at the kind of being *Homo sapiens* is:

1. K-selected organisms (few offspring per mother, each receiving extensive, intensive parental investment) (Gould 1977).

2. Gender dimorphic with a strong division of labor by gender (Whyte 1978).

3. Mammals in which the female has a relatively heavier

investment in each offspring than the male (Charnov 1982; Clutton-Brock & Albon 1982; Fisher 1930; Trivers 1972; 1974; Trivers & Willard 1973).

4. A "marriage" system (not coterminous with our sexual system) which is somewhere between monogamous and polygynous (van den Berghe 1979), but definitely not polyandrous (Divale & Harris 1976).

5. Compared to females, males have the potential to be much more variable in the number of offspring they may sire (Dawkins 1976).

6. Hypergamy (marrying "up" in rank or status) is more a female prerogative than a male prerogative (Dickemann 1979; cf. Altmann 1980). [See also BBS multiple book review of Symons: *The Evolution of Human Sexuality*, *BBS* 3(2) 1980.]

Consequently, if the female is confident of resources (for herself and thereby for her children) and secure in her position within her immediate social hierarchy, she would be expected to have a bias toward an initial son. He is expensive, but a good gamble for many grandchildren. If unsure of resources or tenuous in her social position, she would be expected to have a bias away from a son toward a daughter. Daughters are more hypergamous than sons and they are good candidates for some grandchildren (more than zero); yet a daughter does not have nearly as much potential for many grandchildren as does an attractive, well provisioned male (Mackey and Coney, unpublished).

Socially powerful males – with access to resources and to high position – can draw from a large pool of potential mates. Similarly, a low-ranking female can draw upon an equally large pool of potential mates. Because low-ranking males tend not to marry up a social hierarchy and high-ranking females tend not to marry down a social hierarchy, they have restricted categories of mates.

As a result of these conditions, confident females should be expected to have a bias toward firstborn sons – sons who would be a good bet to sire numerous grandchildren. To avoid dilution of power, influence and resources, successive sons in close proximity of birthing intervals would be avoided. Since males and females follow different, if complementary reproductive strategies, a son, followed by a daughter, would not involve direct competition for the same type or amount of resources. Two sons within a close birthing interval would compete for the same type and amount of resources to the probable detriment of both in terms of attractiveness to females.

Low-ranking, uncertain females should be expected to have a bias toward daughters. Their lowborn sons would be poor candidates for attracting mates. Their daughters would be good candidates for some grandchildren – but not too many.

Accordingly, a mechanism that was insensitive to successive daughters but sensitive to sibling gender following the birth of a son would be expected to arise in the species' phylogeny. G & H present just such a mechanism: selective immunoreaction.

At this point the proximate causation perspective (how) conjoins rather well with the ultimate causation perspective (why). Over geological time, those women bearing successive sons within close birthing intervals have reaped progressively fewer grandchildren than those women with either successive daughters or with a son followed by a daughter.

The placental and uterine mechanisms affecting and being affected by the fetal–maternal biochemistry have been positively selected for a type of immunoreaction which has been biased against successive sons in close birth intervals. The alleles subserving such mechanisms have been an evolutionary success and are preeminent over alternate alleles generating alternate mechanisms. So in the twentieth century, we find patterns of gender bias within our species as described by Gualtieri & Hicks that are neither random nor capricious. They are structured and represent an adaptive response by a social species to their social environment.

Eve first, then Adam

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Selective male affliction is but one manifestation of the ubiquitous principle of the male's greater vulnerability. This principle is evident in embryogenesis insofar as the differentiation of Eve takes precedence over that of Adam. The embryo cannot differentiate as a male if it has only a Y chromosome, but no X, because it is nonviable. By contrast, with an X but no Y (Turner's syndrome) it is able to differentiate as a morphologic female, albeit agonadal, with or without one or more of an array of accompanying somatic deformities, and the possibility of specific nonverbal disability.

For the embryonic and fetal differentiation of the male it is imperative that, under the governance of H-Y antigen, the gonads differentiate as testes, and that they secrete fetal testicular hormones: mullerian inhibiting hormone to vestigiate the mullerian ducts, and testosterone (including dihydrotestosterone) to differentiate the male genitalia. If the testes fail to secrete their hormones, then feminine differentiation takes precedence over male. The same thing also happens if the body is unable to utilize its testicular secretions, which is precisely what happens in the androgen-insensitivity syndrome, also known as testicular feminization.

The absolute dependence of the embryo on testicular hormones if it is to develop as a male is very well substantiated in both the animal experimental literature and the clinical literature. It attests to the general principle that to differentiate a male, nature requires that something be added. The stage thereby is set for error: either too much, not enough, or the wrong component may be added. Herein lies the greater vulnerability of the male, which may be traced across the life span.

The source of the error that induces the greater vulnerability of the male does not need to be only hormonal. Some other intervening factor may interfere with either the synthesis, secretion, or utilization of hormones. Prenatally, the origin of such an intervening factor may be within the fetus itself, fetoprotein, for example, or it may be within the mother. It may be something that the mother has ingested, breathed, or had enter her bloodstream. It may be an infectious agent – and it may be one for which the preferred host within the fetus is a male-hormone producing cell, with which it enters into symbiosis. The interfering factor may also be the product of a maternal immune reaction, which may be male-hormone facilitated.

Although all of the foregoing supplements, rather than vitiates Gualtieri & Hicks's immunoreactive theory of selective male affliction, it also shows that G & H become committed to immunology too soon after targeting it as the source of their theory. Theory building is analogous to differential diagnosis. It requires that one seek out and list as many alternative hypotheses as possible. There is no other way to guarantee against becoming too restricted by a single hypothesis.

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Male-specific antigens and HLA phenotypes

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Although couched in jargon unfamiliar to readers from non-neurobiological disciplines such as myself, the essentials of the

article by Gualtieri & Hicks (G & H) were clearly understandable. As G & H are well aware of the evidence contrary to the favorable data they cite, my comments will be based on the assumption that their theory is essentially correct.

Genetic differences that separate human males from females reside solely in the hemizygocity of X-linked genes in males and the male-specific occurrence of the Y-chromosome. As far as fetomaternal compatibility is concerned, however, the X-chromosome does not enter the picture, unless one invokes a newly sustained X-linked mutation, for the single X-chromosome of a son is invariably derived from his mother. Thus, the mother should always be compatible with her sons with regard to all X-linked immunogens.

As to the Y-linked immunogens (plasma membrane antigens). a part of the Y-chromosome is homologous to the X. Accordingly, human 12E7 antigen is specified by a gene on the short arm of the Y and by its allele located at the tip of the short arm of the X (Goodfellow, Banting, Sheer, Ropers, Caine, Ferguson-Smith, Povey & Voss 1983). The male-specificity of such antigens depends upon polymorphism and a frequency of crossing-over involving the X-linked and Y-linked alleles. With regard to H-Y antigen, there is a debate as to whether or not serologically detected H-Y antigen and H-Y transplantation antigen are one and the same (Silvers, Gasser & Eicher 1982). Nevertheless, major histocompatibility antigen (MHC) dependence of the cell-mediated immune response (and probably also that of the humoral immune response to H-Y antigen) should certainly be pointed out. In the mouse, in order to evoke the specific cytotoxic T-cell response from the female, H-Y antigen on the male target-cell plasma membrane has to be associated with H-2D^b antigen (Matsunaga & Simpson 1978). In humans even humoral anti-H-Y antibody appears to be HLA dependent. One such antibody is able to lyse male cells only if HLA-A2 antigen was present with H-Y antigen (Goulmy, Bradley, Van Leeuwen, Lansberg, Munro, Termijtelen & van Rood 1977).

Needless to say, H-Y antigen is an extremely weak immunogen; thus, the anti-H-Y response can be observed only if the donor and the recipient (a male fetus and his mother) are MHC (HLA) compatible, which occurs but seldom in human matings. Yet, one of the consequences of altered self-recognition by the cell-mediated immune system (Zinkernagel & Doherty 1974) is rather frequent misidentification of altered self MHC antigens as allogeneic MHC antigens and vice versa. In the mouse, for example, the receptor of female cytotoxic T-cells raised against H-Y + H-2D^b antigen complex of male cells may also react against H-2D^d antigen, indiscriminately lysing male and female target cells bearing H-2D^d antigen (von Boehmer, Hengartner, Nablolz, Lernhardt, Schreier & Haas 1979). What is relevant to G & H's immunoreactive theory is the converse situation. Cytotoxic T-cell receptors and antibodies of a mother bearing HLA-A2 antigen raised against one or the other paternally derived allo-HLA antigen of previous fetuses may react against H-Y + HLA-A2 antigen complex of a subsequent male fetus (Ohno & Stapleton 1981). The hypothesis predicts HLA association in the types of selective male affliction discussed.

The Y chromosome message

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Gualtieri & Hicks (G & H) generously refer to my writings and those of my colleagues. Perhaps the best way to explain the points of view that we adopted is to recapitulate them. We opened by quoting Sir Peter Medawar (1969), whose brilliant aphorism ended the nature–nurture controversy: "Heredity proposes and development disposes."

Tersely stated, the theory that Taylor and I (Ounsted and Taylor 1972) set out reads thus:

1. The differential ontogenesis of the two sexes depends wholly on the Y chromosome.
2. The Y chromosome transmits no significant information specific to itself.
3. Transcription of the expressed genomic information in males occurs at a slower ontogenetic pace.
4. The operation of the Y chromosome allows more genomic information to be phenotypically transcribed from any given genome.

We thought there were seven sets of questions one might properly ask in relation to the Y chromosome message. These are:

1. What is the formal nature of the message? What kind of laws does it impose on development? What systems are involved?
2. At what point in development is the message delivered? Is it fundamental to the development of the organism? Can the organism survive at all without it? At what stage in development is the presence or absence of the genomic message phenotypically recognisable?
3. Over what period in development does the genetic message endure? Does its phenotypic expression endure for life or is it transient?
4. How is the message translated developmentally? What physiological steps lie between the genetic instruction and its expression?
5. Which contingencies limit, and which promote the expression of a particular message? Do the contingencies reside in the genome or are they dependent upon developmental experience?
6. How frequently and with what consequences does the genetic order go wrong? Is it possible that certain instructions appropriate in one situation are disastrous in another?
7. How does the genetic message relate to the evolution of the particular species? What advantages does it confer? What consequences has it for the ecology of each creature? Are there advantages to the expression of phenotypic variation in specific ecologies that depend upon a single genetic instruction?

Since we formulated these ideas and put some of them to the test a good deal more evidence has come forward.

It seems to me that Gualtieri & Hicks have not taken the full measure of Sir Peter Medawar's dictum. His up-to-date book *Pluto's Republic* (1982) makes most useful reading for those concerned with biological theories.

Immunoreactive theory: A conceptually narrow theory reflecting androcentric bias

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Gualtieri & Hicks (G & H) propose an intriguing but speculative theory to explain the greater affliction of males with the neurodevelopmental and psychiatric disorders of childhood. Although immune reactions are clearly involved in the development of such disorders, we find the theory conceptually narrow because of both the limited focus on biological mechanisms and the sole focus on male affliction. In addition, the evidence for the theory is often weak and based on selective review or interpretation of prior research.

G & H assume that if biological mechanisms are found to play some role in the development of specific disorders, psychosocial factors are excluded. Such a view of development is naive and not supported by substantial evidence (Lerner 1984; Petersen 1980); most often, psychosocial and biological influences act in concert. For example, stress stimulates changes in an indi-

vidual's immune system (Palmblad 1981); therefore, immunological responses may not be the "cause" of difficulties but rather represent the biological mechanism through which psychosocial factors operate.

The biased focus on biological explanation by G & H is exemplified in their assumption that parity effects seen in data on the National Merit Scholarship Qualifying Test (Figure 3) are explained by cumulative immunological processes in successive pregnancies. First, the *n*'s, r^2's, and *B*'s given for this figure do not make sense (for example, the *n*'s for the two lines are close to but not identical to the total). Second, although there has been much less investigation of psychosocial effects relative to the large body of research examining biological effects on cognition (Petersen 1980), there is evidence for several processes: more intense brother–brother competition and aggression and less brother–brother tutoring and help, to identify just two (Cicirelli 1972; 1973; 1976). G & H's selective bias for biologisms limits the understanding of developmental process.

In addition, an androcentric perspective guides the use of phrases like "uterine inadequacy" and "maternal insufficiency." Whereas G & H note that the fetus itself evokes an "untoward uterine environment," the process is nevertheless labeled as a "maternal immune attack," rather than with more neutral terms such as "maternal immune response." Indeed, the same data could be used to "blame the fetus" and argue for "male fetal pathogenicity." Until there is more compelling evidence one way or the other, however, the mother–fetus *system* should be the focus of investigation rather than presuming that problems may be attributed to the mother.

Even a focus on the mother–fetus system neglects another crucial element in reproduction: the father. Constitutionally "inadequate" mothers (i.e., chronic miscarriers) were four times as likely to reject skin grafts from their husbands compared to those from unrelated sources ("Brain as the Target of Immune Attack" section). Yet the contribution of suitable paternal genetic factors is nowhere integrated into a theory which is otherwise focused on blaming the mother. Complications of pregnancy and delivery constitute a danger to the mother as well as the fetus.

In the broadest perspective, one might ask why females should tolerate the risks associated with producing males. Within evolutionary theory, these issues have been addressed without resolution. The evidence on sex ratios of births among various species is mixed (Clutton-Brock & Albon 1982). Comparative studies do, however, show us sources of individual variation that may be useful in considering this proposal. For example, among baboons observed in the wild, the sex ratio of offspring produced by individual females depends on the mother's social status (Altmann 1980). Dominant females tend to produce daughters, whereas subordinate females produce more sons, showing that in this matrilineal society, sex ratios reflect the effects of the inheritance of social rank by females. In this system, then, biology serves psychosocial functions. (For a review, see Meikle, Tilford & Vessey 1984.) We might well inquire about possible third factors that could cause a relationship between maternal immune responsiveness (presumably partly mediated by social stress) and sex of offspring among humans. We know that sex ratios vary across human cultures and socioeconomic classes (Parkes 1926; Teitelbaum 1970; 1972). It is difficult, however, to obtain accurate estimates of the sex ratio in some Asian cultures, where infant mortality may be 50 times higher than in the U.S. Actual births of female infants are likely to go completely unreported, masking the rate of female infanticide, and invalidating estimates of the sex ratio (Barclay, Coale, Trussel & Stoto 1976). Moreover, in many cultures, accidental mortality and homicide preferentially affect female infants, especially in the first few days of life (World Health Organization 1983).

Finally, the empirical base for the immunoreactive theory is less strong than G & H claim. Their argument is diminished by several instances of incorrect assertion of significance in data presented as well as misattributions of evidence from other research. Perhaps the instances that we have noted are the only ones in the target article. We are concerned, however, that they may equally represent just a sample of more such errors throughout the article.

For example, the theory of maternal immune response is derived from studies of the sex ratio, especially "antecedent brother" effects on sex ratios. On our analysis however, the data presented by G & H show no such effect. (In Table 3, complications of pregnancy are equally predicted by antecedent sisters as by antecedent brothers ($\chi^2 = .82$, $p > .05$).) Furthermore, G & H cite one source which disputes the decrease in sex ratio with antecedent brothers (McLaren 1962). There are other uncited sources that dispute this proposal (Edwards 1966; Greenberg & White 1967). Furthermore, the evidence from other species does not support G & H's contention (Clutton-Brock, Albon & Guinness 1982). Their proposal that the infertile period is longer after the birth of males is not supported in the considerable literature on other species (Clutton-Brock & Albon 1982). Finally, the finding that sex ratios decline or increase, with all male or female antecedent siblings, respectively, simply reflects the differential odds of these combinations.

An example of misattribution may be seen in G & H's claim that "the balance among androgenic, progestational and estrogenic hormones is known to affect fetal brain development." They attribute this finding to Maccoby, Doering, Jacklin, and Kramer (1979), a very interesting study which presents results describing relationships of sex hormone concentrations in umbilical cord blood to sex and birth order of infants; that article does not, however, present data pertaining to fetal brain development.

It is sensible to build a theory based on the possibility that "males and females come to be afflicted by different pathways," especially in a theoretical context that assumes different life histories for each gender. By this view, we should not view males as "selectively afflicted" relative to females, but rather as on a different trajectory, with different forces operating in the course of normal male development. However, the view of the two paths of gender development need not assume antagonism between female and male. Each can be seen as contributing to a cooperative effort of reproduction, in biological, social and cultural evolution (Hartung 1981; Wrangham 1982).

Although we have no doubt that immune reactions play a role in fetal development, the theory proposed is too narrow in its strictly biological focus and androcentric in its sole attention to male affliction and blame placed on the mother. A model that considers the complex interactions among the biological, psychological, and social levels of influence is more explanatory and accurate.

Immunoreactive theory and pathological left-handedness

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Gualtieri & Hicks (G & H) provide some convincing evidence that pre- and perinatal complications are more frequent in males than in females and that these complications can have a lasting neurodevelopmental effect. As part of the evidence to support their immunoreactive theory they cite the work of Geschwind and Behan (1982), in which it was found that left handers were more likely to have autoimmune disorders than were right handers.

It should be noted, however, that Geschwind and Behan attribute the reported increase in autoimmune disorders in left handers to excess production of testosterone during fetal development. Their hypothesis is that testosterone, which is usually

found in greater amounts in male fetuses, slows the growth of the left hemisphere (which they claim can account for the increased incidence of left-handedness often reported in males) and also has a suppressive effect on the thymus gland (an important part of the immune system). Therefore, Geschwind and Behan are invoking a hormonal cause for the increase in autoimmune disorders in left handers rather than an immunoreactive one as do G & H. It is unfortunate that Geschwind and Behan did not report the data for each sex separately. This would have made it possible to determine whether or not the immunoreactive theory IMRT is correct in predicting that left-handed males would be more prone than left-handed females to having the immune disorders.

G & H state that Geschwind and Behan fail to distinguish between familial and pathological sinistrals, and go on to add that "The latter would be expected to exhibit the trait more strongly." It would appear from this that G & H are equating pathological left-handedness with nonfamilial sinistrality (FS−). In my opinion this is a premature and possibly wrong conclusion. For example, although Bradshaw and Taylor (1979) reported that birth complications were more likely in FS− left handers than in FS+ (positive history of familial sinistrality) left handers, Bakan, Dibb, and Reed (1973) found just the opposite. In addition, Searleman, Tsao, and Balzer (1980) examined three different populations of students (high school, community college, and private university) and although they reported that FS was not strongly related to reported birth stress, what little evidence was found of a relationship was confined to the FS+ group. Furthermore, if FS− were synonymous with pathological left-handedness, one might expect to find evidence that individuals with that trait were at a cognitive disadvantage when compared with their FS+ counterparts. However, there is a growing body of evidence that it is the FS+ left handers that are more likely to do worse on cognitive ability–intelligence tests (Bradshaw, Nettleton & Taylor 1981; Briggs, Nebes & Kinsbourne 1976; Burnett, Lane & Dratt 1982; Searleman, Herrmann & Coventry 1984).

There is evidence from the lateral preference literature consistent with the IMRT. For example, specific birth stressors (e.g., premature birth or low birth weight) are correlated with shifts away from the dextral norm (Coren, Searleman & Porac 1982). These shifts are found for all four lateral preferences (hand, foot, eye, and ear) and are particularly evident for males. In fact, a major theme of a paper reviewing the evidence that pre- and perinatal complications can result in a shift from right-sidedness to left-sidedness is that males are much more likely to show this shift than are females (Searleman, Porac & Coren, in preparation). This certainly supports the selective male affliction phenomenon at the core of the IMRT.

The antecedent brother effect proposed by G & H may also prove useful in helping to clarify some controversial issues. For instance, it has long been debated whether or not left-handedness, particularly in males, is related to birth order by a U-shaped distribution. Perhaps by taking into account the sex of preceding siblings some clarity can be achieved in this area. If it is the case that more males with antecedent brothers are left-handed than are males with antecedent sisters, then a useful method for helping to distinguish pathological from natural male left-handers will have been found.

Development rate is the major differentiator between the sexes

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But male "affliction" is not limited to neurodevelopmental and psychiatric problems! It persists, with few exceptions, in all health related spheres. Its profound effect upon population structure is such that, in Western societies currently, the male advantage of 105 births per 100 female births is dissipated by the age of 45 and by age 70 there are twice as many females as males (Taylor 1981). An explanation of so ubiquitous a phenomenon which derives from "maleness" itself must have great generality. The best explanation for the precarious nature of maleness comes with the knowledge that, unless persuaded otherwise, the mammalian genome adopts female development. Males are attempting something extra all through life, and, in the sequence of male differentiating mechanisms, the resources of the genome are explored more in males than in females. Consider human height as an example. At whatever level of genetic endowment, the stature of male progeny exceeds that of the females from the same mating dyad. But many environmental and nutritional as well as neural and endocrine factors stand between a genotype and its phenotypic expression. Modification of any one of these factors may diminish the effect of the sex difference.

Similarly, sex differentiation, though genetically contrived, is achieved through a wide variety of mechanisms acting in sequence and in concert and its phenotypic expression can be modified by the degree of expression of its many constituent parts. We (Ounsted & Taylor 1972) referred to this persistent striving for which the words "male" and "maleness" were in danger of being inadequate as "the Y chromosome message." As each component of the male differentiating sequence operates there are consequences, both within the fetus and between the fetus and its environment. The same obtains postnataley from birth to death. Gualtieri & Hicks (G & H) have, perfectly reasonably, selected one such consequence for special treatment (although it has to be said that such antigenic dissimilarity as exists between a woman and her male conceptus is an expression of the action of his Y chromosome in soliciting from the genome something beyond what would otherwise have the same range of choice as a sister's).

We were persuaded by our data, and have since seen no cause to modify our position that the one most persistent theme in male–female differentiation was *pace* difference in the rate of development. If female fetuses, newborns, and children have the advantage of relative maturity, then they have a substantial benefit in terms of developmental disorders. We have suggested that their developmental advantage is perhaps about three weeks at birth to five years by the age of 30. Whether the pace difference is actively maintained in the cells as some aspect of Y-chromosome presence or whether the message is given once only, and is brief and rather dull, is an interesting question. In the 15 years since we proposed that developmental pace would be of profound importance as a differentiating mechanism, considerable supportive evidence has accrued that experiments in embryology can produce changes in morphology which are crucially dependent upon the timing of the intervention but which vary in a precise and predictable way between the sexes (Ferguson 1981). Our theory that the information on the Y chromosome is exceptionally sparse and of a different order from other genetic messages (in relating not to structures but to pace) has been vindicated conceptually by findings in alligators (Ferguson & Joanen 1982) that there is no chromosomal information at all determining sex; rather, sex determination and differentiation is initiated by incubating eggs in nests of different temperatures. With viviparity and a homothermic environment only a very modest intracellular mechanism would be required to unbalance developmental rates. It is likely that the differences will turn out to be due to different rates of DNA turnover in cells.

I would also argue with G & H on certain specific matters.

1. Some handicapped children are born because they are retained in utero rather than being rejected as they might be when their antigenic dissimilarity becomes intolerable; in essence this is a failure of abortion rather than an undue propensity to abort.

2. Maternal insufficiency is an unfortunate term, because a dyad is reproducing by forming a triad (any one of which might be responsible for the reproductive failure). In analysing sex differences one needs to be aware of the very large range of possible effectors which might be responsible for the differences in numbers of males and females.

3. If mothers do develop some antigenic response to their male fetuses it seems unlikely to be a result of the fetuses' "maleness" (which as we have said is not coded structurally – the current status of the H-Y antigens is somewhat confused), but rather more a result of the range of products called into being in the evocation of maleness. Even then the normal effect is to increase birth weight with each male pregnancy, generally a biological advantage rather than disadvantage.

4. It has not been easy to replicate Toivanen's (1970b) results with toxemic mothers.

The sexual strategy of reproduction in humans may do more than set up male and female forms of human being for selection. If the male genome is explored to a greater range of variation, if the slower pace of male development exposes him to greater hazard and to greater advantage, then the *human* gene pool is being carried at different levels of risk between the more conservative female and the more exploratory male genome. The increased hazard this gives to males is offset by his 105 to 100 numerical advantage at birth, an advantage that just about sees him through his reproductive life. (Taylor, in press)

Sex differences in neurodevelopmental and psychiatric disorders: One explanation or many?

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This immunoreactive theory is an interesting contribution to the explanation of gender differences in childhood disorders. Its theoretical status is rather complex, however. It proposes an additional factor in a domain where many factors are considered to operate; it does not seek to replace any other agents (except perhaps psychosocial influences determining parity effects on IQ). Accordingly, if maternal immune attack upon the male fetus is to be detected epidemiologically, much else must be allowed for or controlled. The hypothesis, while falsifiable in principle, may therefore be difficult in practice to test with precision.

The mediating factor in selective male affliction is, for Gualtieri and Hicks (G & H), a high male prevalence in complications of pregnancy and childbirth. Such complications will need to be rather powerful in their action if they are to account for the very large differences that obtain between the sexes for a large and heterogeneous range of conditions. Furthermore, they must be supposed to operate with power even in children without overt neurological disease or intellectual handicap, because of course most of the difference in rates of psychiatric disorder between the sexes is accounted for by neurologically normal individuals. These requirements are, on the face of it, at odds with much recent research. Most large-scale studies have found that the known complications of pregnancy and childbirth are associated only rather weakly with later impairments of cognition or behaviour, when allowance has been made for social factors (Davie, Butler & Goldstein 1972, Nichols & Chen 1981). Biological disadvantage interacts with social, so that those reared in good psychosocial conditions enjoy considerable protection against later cognitive and psychiatric disorders. The case history data, briefly cited here from an unpublished study by G & H, do not seem to contradict this point: they are taken from a group of intellectually handicapped children and social factors are not controlled. If, then, the effects of the known complications of pregnancy and childbirth are generally present but weak, their ability to engender so great a difference between the sexes is rendered very doubtful. For this reason, the theory is dependent on a new pathogen (namely, direct immune attack on the fetal brain) whose influence is different from that of the recognized complications.

Similar considerations arise with regard to the immunoreactive theory's (IMRT) account of parity effects. They are important for the hypothesis, as its attractiveness over other neuropathological explanations is precisely its ability to account for birth order effects. Plausible psychosocial explanations are equally available, however. Observations of mother–child interactions have shown the presence of systematic differences, dependent upon the birth order of the child, of the kind required to be operative in a psychosocial hypothesis (Rutter 1984). The arguments adduced by G & H against "stimulation" effects do not seem to us to be persuasive. Evidence against Zajonc's "confluence" model is no argument against the role of family relationships, but only against one speculative formulation of that role. Furthermore, we are unable to share G & H's view that psychosocial explanations are "clearly" inapplicable to specific learning disabilities, intellectual retardation, and school failure (Rutter 1984; Rutter and Madge 1976). The hypothesis, then, is able to explain negative parity effects, which already had an explanation. It is not capable of accounting for positive parity effects, which are equally in need of explanation. Later-born children are less prone to some types of emotional disorder and aggression which also show gender differences of the kind that the theory is trying to embrace (Rutter, Tizard & Whitmore 1970).

Some further predictions follow from the immunoreactive hypothesis in this context. There should, for instance, be no parity effect in adoptive sibships; and presumably no parity effect should be discernible when the influence of complications of pregnancy and birth is allowed for. Considering these predictions, however, emphasises the difficulties of testing. The predictions will only apply if the IMRT replaces other causative influences: if the IMRT coexists and interacts with psychosocial effects, then it survives many challenges but at the price of a reduced sharpness of prediction.

It is not easy to see how the immunoreactive hypothesis can account by itself for the particular pattern of sex differences found for different disorders. The sex ratio is lowest (about 1.3 to 1) for neuroepileptic disorders, which show a substantial association with perinatal complications, and highest (about 5 to 1) for psychosocial disturbances such as delinquency which have but a trivial association with perinatal complications. Other conditions, such as autism and specific reading retardation, with a sex ratio of 3 or 4 to 1, often appear to involve a strong association with neurodevelopmental impairment but yet have only modest associations with perinatal complications. It may well be that rather different explanations are necessary for different conditions.

In summary, we have read G & H's proposals with interest as a useful suggestion for the future investigation of the mechanisms of pathogenesis of congenital neuropsychological disorders. We are left rather doubtful about the wider explanatory power of the hypothesis; and even more sceptical of its potential to replace psychosocial factors as a main part of the environmental influence on impairments of cognition and behaviour.

Possible pathogenic effects of maternal anti-Ro (SS-A) autoantibody on the male fetus

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As the existence of a maternal immune response towards fetal antigens is fundamental to Gualtieri & Hicks's immunoreactive

hypothesis it is worth remembering that as far as cell-mediated responses are concerned it has been notoriously difficult to demonstrate them at all in normal or pathological pregnancy. With humoral immunity, the development of HLA-related lymphocytotoxic antibody, far from being associated with abnormal pregnancy, may be a part of a wider antibody response, which evoked as a response to some fetal signal and essential for immunological homeostasis between the mother and the fetoplacental unit. It is relevant that failure to develop such antibody has been taken as an indication that women suffering from recurrent spontaneous abortion can be treated with immunotherapy to boost their responsiveness to paternally derived antigens. The correct maternal immune response compatible with successful gestation has been so poorly defined that it is difficult to reconcile the concepts of an obligatory maternal response on the one hand and an aberration and possibly deleterious reaction on the other with a compounding effect of "male antigenicity" in between.

One factor which may tip the balance is the presence in the mother of autoimmune disease which is accompanied by a spectrum of autoantibodies; it may be easier to define the pathological aspect of the maternal immune status by looking at fetal effects in those cases. We have studied a group of women who gave birth to babies with a complete congenital heart block (Scott, Maddison, Taylor, Esscher, Scott & Skinner 1983). The antibody profiles revealed a significant association between the occurrence of the disease and the transplacental passage of anti-Ro (SS-A) antibody from the mother to baby. This antibody, reactive with a nonhistone ribonucleoprotein antigen, also seemed to be associated with other types of pregnancy pathology. It seems to be directly toxic in various tissue culture systems and is reactive with heart and brain cells when these are subjected to environmental factors such as ultraviolet light (Taylor & Griffiths 1984). In this respect it is interesting that Ro (SS-A) antigen has been shown to be ten times more abundant in the heart and brain than in any other body tissues (Wolin & Steitz 1984). Although the sex ratio in the affected babies was 57, this surviving group may be very different from those dying in utero, for whom data were not obtainable. An association with androgen-related effects may be relevant to the G & H's immunoreactive hypothesis. It is of interest that although complement-mediated cytotoxicity of anti-Ro (SS-A) antibody could not be shown on skin cells under normal conditions it was significantly demonstrable on cells derived from sexual skin. These have intracellular testosterone receptors and one can speculate that testosterone binding may interact in some way to influence the susceptibility of the cells to autoantibody damage.

Authors' Response

The immunoreactive theory: What it is, what it is not, what it might be

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The immunoreactive theory (IMRT) covers a broad range, and so do the commentaries. To lend coherence to the discussion, we will organize our response in the following manner:

1. We will reiterate what the IMRT is, and what it is not. Some commentators objected to a perceived claim of global significance or of universal inclusiveness. Other commentators have carried the theory well beyond its intended boundaries, impelled by enthusiasm or disapproval. Still others have attributed a degree of exclusiveness to immunoreactivity we never intended and that we tried to eschew.

2. Specific remarks will address questions raised about parity effects, perinatal complications, the sex ratio, and sinistrality.

3. Commentaries from immunologists have expanded on the complexity of the maternal–fetal interaction. These views will be placed in a perspective that supports the theory in its main thrust if not in fine detail.

4. We will try to address certain errors and ambiguities raised by the commentators. We apologize to our readers for the weaknesses in exposition that are, no doubt, responsible for these errors.

What the immunoreactive theory is. The neurodevelopmental disorders of childhood should be of signal concern to medical science by virtue of the frequency and severity such afflictions cause to children and families. Neither the quality of science in the area, nor the general interest in the topic have been commensurate with the importance of the problem. For example, in seven years of publication, *BBS* has never published a target article bearing directly on mental retardation, autism, childhood epilepsy, dyslexia, developmental dysphasia, or hyperactivity. In a similar vein, one of the most striking differences between the sexes, selective male affliction in the neurodevelopmental disorders, has received very little attention in the otherwise expansive and fertile study of psychological sex differences.

That the genesis of *most* cases of developmental handicap is unknown would ordinarily impel scientists to search energetically for new avenues to explore. Selective male affliction with its likely roots in male antigenicity, "male hormones," or both is one such opportunity. We agree that the developmental disorders are so diverse a population that it may be unrealistic to seek any degree of unity therein. But if there is a common facet to this population of grievances, it is – with exceptions as noted – selective male affliction. We hoped with the target article to bring to the topic at least a measure of the attention it deserves.

Selective male affliction has been credibly dealt with from time to time, most notably in the maturational theory of D. C. Taylor and Ounstead, and in the endocrinologic theories summarized in **Money**'s commentary. However, the alternative theories described in our target article and reiterated in many of the commentaries have not been dramatically successful in reducing what Medawar referred to as an "unexplained residue . . . of staggering proportions" (Medawar 1963, p. 324). Furthermore, the relative antigenicity of the male fetus had not been proposed as a factor that might be relevant to the phenomenon. It has not been difficult to discover information in diverse sources to suggest that it might be. A possible immunoreactive origin of neurodevelopmental disorders was last advanced by Adinolfi (1976). His work

and other developments in the field of reproductive immunology do not yet seem to have had much impact on developmental neuropsychiatry, neuroscience, or the study of sex differences.

The essential concern of the IMRT is the immunologic environment of the developing fetal brain. The theory is concerned with pathology – how the delicate immunological balance of mother and fetus may sometimes go awry and how the pathological consequences of this imbalance may be measured in human beings. The theory's premises are conservative: maternal immune attack may occur, the development of the fetal brain may be hindered by such an attack and there are specific factors rendering maternal immunoreactivity more likely. Some mothers are by virtue of inheritance more immunoreactive; some fetuses are more antigenic than others, and, on balance, male fetuses are more antigenic than females. We do not presume, however, that the simplicity of these assumptions belies or diminishes the complexity of the actual process, or the degree to which it may be obscured by other events in gestation, parturition, or childhood. The theory, as presented, is probably an oversimplification, but it has a certain appeal. We are encouraged by the favorable reception it has received from some of its most important commentators and also by the grudging agreement, from some of its harshest critics, that there may be something to it after all.

What the Immunoreactive theory is not. In light of at least some of the commentaries, it is important to clarify exactly what the IMRT is not, and what it does not pretend to be. Although indirect evidence in support of the theory is drawn from a broad range of divergent areas, we do not presume to have provided a global theory of evolutionary biology, sexual differentiation, or differential morbidity. Although we find commentaries that attempt to lend a wider biological perspective to the theory both interesting and important, we remind the reader that our primary concern is with the specific issue of selective male affliction in the neurodevelopmental disorders.

We are in the peculiar position of having to admonish two of our harshest critics that the connection between maternal immunoreactivity and neurodevelopmental disorders is not an established scientific fact: "Immune reactions are *clearly involved* [our italics] in the development of such disorders" (**Petersen & Hood**); "some birth problems are caused by maternal [immunoreactivity]" (**Boklage**). Neither of these statements is correct. Most of the commentators agree with us that the theory is speculative and that its basis consists almost entirely of indirect evidence.

The IMRT is not globally inclusive. The theory is not about differential morbidity and mortality across the life span nor does it pretend to include all the disorders in which humans succumb. It is possible to suppose that the male preponderance in developmental handicap is simply another manifestation of differential male morbidity and mortality, but that view is neither accurate nor heuristic. Differential male morbidity is the sum of myriad factors; immunological, genetic, endocrine, and environmental elements play different kinds of roles depending on the disorder in question. With respect to the congenital disorders, however, the uterine environment of the fetus should be expected to have a special salience, and in the specific study of congenital disorders of brain development, maternal and fetal factors that influence the uterine environment should be of prime concern. Such factors, however, may have no bearing at all on subsequent development or disorders of later life. Likewise, the antigenic nature of the male fetus may be of importance to the intrauterine environment but not to subsequently. The relative immunocompetence of a mother may be crucial in her capacity to support a successful gestation, but it is not necessarily the central element to every pathological condition that may occur during a woman's life.

The IMRT is not intended to be exclusionary. To propose an additional "pathogen" is not to deny the validity of others. It is not quite justified to fault an article concerned with one particular aspect of human development for not giving equal weight or emphasis to all other aspects. A biological theory is not, for example, an argument against psychosocial theories. An immunological theory does not diminish the importance of endocrine effects.

Thus we can allay **Gillberg**'s fears that the IMRT fails because it attempts to be a "universal explanation," reconciling the occurrence of extremely different conditions with one "underlying pathogenetic mechanism." He cites two conditions, trisomy 21 and the fragile-X syndrome on which, we agree, the theory may have no bearing whatever. These conditions do not weaken the theory, they are irrelevant to it. They are chromosomal disorders that lie fairly and squarely in the "explained residue." Our caveat to the reader of the target article that the IMRT "is by no means a global explanation for all of the neuropathic disorders of childhood" is in our opinion neither very obscure nor nonspecific, but common sense.

Hoyenga also introduces an important issue with respect to chromosomal disorders by pointing out that levels of H-Y antigen are higher, for example, in XYY males (Fraccaro et al. 1982) and in XO females (Müller et al. 1983). Since both disorders are associated with higher levels of H-Y antigen as well as with an apparent increase in the incidence of neurodevelopmental disorders, we had at one time thought of citing these data in support of the IMRT. However, the ambiguity of the clinical data alluded to by Hoyenga, weighed against including them. We elected to marshall only evidence sufficient to render the theory credible, not to include every conceivable example that could support it.

Although the theory makes no claim of universality, **Hoyenga** raises the question whether *all* examples of differential morbidity go in the direction predicted by the theory. Not surprisingly, she discovers that they do not. Her discussion of differential vulnerability to chronic disabling conditions such as sickle cell disease, X-linked disorders, antisocial behavior in adolescence, and dopamine metabolites in schizophrenics comprises simply too diverse a collection of phenomena to bring to bear on the IMRT of neurodevelopmental disorders. Two specific remarks are in order, however, on matters that are germane to the theory. Even in samples where males are more frequently afflicted with severe developmental handicaps, the relative proportion of females with severe afflictions is higher than in mild and moderate conditions.

The report Hoyenga cites of more positive symptoms in male schizophrenics is based on a single study of only 18 patients (Opler et al. 1984).

Hoyenga, Mackey and **Ferguson** attempt to place the IMRT into a broader evolutionary famework; however, this is a highly theoretical issue on which we do not feel qualified to comment. It is not unreasonable to seek antecedents in evolutionary biology for a phenomenon such as the one we describe. If maternal immunoreactivity plays an important role in human development, it must have some kind of adaptive rationale. We prefer to focus on the validity of the theory before we make such a theoretical leap.

We are delighted with **Jensen**'s remark that maternal IMR with respect to the neurodevelopmental disorders may represent only the tip of the iceberg; however, its wider application can be made only with caution. We ourselves would be quite content if the theory were to hold even for only a small group of disorders in our specific realm of endeavor. On the other hand, it is by no means unreasonable to suspect that a mechanism that may account for pathological outcomes in brain development could also influence intellectual development in normal populations.

Our warning that the IMRT is by no means intended to exclude alternative factors in the genesis of the neurodevelopmental disorders was echoed by many of the commentators who pointed to the salience of specific factors or emphasized the importance of a multifactorial point of view. A multifactorial model of selective male affliction has been called for by **Beatty, Beatty & Goodkin, Diamond, Ferguson, Gorczynski, Money, Petersen & Hood, E. Taylor & Rutter,** and **P. Taylor,** as well as by our target article. The development of a unified and integrated theory, especially one that embraces such an expanse of data, is a perilous exercise; it requires critical selection among views and data that may be parallel, divergent, or contradictory. Although there is necessarily much that is subjective in this, there is no need to apologize for being selective. Nor is it necessary to apologize for simplifying what is obviously an extraordinarily complex issue or to be defensive for having neglected the relative importance of other dimensions of the problem. It is the mind's inherent bias to seek order in disorder and coherence in noise. Whether in the case of the IMRT this has been a fruitful exercise or simply an artful concoction is an open question.

Money is concerned that we have become committed to immunology too soon and that we have been too restricted by a single hypothesis. Yet it is he who is able to posit a single element – the secretion of testicular hormones – as the central mediator of the entire range of male morbidity across the life span. **Gorcyznski** has also decided that any hostile uterine environment is the consequence of endocrine factors but not of maternal alloreactivity. These contentions are far more sweeping than any we have made. There is certainly a complex interplay between endocrine and immunological factors, and the relative weight of these elements will vary in different conditions. The reader is referred to the more balanced views of **P. V. Taylor** and of **Diamond.**

Parity effects. It may be that **E. Taylor** and **Rutter** are skeptical of the potential of the IMRT to replace psychosocial explanations, but the degree to which it may replace, complement, augment, or be irrelevant to psychosocial factors in development is an empirical question best considered with respect to specific issues. Taylor and Rutter find fault with our development of an alternative, biological mechanism for negative parity effects in the occurrence of severe mental handicaps like dyslexia, autism, and mental retardation because there is already an explanation that presumably has as its basis the role of family relationships. Taylor and Rutter fail to expand upon its nature or to give important details. Family relationships play no small role in the lives of handicapped individuals but they do not cause autism, mental retardation, or dyslexia. We are aware of no data that support a psychosocial explanation for negative parity effects in the occurrence of neurodevelopmental disorders.

Parity effects of IQ in normal populations were found in Belmont's study even when social class was controlled (Belmont & Marolla 1973). The effect on IQ was steeper for lower-class families and it also seemed to occur in adopted children. This suggests that psychological factors are germane to the issue. One would expect an even steeper parity–IQ gradient in families in very poor nations (if such research were ever undertaken) implying that in some circumstances maternal nutrition may also play a role in the negative parity effect on IQ. However, the parity–IQ gradient is clearly consistent with an immunoreactive explanation, and the existence of an antecedent-brother effect renders this view cogent indeed. The existence of other elements that may contribute to this gradient is not sufficient reason to discredit an immunoreactive hypothesis.

The question of parity effects on IQ is also raised by **Costeff,** who may be right in asserting that normal population studies or studies of academically capable students, with whom most such research is conducted, may be irrelevant to the IMRT and its central focus on neurodevelopmental disorders. The parallel between negative parity effects on IQ and the incidence of developmental disabilities, however, is remarkable and at least suggests a common mechanism. Furthermore, we do not agree that the parity–IQ data are as equivocal as Costeff characterizes them. The exquisite Dutch study of Belmont and Marolla (1973) is not of a piece with that of the Scottish Council for Research in Education (1949), which involved only 1100 eleven-year olds, or with the Enquete Nationale (1973), which used only a nonverbal intelligence test. The authors of the latter study in fact felt that certain elements of family structure in their population may have rendered the findings spurious (Ernst & Angst 1983).

We agree with **E. Taylor & Rutter** that the IMRT does not account for positive parity effects such as those described by Rutter and Graham (1970) in neurotic and what they term "nonsocialized" antisocial children in the Isle of Wight Study (Rutter, Tizard & Whitmore 1970). On the other hand, the opposite trend, a negative parity effect, was reported by the same authors in "socialized" antisocial children. Given the ambiguities of psychiatric diagnosis in children, the sample size (total $N = 109$), and the fact that statistical analysis compared eldest to youngest, one need not give much credence to this purported exception to the rule. (Incidentally, the Isle of Wight

Study did detect a negative parity effect for mental retardation and dyslexia; Rutter et al. 1970.)

Boklage refers to our examination of the primiparity effect in the data of Deykin and MacMahon (1980) and in Schoenbaum et al. (1975). We had thought that our text and Figures 6 and 7 were clear in demonstrating a preponderance of affected cases in firstborns. The point to be made here is that the unique problems of primiparas may obscure the existence of a parity effect in children born to multiparas. Boklage's subsequent explication of these data is very difficult to understand, but it does not seem to diminish the importance of the primiparity effect.

Boklage interprets Figure 9 and the accompanying text as if it alluded to the "male fraction of mental retardation"; that is, the proportion of mentally retarded males at birth order one, two, three, and so on. In fact, the figure refers to the sex ratio of sibships that included a handicapped individual. The decrease in sex ratio normally observed with parity is sharper in the families of handicapped individuals. If one grants that the decrease in the sex ratio with parity has an immunoreactive basis, and if the families of handicapped individuals are typified by an excess of maternal immunoreactivity, one would expect to see this distortion in the sex ratio–parity regression line.

Parity effects in sex steroid levels in umbilical-cord blood were reported by Maccoby et al. (1979), as noted by **Hoyenga.** However, consistent parity effects were only noted for progesterone and estradiol. The parity effect on testosterone was described by the authors as tentative, and there was no effect for adrostenedione or estrone. The birth-order analysis there, however, compared firstborns to later borns; in fact, a primiparity effect.

Petersen & Hood attribute a "misattribution" to us in citing Maccoby et al. (1979) since the article did not "pertain . . . to fetal brain development." For the record, Maccoby et al. (1979) discussed their findings in light of endocrine effects on brain development, including parity effects on IQ and the effects of progestins on intellectual development, and cited an extensive literature related to these topics.

One vexing aspect of psychosocial arguments is their inexhaustible capacity to provide alternative (and untestable) explanations for virtually every human circumstance. **Boklage** offers an unwitting display of this in his discussion of parity effects on the occurrence of neurodevelopmental disorders. First, the reader is asked to agree that the likelihood of stopping further procreation after the birth of an affected child will increase in proportion to the number of previous children. So far this sounds like a reasonable idea. Then, two paragraphs later, another rhetorical question vis-à-vis the primaparity effect: "Wouldn't the neurodevelopmentally disabled child be more of a problem for new parents and more likely to reduce further reproduction?" Neither proposition is by itself unreasonable, but they appear to be contradictory.

Readers will understand and perhaps sympathize with our decision not to respond to the suggestion that an immunoreactive study of selective male affliction is "androcentric" or that we "assume antagonism between female and male" in any realm beyond the immunological environment of the gravid uterus. Nor do we understand the basis of one question posed by **Petersen & Hood,** "why females should tolerate the risks associated with producing males."

We do not agree with **Berglin** that population controls are always necessary for a proper birth-order analysis. Our analysis was concerned with the interaction between parity effects and sex, which is the contrasting dimension, and a normal population control is not needed here. In his reanalysis of the data from Reed and Reed (1965), Berglin presents an alternative method of analysis that has neither been published nor, to our knowledge, peer-reviewed. It is reassuring that he has strengthened our original observation, but we cannot be sure that his method is valid, or, on the basis of his remarks, that ours is a "mistake."

Neither **Petersen & Hood** nor **Berglin** have understood the statistical analysis of the data in Table 3, which clearly shows an antecedent-brother effect for autistic boys, not an antecedent-sister effect. Both their reanalyses purport to show a nonspecific parity effect. However, the overall parity effect is meaningless because antecedent sisters contribute nothing to it. It only means that the noise sisters contribute to the data is not sufficient to vitiate the brother effect. A reanalysis, comparing antecedent brothers by complications of pregnancy (linear) to antecedent sisters by complications of pregnancy (linear) yields a chi square statistic = 5.589, which is highly significant. The antecedent-brother effect is significant and the antecedent-sister effect is nonexistent.

Perinatal problems. The issue of perinatal complications is addressed by **E. Taylor & Rutter** and **Costeff.** Taylor and Rutter appear to have misread our intent, however, in raising the question to begin with. We postulated that perinatal complications are a manifestation of maternal immunoreactivity, not its sole and exclusive mediator. Perinatal problems are a concomitant of maternal immunoreactivity but neither a necessary nor a sufficient condition for its occurrence. Perinatal complications may arise in the absence of maternal immunoreactivity, and maternal immune attack may occur without outward signs of perinatal complications. Taylor and Rutter also impose an interesting but impossible criterion on the IMRT by demanding a kind of dose–response relationship between perinatal complications, sex ratio, and the presumed neuropathic origins of developmental disorders. Such a criterion would only be valid, of course, if one assumed that no other factor but maternal immunoreactivity had a role to play in the genesis of these conditions. It is *argumentum ab extremis.*

In **Costeff**'s data, complications of pregnancy and delivery were found to be equally common in males and females with nonspecific mental retardation. He was not able to control this analysis for sex of antecedent siblings. Thus, it is not a fair test of the IMRT. The same may be said for the cerebral palsy data he cites (Stanley & Blair 1984). His report that perinatal complications are associated with smaller family size is entirely consistent with the IMRT. We have dealt with the putative relationship between maternal insufficiency, neurodevelopmental disorders, and infertility.

Costeff also mentions that the sex ratio of fetal deaths decreases by month of gestation (McMillen 1979), which

it does, and which is not predicted by the theory. He neglects to mention, however, that it increases again at term (McMillen 1979). This argument, however, would only be valid for primiparas, who can develop fetotoxic antibodies during the course of a first pregnancy. The data reviewed by McMillen (1979) did not distinguish between primiparas and multiparas, however. In any event, the timing of an intrauterine insult is, as Costeff is well aware, extremely important to the outcome of a pregnancy. An early insult can produce a severe disorder or fetal death, whereas a later event has less grave consequences. A pertinent example from the target article is the pregnancies of acutely schizophrenic mothers, where early psychosis is associated with fetal death whereas psychosis occurring later in pregnancy is associated with fetal malformation (M. A. Taylor 1969).

We thank **Gillberg** for reanalyzing his data, which tend to support our finding of an antecedent-brother effect in autistic boys. We agree with him that certain neurodevelopmental disorders may have a more likely immunoreactive explanation than others, and autism may indeed be a prime candidate. To be sure, Gillberg's data on the association of atopic disease with minimal brain dysfunction or with pathological left-handedness are hardly supportive of the IMRT, although his use of the latter term is different from ours (see below). Neither is **Benbow**'s stunning report of an increased incidence of atopic disease in intellectually gifted students, but before drawing conclusions about their findings, we would prefer to review the data. It is not unlikely that the complexity of immunological events in pregnancy and thereafter and the complexity of immunoendocrine relationships will influence certain outcomes, like theirs, in ways that are not predicted by the IMRT. A biological mechanism may confer advantage in some circumstances and disadvantage in others.

Sex ratio. Several commentators have dealt with issues pertaining to sex ratios. **Hoyenga** believes that factors other than maternal immunoreactivity may influence the secondary sex ratio and we are inclined to agree, although the examples she cites – maternal age, breast feeding, and sex hormone levels at birth – are not well chosen. A host of factors have been claimed to influence the secondary sex ratio, including paternal age, race and color, paternal baldness, frequency and timing of intercourse, and SES (socioeconomic status) (Teitelbaum 1972). Teitelbaum reports a significant negative association between secondary sex ratio and birth order, a significantly lower ratio for blacks than whites, and a significant association with SES. Neither paternal nor maternal age have been convincingly related to secondary sex ratio.

Boklage is concerned that the effects of maternal age on developmental disorders were not addressed, but they have been. In the Perinatal Collaborative Project, for example, parity effects on perinatal mortality are apparent even when maternal age is controlled (Niswander & Gordon 1972).

Hoyenga doubts that an implantation advantage enjoyed by males, presumably by virtue of heightened antigenicity, could influence the sex ratio at conception. In fact, the primary sex ratio in human beings is necessarily an estimate, and it would be more proper to refer to the sex ratio early in pregnancy. A high sex ratio early in pregnancy may mean that more male zygotes are formed at conception and that males and females are implanted with equal frequency or that males and females are conceived at an equal rate but that males are more likely to be implanted (Kirby et al. 1967). In our opinion the weight of the evidence favors the latter. **Bixler** presents an alternative view, suggesting a primary sex ratio of 100, with disproportionate loss of female embryos. We agree with Bixler that estimates of the primary sex ratio are uncertain, although the weight of the evidence once again favors a value that is higher than unity.

James's suggests that maternal gonadotrophin levels at the time of conception may be "responsible for the sex of the infant," although the evidence he cites does not directly confirm this opinion. It is neither demonstrated nor likely to be shown that "almost all of the observed variation in the human sex ratio" is explicable in terms of gonadotrophins. In fact, at least one of his citations (James 1980), which reports the low sex ratio of relatively infertile mothers, is equally amenable to an immunoreactive explanation.

James is right in pointing out that the data of Malinvaud (1955) and of Ben-Porath and Welch (1976) on the sex ratio do not agree with ours, but he overstates the case with a claim of unanimity, countered by data published by Renkonen et al. (1962) and by Gualtieri, Hicks, and Mayo (1984b) from very large samples supporting the existence of a negative antecedent-brother effect on sex ratio. He is not right in attributing this discrepancy to a statistical weakness on our part and he is advised to review our 1984 publication. The analysis there was *not* confined to families with same-sex antecedent siblings, but a second analysis included family configurations with mixed sibships. The association between antecedent brothers and a decline in the secondary sex ratio held in both analyses, and the size of the regression coefficients in both analyses was about equal.

Both **Hoyenga** and **Adinolfi** allude to a purported increase in the secondary sex ratio at parity four and five. We are hard put to explain this increase, since we did not observe such a trend in our research (Gualtieri, Hicks & Mayo 1984b). The relative infrequency of such sibships in humans, however, renders it inadvisable to draw serious conclusions about a definite trend. In any event, it is known that certain types of maternal antibodies will only develop – if at all – at parity one, two, or three, but not thereafter. The occasional development of maternal tolerance to H-Y (or other) antigens, as described by **Loke**, is another conceivable explanation for the phenomenon, if it does indeed exist in humans.

Immunological aspects of pregnancy. The commentaries from immunologists lend a degree of support to a theory that embraces some form of immunological attack on the developing brain. The immunological commentaries did not take serious issue with the idea of relative male antigenicity, although its mediation may be an open question. Perhaps H-Y antigen is the mediating factor, perhaps it is H-Y in concert with other antigen systems, perhaps there is an alternative antigen system that does not involve H-Y. **P. V. Taylor** aptly captures the complexity of the field: "The correct maternal immune response

compatible with successful gestation has been so poorly defined that it is difficult to reconcile the concepts of an obligatory maternal response on the one hand and an aberration and possibly deleterious reaction on the other. . . ."

Caught in this tangled net are the following ideas:

1. The precise behavior of H-Y antigen with respect to mammalian reproduction is imperfectly understood (**Loke**).
2. There is indirect evidence of the existence of more than one "male antigen" (Silvers, Gasser & Eicher 1982).
3. In some instances tolerance rather than sensitivity to H-Y antigen may develop with successive pregnancies (**Loke**).
4. The development of a certain class of maternal antibodies may be the prerequisite for successful gestation (**P. V. Taylor; Loke**).
5. Some cases of habitual abortion may be treated successfully by enhancing the maternal immune response (**Gorczynski, P. V. Taylor**).

Where H-Y antigen fits into this puzzle is obscure, and we are sympathetic to **Loke**'s suggestion that the attribution of selective male affliction to H-Y antigen may be premature. Although the antigenicity of H-Y is not doubted (Loke), it is a comparatively weak immunogen (**Ohno**) and may only work its deleterious effect by acting in concert with other antigen systems. Loke, for example, has suggested that the expression of a weak antigenic system like H-Y "may be dependent on the degree of interaction with other stronger, histocompatibility systems" (Loke 1978, p. 165). Ohno has expressed the belief that the antigenicity of H-Y may be major-histocompatibility-antigen (MHC) dependent, and in at least one preclinical study, male target cells were killed only when they expressed both the H-Y and the HLA-A2 antigen (Goulmy et al. 1977). (We apologize to **Petersen & Hood,** who object to the martial phraseology of immunological science, but such is the *lingua franca.* No amount of wishing will make killer lymphocytes and cytotoxic antibodies cooperate, share, or resonate with their targets.)

Ohno introduces the idea of antigenic "misidentification," which may speak to a specific mechanism by which the expression of a weak immunogen like H-Y may have damaging consequences. **Bukovský & Presl** also present a hypothetical mechanism by which an immunological reaction may exercise a negative effect on brain development. We appreciate their willingness to share unpublished data that suggest that class I MHC-molecules and "differentiation antigens" of lymphocytes may be demonstrated on developing brain cells. These putative mechanisms suggest that the detection of H-Y antigen on developing neuronal tissue may not be a prerequisite for the IMRT, as **Gorczynski** claims it must be.

The relevance of autoimmune disorders is highlighted by the commentary of **P. V. Taylor** and her reference to a study of congenital heart block in the offspring of mothers with connective tissue disease. Maternal antibodies to soluble tissue ribonucleoprotein antigens appeared to cross the placenta and were associated with the development of congenital cardiac abnormalities; extracardiac defects were not the topic of the paper (Scott et al. 1983). It is therefore extraordinary news to discover that anti-Ro (SS-A) antibody is cross-reactive with neural cells in tissue culture and that it is ten times more abundant in heart and brain than in other body tissues. It will be interesting to learn whether the children in this study will be developmentally handicapped, and whether the degree of handicap is related to the strength of the maternal antibody response or to the level of hypoxia experienced by the children in early life.

Although the potential importance of H-Y antigen is not diminished by commentaries of the immunologists, we agree that it would be premature to commit ourselves to a single-antigen system and that maternal–fetal interaction is probably a great deal more complicated than we suggested in our target article. P. V. Taylor also alluded to a specific association between complement-mediated cytotoxicity of anti-Ro (SS-A) antibody and androgenic hormones. This affirms the wisdom of suggestions by **Diamond** and others that endocrine factors may not be irrelevant to the study of immunoreactivity and that endocrine and immunological mechanisms may be independent.

Hoyenga believes that the increased incidence of autoimmune disease in females is a critical problem for the IMRT. On the contrary, it is strongly consistent with the theory, which presumes that the mother is immunoreactive whereas the fetus is antigenic. The "superior immuno-competence of females" (Purtilo & Sullivan 1979, p. 1253), presumably related to X-linked genes, may explain the differential vulnerability of males to infectious disease and cancer as well as to the special female vulnerability to autoimmune diseases.

Gorczynski claims to have no knowledge of an increased incidence of developmental disorders in the offspring of mothers with autoimmune disorders. The research has never been done because the appropriate question has not been raised. There is, however, a clear increase in reproductive inefficiency and spontaneous abortion in these disorders, as we have mentioned. We do not agree that there is anything approaching good evidence for a "psychoneuroendocrine axis" in the autoimmune disorders. The reference cited (Solomon 1983) is a philosophical essay, not a scientific paper.

We agree with **Costeff** that maternal alloreactivity might cause damage to the fetal brain via indirect pathways, and that an actual immunological reaction against fetal nervous tissue is not necessary to account for relative failures in development. Direct immune attack against the brain may not be necessary for the occurrence of neuropathic damage, and indirect mechanisms may play a role. Rh incompatibility, erythroblastosis fetalis, and kernicterus are examples of such an indirect effect. However, a direct immunological mechanism is neither harmful to the theory, as Costeff maintains, nor is it unlikely.

The sharpness or predictiveness of the IMRT, about which **E. Taylor & Rutter** are concerned, will depend not so much on its interaction with psychosocial effects but more probably on the identification of specific immunological mechanisms that may be fetotoxic and specific subgroups of immunoreactive individuals.

Adinolfi's critical comments deserve careful scrutiny, first because he is a respected immunologist, and second because his work has in important ways presaged the IMRT: "Are maternal abnormal states, with regard to hormones and immune reactions, responsible for some of the as yet unclassified congenital forms of "global" mental

retardation or, possibly, some specific brain defects and selective neurological handicaps?" (Adinolfi 1976, p. 244).

We cannot agree with **Adinolfi** that we have misrepresented his work and that of others and that we have not exercised sufficient critical judgment in our analysis. We have "miscited" his work, he judges, because he has "not shown transfer of lymphocytes across the placenta." In fact, we did not suggest that he had done so; the transplacental transfer of maternal humoral antibodies is sufficient to effect fetal damage. The entry of maternal cells into the fetal circulation *may* occur under certain circumstances, as Adinolfi is aware (Adinolfi & Wood 1969), although the issue is controversial. When he maintains that there is little or no traffic in lymphocytes across the placenta, he seems to be misrepresenting his own work: "Transfer of fetal lymphocytes into the maternal circulation seems to occur in almost all normal pregnancies" (Adinolfi & Wood 1969, p. 50).

Adinolfi also maintains that we misrepresented his views by citing references that dealt with a different topic. The fact is that Adinolfi himself raised a question central to the IMRT in one of his cited papers: "Immune reactions based on the transfer of antibodies [are] slowly emerging as a possible component of the causation of mental retardation" (Adinolfi 1976, p. 245). We might stand fairly accused of borrowing his ideas but not of misrepresenting the thrust of his work.

Nor were the citations from Loke (1978) taken out of context. **Adinolfi** is referred to **Loke**'s commentary, which is critical of the IMRT but careful and fair. Loke (1978), for example, referring to the work of McLaren (1962), which Adinolfi cites, commented that "it must, however, be remembered that experiments on isogeneic strains of mice may not be directly comparable with the situation in man" (p. 165). One of Loke's conclusions was that "sex-linked antigens do have some influence on the human fetal–maternal interaction, but the exact consequence to the fetus is, at present, unclear" (Loke 1978, p. 166), a conclusion neither inconsistent with the IMRT nor with our own representation of Loke's views.

The Lawler et al. (1975) reference was cited as an illustration of interindividual variability in maternal–fetal immunoreactivity, not to support the increased antigenicity of the male fetus, as **Adinolfi** suggests. Even with male fetuses maternal reactivity is neither inevitable nor inevitably harmful. Adinolfi also claims that "more recent investigations . . . have not confirmed a higher incidence of male than female conceptuses" in toxemia of pregnancy. The study of Juberg et al. (1976), which he cites, involved 373 patients with toxemia, 95% of whom were black; a study that is not, strictly speaking, comparable to the Finnish sample of 1,064 offspring of toxemic women described by Toivanen and Hirvonen (1970b). Juberg et al. themselves wondered whether "some of the patients had chronic hypertension or renovascular disease instead of pre-eclampsia because both of these diseases are more common among blacks than caucasians" (p. 302). The study of Redman et al. (1978), which Adinolfi also cites, involved only 80 pre-eclamptic women, and the sex ratio of the offspring was apparently deemed by the authors of so little importance that it warranted neither analysis nor discussion. Redman's paper strongly supported the idea of toxemia as an immune disorder, however, and discussed in some detail "immune attack on fetal tissues by maternal cells" (p. 399). Support for the findings of Toivanen and Hirvonen (1970b) is cited by Loke (1978) and in Salzmann (1955) and Scott, Beer & Stastny (1976). Toivanen and Hirvonen advanced an immunoreactive theory of toxemia based on H-Y antigen, whereas Salzmann favored an endocrine hypothesis based on maternal reaction to male fetal hormones (Loke 1978).

Hoyenga also refers to the issue of toxemia of pregnancy, and wonders whether the fact that primiparas are at greater risk for the disorder is not inconsistent with the IMRT. This may be another example of the primiparity effect, which, as we have said, may obscure a parity effect. What is the subsequent fertility of severely toxemic primiparas? In addition, it is known that maternal antibodies may develop during the course of a first pregnancy. The antecedent-brother effect has not been tested in toxemia of pregnancy.

Beatty, Beatty & Goodkin complain that there is no direct pathological evidence of maternal immune response in the neurodevelopmental disorders. This is perhaps too facile a criticism. They are themselves "overly enthusiastic" about the capacity of neuropathologists to detect immunological "calling cards" or serologic abnormalities years after a transient alloreactive event. **Gorczynski** also alludes to the importance of monitoring the maternal–fetal interaction *in situ*. How direct evidence of this kind can actually be obtained in a prospective fashion in human beings is a practical question that we, as clinical scientists, invite Beatty et al. to expand upon.

Beatty et al. refer to abnormalities that are "clearly definable and reproducible in animal models." We are mystified by their apparent suggestion that there may actually be animal models for the neurodevelopmental disorders at issue. We have, however, alluded to animal models of maternal antibody attack against fetal CNS tissue (Brent 1971; Johnson et al. 1980).

Direct (or indirect) evidence will have to await the development of specific hypotheses concerning fetal antigens and the precise nature of the maternal immune response along the lines of those suggested by **Ohno, P. V. Taylor,** and **Bukovský & Presl. Beatty et al.** fail to understand the purpose of the theory; perhaps **Ounstead** ought to advise *them* to read Medawar's (1982) book. Were direct evidence for immunoreactivity in neurodevelopmental disorders to exist, one would not need to promulgate the theory. The central purpose of the theory is to guide the development of testable hypotheses. Without a theory it is unlikely that scientists would seek either direct or indirect evidence. Remember, we pointed out how research on the association between pregnancy complications and neurodevelopmental disorders has traditionally failed to consider as relevant variables the sex of other proband, birth order, the sex of antecedent siblings, or the family history of maternal insufficiency, allergy, or autoimmune disease. This may be the reason why so much of the work on perinatal complications has been inconclusive (**E. Taylor & Rutter**).

Costeff, who is as skeptical of the theory as we ourselves, agrees that the IMRT guarantees that such factors will be incorporated into future epidemiological studies of developmental handicap. Judging from **Gillberg**'s data,

we believe that when they do, the results will indeed be interesting. **Jensen** introduces the relevance of immunoreactivity to studies of the heritability of intelligence, an area of vast importance we had not considered, and **Hoyenga** mentions its relevance to XYY and XO syndromes, which we had. The measure of the value of a theory is not, after all, how convincing it is (**Adinolfi**) or how enthusiastically it reaches conclusions (**Beatty et al.**) or even how elegant (**Loke**), intriguing (**Petersen & Hood**), or interesting (**E. Taylor & Rutter**) it may seem to be. The real measure is whether or not it engenders testable hypotheses and productive research.

Beatty et al. have also misconstrued our interpretation of the salience of genetic influences on sex differences in the neurodevelopmental disorders. We have never assumed that the "most devastating departures from normal development are primarily the results of genetic influences." We have simply cited evidence in support of the idea that genetic influences in certain conditions lead to more specific outcomes, whereas mediation via the occurrence of perinatal complications leads to more diverse pathological outcomes. Nor have we assumed that genetic influences are lost on the male conceptus or that perinatal complications are irrelevant to the female. The issue is one of relative weight between the sexes. The relatively lower proportion of the males in the most profoundly handicapped categories may speak simply to this phenomenon: A male with an untoward genetic complement and severe maternal alloreactivity is not likely to survive the gestational period at all.

Beatty et al. also seem to be in error in their belief that the genotype necessarily exercises equivalent effects in males and females. The premise of a dual threshhold model is just the opposite. Males are afflicted by a less severe genotype, whereas females require a higher genetic load for expression of an untoward phenotype. It may also be wrong to seek a statistical parallel to a clinical dimension as Beatty et al. do. We reiterate the finding of Mednick et al. (1977) that there is more clinical diversity in the pathological outcome of sons of schizophrenic mothers compared to daughters. This qualitative diversity is not translatable into statistical variability on a unidimensional scale, as Beatty et al. propose.

Developmental pace. We have tried to give proper attention to alternative theories of selective male affliction, and especially to the maturational theory of **Ounstead** and **D. C. Taylor.** We are pleased that both of these eminent scientists have taken the opportunity to reiterate their ideas in individual commentaries. We regret to find, however, that the only new evidence they adduce in support of their theory is **Ferguson**'s study of sex differences in *Alligator mississippiensis* (Ferguson & Joanen 1983). This work is also described in Ferguson's commentary. It is ironic, though, that Ferguson himself propounds a maturational theory that is the precise opposite of **D. C. Taylor** and **Ounstead**'s. According to Ferguson, the developmental pace of the male organism is faster than that of the female; androgens hasten senescence and degeneration and *this* may account for increased male morbidity and mortality. Perhaps the forms of life Ferguson mentions, intriguing though they are in their own right, are, like isogeneic strains of mice, not germane to the question of neurodevelopmental disorders in human beings. It is nevertheless interesting to learn that packrats feed enriched milk to their daughters but not to their sons and that by incubating eggs at low temperature, one may produce female lizards or, alternatively, male turtles (Ferguson & Joanen 1983).

With respect to **D. C. Taylor** and **Ounstead**'s theory, however, we are familiar with only one clinical study (the relative vulnerability of boys and girls to febrile seizures) that is directly supportive. However convincing their theory may be, it does not seem to have generated much in the way of research although this may be as much the fault of other researchers. It might be reasonable to apply Taylor's and Ounsted's ideas, for example, to studies of autism or schizophrenia, or to other severe neurodevelopmental disorders with a variable age of onset. Perhaps future work from D. C. Taylor and Ounstead will offer some concrete and testable hypotheses based on the theory. We hope so; the idea is too important to lie fallow.

It is important, however, to register a disagreement with **Ounstead**'s contention that "the Y chromosome transmits no significant information specific to itself," since the expression of H-Y antigen is a direct manifestation of the Y chromosome. The significance of this expression is, according to the IMRT, rather high.

Nonright-handedness. In reply to **Searleman,** we do not equate pathological nonright-handedness with nonfamilial sinistrality. A nonfamilial left-hander is not necessarily pathological. Pathological nonright-handers are defined clinically as individuals with developmental impairment. In handicapped populations, the frequency of nonright-handedness is almost always higher than in the population at large. We only suggested that if Geschwind and Behan's (1982) study were to be replicated in such a group, the incidence of allergies and autoimmune diseases would be even higher than in a normal group of nonright-handers. Nor do we agree that family configuration might be used to determine whether an otherwise normal individual came by his sinistrality in a "natural" or a "pathological" way. If handedness is, in fact, a continuously distributed variable, then sinistrality will occur in some individuals in the absence of a clear family history and irrespective of family configuration.

We feel that **Boklage**'s assertions that the neurodevelopmental disorders "represent anomalies of lateralization or lateralized function" or that neuroendocrine relationships are lateralized are unduly sweeping and premature. His discussion of cell-surface interactions and tissue-specific growth rates is obscure, and extremely difficult to appraise since the two salient references (Boklage & Fraser 1984; Boklage & Fraser in preparation) are not available to us.

Conclusion. The IMRT developed out of our curiosity over the problem of selective male affliction. As we expressed on several occasions in the target article, the origin of this puzzling phenomenon is almost certainly multifactorial, but we were dismayed by the clear failure of most "multifactorial models" to pay any heed at all to the potential significance of male antigenicity. The further we delved into this obscure and relatively neglected corner, the more convinced we grew of its potential

significance. We also became convinced that a theory based on male antigenicity and maternal sensitization had the potential to generate specific testable hypotheses in many important areas. If any major part of the IMRT were found to be correct, it could influence clinical practice in predicting or preventing at least some of the neurodevelopmental disorders.

If sufficient indirect evidence were to accrue in support of the theory, one might decide to address the question of specific immunological mechanisms that could mediate maternal immune attack and design specific experiments to test the validity of such mechanisms. Considering the expense involved in actually mounting a series of such immunological studies in humans, the technology required and the invasiveness of such research were it conducted in the proper prospective fashion, we deemed it wise to focus initial efforts on the accrual of indirect evidence and to share the results of this endeavor with other members of the scientific community. We have always considered the theory speculative, but the literature of reproductive immunology suggested that it was neither outlandish nor impossible to test.

The generally favorable reaction of the commentators, especially those who have a background in reproductive immunology, seems to support our opinion. The least favorable commentaries seem to have come from proponents of either one specific point of view or from proponents of the "multifactorial model." We feel quite strongly that no one single mechanism will ever suffice to explain the extraordinary phenomenon of selective male affliction or the larger issue of differential male morbidity and mortality. We fault the multifactorial model, however, for having neglected a very important factor in fetal antigenicity.

We have mentioned that the IMRT is capable of generating testable predictions. May we indulge, at this point, in making a few predictions *about* the IMRT:

1. In its current formulation, the IMRT will almost certainly prove to be wrong. Major modifications of the theory will occur as time goes on. In its ultimate embodiment in the archives of medical wisdom, it will be unrecognizable. As it stands, the IMRT is not only speculative but naive, oversimplified, and much too broad. Our present understanding of the immunological and endocrine events that support a successful gestation, the antigenic nature of fetus, and even the nature of the so-called sex-linked antigens is very limited.

2. Nevertheless, the fundamental premise of the theory will hold. The effect of maternal alloreactivity on fetal development, especially brain development, simply must be reckoned with. So must the related issues of selective male affliction and male antigenicity. The application of the theory to issues like sex ratio or to parity effects on IQ could be far-fetched or right on. Its relevance to evolutionary biology may be high or low, but it will occupy an important place in the future of developmental neuropsychiatry.

3. The problem of selective male affliction will obtain at least some measure of the importance it deserves. There are few indisputable facts in the field of developmental neuropsychiatry, but this is one. It will become an important element in the study of sex differences.

4. It will no longer be possible to maintain that environmental effects on fetal development begin at parturition or that maternal nutrition, freedom from infectious disease, and good obstetrical care are the sole determinants of a successful gestation.

5. The immunoreactive theory will affect research in the neurodevelopmental disorders by turning the attention of some developmental scientists to the field of reproductive immunology. The interaction of immunological and endocrine factors in promoting or retarding neural development will be a fertile area for such research. The extraordinary complexity of both domains will prevent any early resolution of the questions we have raised. Scientists will, as usual, succeed in developing more questions than answers.

6. It is an open question whether the fruits of this theory will someday be translated into practices that can improve the human condition or reduce the number of developmentally impaired individuals. This we cannot predict, but we are hopeful.

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