Hepatitis B Virus and Sex Ratio of Offspring

The response to hepatitis B virus infection in parents is related to the sex ratio of their children.

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On a genetic basis, one would expect the ratio of males to females at birth to be one. In humans, this is not the case. In most human populations there is an excess of males born, and the secondary sex ratio (the number of males per 100 females at birth) falls within a range of 104 to 107 (*1*). It is not known whether this phenomenon is due to a high sex ratio at conception, or to a high mortality of female zygotes in the earliest stage of pregnancy (that is, before pregnancy is recognized). Observations on spontaneous abortions, stillbirths, and postnatal mortality show that male mortality exceeds female by anywhere from 40 to 145 percent (*2*). Hence, by the time reproductive age is reached the sex ratio is closer to 100 (*3, 4*). It is probably this ratio that is stabilized by natural selection (*3–5*).

There are geographic and racial differences in secondary sex ratio. For example, black populations have consistently lower sex ratios at birth than nonblack populations (*1, 6*). However, significant deviations from the range of 104 to 107 are infrequent in countries with adequate ascertainment (*1, 7*). Temporal variations in sex ratio have been observed in relation to environmental factors, such as wars (*8*) and seasons (*9*); but sustained changes in secondary sex ratio probably occur too slowly to detect (*3–5*).

It has been suggested that a cultural preference for offspring of one sex could affect sex ratio. This has been seen in regard to postnatal sex ratios in societies in which a preference for one sex results in infanticide of the other (*10*). Birth control alone cannot affect secondary sex ratio, however, because the probability of a male at each birth is independent of the sex of previous births. In contrast, if couples within a population vary in their inherent or biological probability of having a male, sex preferences, expressed in terms of effective birth control, could affect the secondary sex ratio (*4, 11*).

Intrapopulation variations in sex ratio have been attributed to genetic and environmental as well as racial differences (*12, 13*). Sanghvi (*12*) found an association of the ABO blood groups of mothers and their children with secondary sex ratio. In both Bombay and New York, the sex ratio of "O" infants born to "O" mothers was significantly higher than that of "A" infants born to "A" mothers. Jackson *et al.* (*13*) found a relation between the Xg^a blood group system and sex ratio. Sex ratio was significantly higher among offspring of Xg^a+ father × Xg^a- mother matings than among those of all other Xg^a combinations. They suggested that sensitization of Xg^a- mothers by Xg^a+ female fetuses might lead to a preferential loss of such embryos. In a recent analysis of data from the United States, Erickson examined the simultaneous effects of mother's age, father's age, mother's race, birth order, legitimacy, and paternal education on sex ratio. The only significant effect detected was a negative association betwen birth order and secondary sex ratio (*14*).

A relation between sex ratio of offspring and an infectious agent has been observed in some species of *Drosophila*, in which maternal infection with small spirochetes, presumably treponemata, is associated with a reduction in male (specifically single-X chromosome) offspring (*15, 16*). This phenomenon appears to be the consequence of a disturbance in the development of male zygotes, resulting in 50 percent mortality (*15–17*).

A relation between sex ratio of offspring and an infectious agent in a human population was reported in 1975. Hesser *et al.* (*18, 19*) found a significant association between sex ratio of offspring and the responses of parents to infection with hepatitis B virus (HBV) in a Greek population. In this article, we report our investigation of the relation between HBV and sex ratio, and suggest a possible explanation for this phenomenon.

Host Responses to HBV Infection

Hepatitis B surface antigen (Australia antigen; HBsAg) is in the outer coat of the Dane particle, the presumed virion of HBV. Three types of particles (spherical, rod-shaped, and Dane particles), all with HBsAg on their surfaces, may be found in the blood of patients infected with HBV. When infected, an individual may respond by developing acute hepatitis, which is demonstrated by the transient appearance of HBsAg in his blood, elevated serum transaminase, and sometimes jaundice. Infection is followed by the development of antibody against HBsAg (anti-HBs) and the resolution of the viremia and clinical symptoms. In some cases, however, people become chronically infected with HBV, with little evidence of liver damage and few clinical symptoms. Many of these people do not develop anti-HBs, and they may be HBsAg(+) for years (*20*). Such people are termed "chronic carriers" of HBV. They may infect other uninfected persons (by transfusion, for example) and apparently are at increased risk of developing certain chronic liver diseases such as chronic aggressive and chronic persistent hepatitis, postnecrotic cirrhosis, and primary hepatocellular carcinoma (*21*).

HBV and Sex Ratio at Birth

HBV can be transmitted from mothers to offspring in the perinatal period, that is, in utero, during, or soon after birth. Infection early in life with HBV appears to increase the likelihood of becoming a chronic carrier of the virus (*22*), and vertical transmission of HBV from mother to child has been implicated as a major mechanism for the establishment of carriers in at least one population (*23*). Transmission from father to child has not

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Table 1. Number of male and female live births according to parents' response to HBV (*55*).

Parents' response to HBV	Couples (No.)	Live births*		Sex† ratio
		Male	Female	
Either parent HBsAg(+):anti-HBs(−)	33	60 (1.82 ± .22)	24 (0.73 ± .11)	250.0 (161.1, 429.1)
Both parents HBsAg(−):anti-HBs(−)	29	51 (1.76 ± .24)	35 (1.21 ± .23)	145.7 (95.7, 230.0)
Both parents HBsAg(−):either parent anti-HBs(+)	154	241 (1.56 ± .10)	222 (1.44 ± .10)	108.6 (90.5, 130.9)
Neither parent HBsAg(+):anti-HBs(−) and either parent HBsAg(+):anti-HBs(+)	16	25 (1.56 ± .39)	27 (1.69 ± .42)	92.6 (52.7, 161.1)

*The numbers in parentheses indicate the number of live births per couple (mean ± S.E.). †The numbers in parentheses indicate the 95 percent confidence limits in the sex ratio.

been studied extensively but appears to be less common (*24*).

An association between hepatitis infection and sex ratio at birth was previously suggested by Robertson and Sheard, who found a relation between an outbreak of hepatitis (of unknown etiology) and a subsequent decrease in male live births (*25*). Mazzur and Watson described a high proportion of males among siblings of HBsAg carriers in Melanesia (*26*). In 1973, we studied differences in sex ratio associated with HBsAg in parents from the Greek village of Plati in southern Macedonia (*27*). When either parent was HBsAg(+) there was a significantly higher sex ratio of live births than when both parents were HBsAg(−) (*18, 19, 28*).

The original analysis of the Plati data considered only the presence of HBsAg. We subsequently hypothesized that anti-HBs would be associated with a sex ratio alteration opposite in direction to that associated with HBsAg. In this article, we present an analysis of the Plati data, including the data on anti-HBs as well as other factors thought to affect secondary sex ratio such as parental age, number of years of marriage, and order of birth and pregnancy. The conclusions from the Plati data are compared to observations from other studies showing an interaction of HBV with sex, and a hypothesis explaining the interaction is proposed.

Results from Plati

Serums were obtained from 326 wives and 248 husbands, representing a total of 390 families. Reproductive histories, including the number and sex of live births and the number of abortions, were obtained from all the women and from those men whose wives were not available for the study. The sex ratio of the 1558 people (including parents and children) ascertained in this community was 111. This may seem high, but it is not unusual for Greece and is not significantly different from sex ratios encountered in most human populations. The normal range of sex ratios (from 104 to 107) falls within the 95 percent confidence limits of the ratio in Plati (from 100.4 to 122.7) (*6*).

Complete information, with respect to HBV serology and sex of all live births, was available from 232 couples. These couples were categorized according to immune responses to HBV, as defined by the presence or absence of HBsAg and anti-HBs in the serum of each parent (*29*). The sex ratio of offspring of 33 couples in which either parent was HBsAg(+):anti-HBs(−) was compared to that of 183 couples in which both parents were HBsAg(−). Among the 183 couples, the offspring of 29 couples in which both parents were anti-HBs(−) were compared to those of 154 in which either parent was anti-HBs(+). There were 16 couples in which neither parent was HBsAg(+):anti-HBs(−), but at least one parent was HBsAg(+):anti-HBs(+). These 16 couples are included in Table 1 but were excluded from further analysis (*30*).

Table 1 shows that sex ratio of live births was highest in families in which at least one parent was HBsAg(+):anti-HBs(−) [hereafter called HBsAg(+) couples] (*31*), intermediate in families in which both parents were HBsAg(−):anti-HBs(−), and, as predicted, lower when both parents were HBsAg(−) and at least one was anti-HBs(+) [hereafter called anti-HBs(+) couples]. A sex ratio of 145.7 may seem extreme for the HBsAg(−):anti-HBs(−) "control" population, but the 95 percent confidence limits include the normal range of 104 to 107 (Table 1). The corresponding limits for the sex ratio of children of HBsAg(+) couples do not include the normal range. The sex ratio among the 16 HBsAg(+):anti-HBs(+) families is similar to that of the anti-HBs(+) couples and suggests that the effect of anti-HBs overshadows that of HBsAg when both are present in one parent (*32*). From the analysis of these results (see Table 1), we concluded that the hypothesis that anti-HBs would be associated with a sex ratio alteration in the opposite direction from that observed with HBsAg was confirmed.

The relation between response to

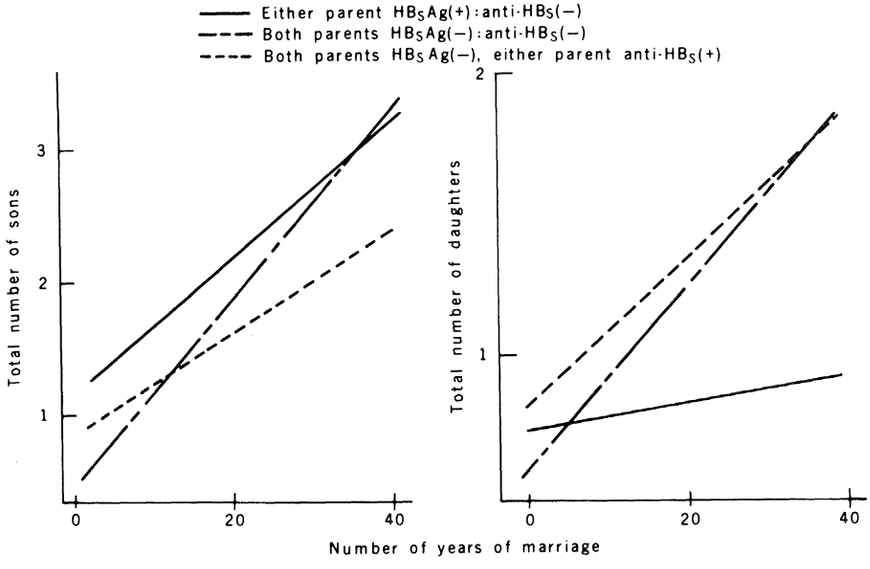

Fig. 1. Least-squares fits for the regressions of sons and daughters as a function of the number of years of marriage. By analysis of covariance (*56*), the number of sons per years of marriage is significantly higher ($P < .02$) and number of daughters significantly lower ($P < .02$) for HBsAg(+) as compared to anti-HBs(+) couples.

HBV in parents and sex ratio of offspring was further characterized by comparing the mean numbers of sons and daughters born per family to each category of parents. Table 1 shows that HBsAg(+) couples had similar numbers of sons but significantly fewer daughters per family as compared to anti-HBs(+) couples ($P = .0007$) (*29*).

Some sex ratio effects might be explained by other factors such as parental ages, number of years married, birth order, and fetal loss. Age is of particular importance because differences in the frequencies of HBsAg and anti-HBs by age are well documented (*33*). We tested the hypothesis that these factors could account for our observations in several ways. First, we compared the sex ratios and mean numbers of sons and daughters per family for only couples married more than 15 years. In this way we could examine presumably "completed" families and therefore control for effects of parental ages and birth order. This subgroup included 18 HBsAg(+), 17 HBsAg(−):anti-HBs(−), and 97 anti-HBs(+) couples (for a total of 132 families, more than 60 percent of the total sample). Again, HBsAg(+) couples had a significantly higher sex ratio ($P = .002$), the same number of sons, and fewer daughters ($P = .002$) than anti-HBs(+) couples. We then compared by analysis of covariance the least-squares fits for the regressions of sons and daughters as a function of number of years of marriage. HBsAg(+) couples had significantly more sons ($P < .02$) and fewer daughters ($P < .02$) per number of years of marriage than did anti-HBs(+) couples (Fig. 1) (*34*). The fact that in HBsAg(+) couples total number of sons per family was similar, but that there were more sons per number of years married than in anti-HBs(+) couples, suggests that the HBsAg(+) couples had sons earlier in marriage than the anti-HBs(+) couples.

Figure 2 presents the proportions of males born to HBsAg(+) compared to the number born to anti-HBs(+) couples; these data take into account paternal and maternal ages and pregnancy and birth order (*35*). The HBsAg(+) couples had consistently higher proportions of male live births than anti-HBs(+) couples, regardless of the effects of the other four factors. These overall differences, as compared by the Mantel-Haenszel method for stratified analysis (*36*), were significant (see legend to Fig. 2).

We considered two additional questions. (i) Although parental ages and pregnancy and birth orders individually did not account for the relation between response to HBV in parents and sex ratio of offspring, could these factors account for the phenomenon if considered simultaneously? (ii) What are the relative contributions of parental response to HBV and other reproductive factors to the sex ratio of offspring?

To address these questions, we used a weighted multiple linear regression analysis for estimating sex ratio (*37*). To simplify interpretation, we modeled an adaptation of the sex ratio statistic (number of males divided by the number of females) on a logarithmic scale so that positive values of the log of the sex ratio indicated more males and negative values indicated more females. We considered seven factors: HBsAg and anti-HBs in mothers and fathers, total number of pregnancies, fetal loss, and number of years of marriage (*38*). An initial analysis suggested that the presence of HBsAg in parents favors males and that anti-HBs in mothers favors females. However, anti-HBs in fathers, total number of pregnancies, number of years married, and fetal loss did not have important effects on sex ratio. We then decided to consider together the three HBV-related factors—HBsAg in fathers, HBsAg in mothers, and anti-HBs in mothers—as one "HBV response" variable. Anti-HBs in fathers was disregarded since its effect on sex ratio was negligible. This HBV response variable had three possible values: "−1" when both parents were HBsAg(−) and the mother was anti-HBs(+), "0" when both parents were HBsAg(−) and the mother was anti-HBs(−), and "+1" when either parent was HBsAg(+) [and anti-HBs(−)].

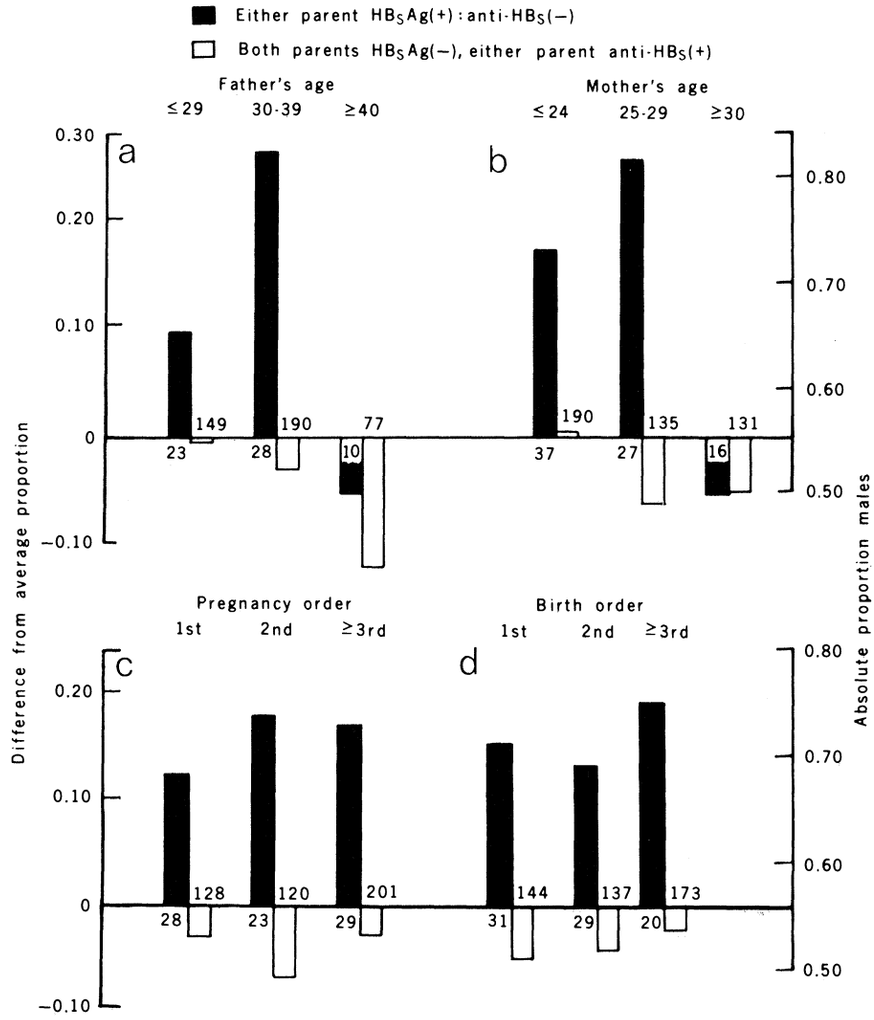

Fig. 2. The proportion of male live births according to parents' response to HBV, paternal (a) and maternal (b) ages, and pregnancy (c) and birth (d) orders. Total numbers of children are indicated at the baseline. The baseline is the proportion of males among all 633 children. The absolute proportions of males are indicated by the crossbars in reference to the scale at the right. The differences of each category from the baseline proportion are outlined by the enclosed areas in reference to the scale at the left. The Z and P values (two-tailed) calculated according to the method of Mantel and Haenszel (*36*) are as follows: (a) $Z = 2.759$, $P = .006$; (b) $Z = 3.088$, $P = .002$; (c) $Z = 3.187$, $P = .001$; and (d) $Z = 3.207$, $P = .001$.

This combined variable is significantly related to sex ratio ($\chi^2 = 5.20$). In addition, fetal loss, although not significant as an individual factor, or in relation to anti-HBs(+) or HBsAg(−):anti-HBs(−) mothers, appeared to be important when considered in reference to HBsAg(+) mothers. The sex ratio of children born to HBsAg(+) mothers who had experienced abortions or stillbirths (or both) was noticeably lower than that of children of HBsAg(+) mothers who had not experienced fetal loss. Thus, a "combined HBsAg in mothers:fetal loss" variable took the values "−1" when the mother was HBsAg(+) with fetal loss, "0" when the mother was HBsAg(−), and "+1" when the mother was HBsAg(+) with no fetal loss. This combined variable was also important in predicting sex ratio ($\chi^2 = 2.61$). When only the two combined variables are considered, the analysis predicts sex ratios for five possible categories of parents. Table 2 shows these five categories with the total number of sons and daughters, the observed sex ratio, and the sex ratio predicted by a two-variable model with the following equation: predicted sex ratio = exp [0.319 + 0.296 × HBV response + 0.553 × fetal loss].

By observation, the observed and predicted sex ratios are nearly equal. However, the model is descriptive and requires further testing with another set of data (*39*). Fetal loss in HBsAg(+) mothers has only marginal statistical significance, is based on a relatively small sample size, and is indicative of the tentative status of this model. Nonetheless, the results of this analysis reject the hypothesis that the relation between parents' responses to HBV and secondary sex ratio can be accounted for by other factors thought to affect sex ratio such as birth order, parental ages, and number of years of marriage. In addition, the analysis suggests some new hypotheses. (i) Anti-HBs has an effect on sex ratio only when it is present in mothers with HBsAg(−) husbands but not when it is present in fathers only. (ii) Fetal loss is important only in HBsAg(+) mothers and, when it occurs, is accompanied by a decrease in the generally high sex ratio of offspring of other HBsAg(+) couples. This suggests that, since HBsAg(+) mothers without fetal loss have a very high proportion of sons, those with fetal loss experience a preferential loss of males.

The regression analysis also suggested that the three original categories of HBV response be changed to the following: (i) either parent HBsAg(+):anti-HBs(−), (ii) both parents HBsAg(−):mother anti-HBs(−), and (iii) both parents HBsAg(−):mother anti-HBs(+). Figure 3 shows that these new category definitions yield clearer distinctions between the least-squares fits for the regressions of sons and daughters as compared with the number of years of marriage than did the original definitions (Fig. 1).

Table 2. Sex ratio in Plati, observed and predicted by a two-variable model including HBV response and fetal loss.

Parents' category	Sons	Daughters	Sex ratio	
			Observed	Predicted
Both parents HBsAg(−), mother anti-HBs(−)	112	86	1.302	1.376
Both parents HBsAg(−), mother anti-HBs(+)	146	140	1.042	1.023
Father HBsAg(+)	13	7	1.857	1.850
Mother HBsAg(+) without fetal loss	17	5	3.400	3.216
Mother HBsAg(+) with fetal loss	10	9	1.110	1.064

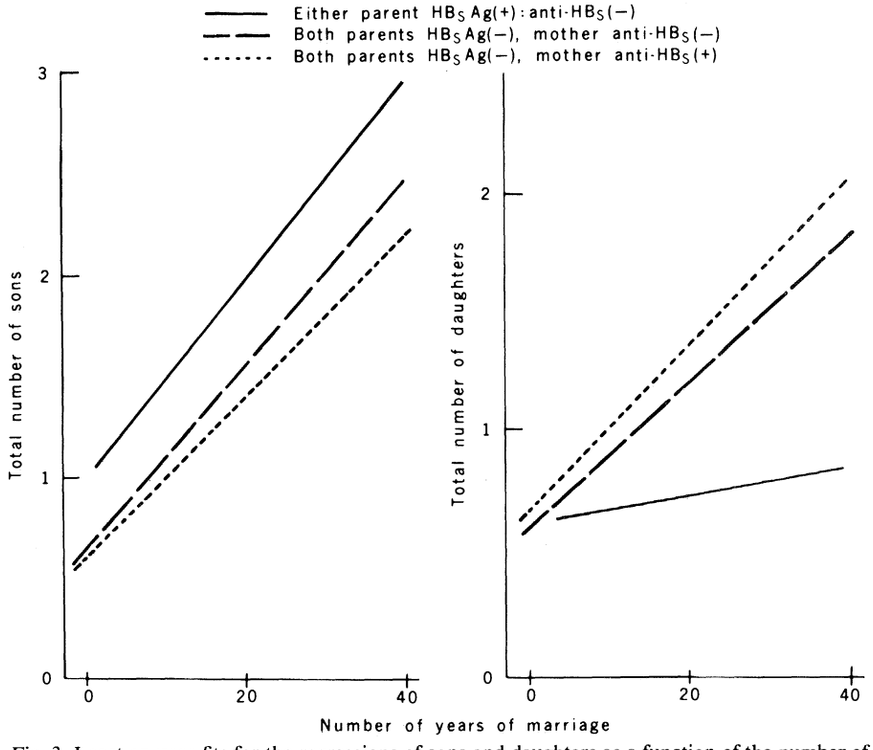

Fig. 3. Least-squares fits for the regressions of sons and daughters as a function of the number of years of marriage; revised category definitions were used. By analysis of covariance (*56*), the number of sons per years of marriage is significantly higher ($P < .02$) and number of daughters significantly lower ($P < .02$) for HBsAg(+) as compared to HBsAg(−):mother anti-HBs(+) couples.

Other HBV-Sex Interactions

In considering possible explanations for the association between parents' response to HBV infection and sex ratio of offspring, we examined two other instances in which HBV seems to interact with sex.

1) There is a sex difference in response to HBV infection. In most populations where the prevalence of chronic carriers is high, HBsAg is detected from 0.2 to 5 times more often in males than in females (*33*, *40*). Similarly, both postnecrotic cirrhosis and primary hepatocellular carcinoma are more common in males (*21*, *41–43*) and, although lupoid chronic [HBsAg(−)] hepatitis is more common in females, HBsAg(+) chronic hepatitis is more common in males (*44–46*). It has been argued that such differences are due mainly to an increased exposure of males to HBV infection (*47*). However, we have recently demonstrated that, among patients with end-stage renal disease treated with chronic hemodialysis, sex differences in HBsAg prevalence are due to a sex difference in response to HBV. We controlled the exposure variable by studying the responses to HBV infection, by sex, among 77 patients with renal disease, all

of whom became infected with HBV while receiving treatment at a single hemodialysis clinic (*48*). Among these patients, males had a 68 percent chance of remaining HBsAg(+) persistently once infected with HBV, whereas females had only a 33 percent chance. Conversely, females had a 55 percent chance of developing anti-HBs once infected with the virus, whereas males had only a 30 percent chance. These differences in response were significant and were not related to sex differences in age, underlying renal disease, or incidence of infection.

2) We found that the response of renal graft recipients to HBV infection before transplantation and the sex of their kidney donors was associated with the duration of graft survival. We studied the survival of 87 grafts in 79 patients whose responses to HBV infection were assessed before transplantation (*49*). Kidneys from HLA nonidentical male donors which were transplanted into male or female patients who had anti-HBs prior to transplantation had very short survival. Eight of nine such grafts were rejected within 4 months of transplantation. Survival of grafts from male donors was significantly longer in both uninfected patients and chronic carriers of HBsAg (median survival for both groups was more than 22 months). Among the few patients who received grafts from female donors, there were no significant differences in graft survival between anti-HBs(+), uninfected, and HBsAg(+) recipients (*50*).

How Can HBV Interact with Sex?

These two observations, together with the results of the Plati sex ratio study, led us to the hypothesis that there is cross-reactivity between HBsAg and a male-associated antigen (*51*). If HBsAg cross-reacts with a male-associated antigen, males would be more likely to recognize HBsAg as "self" and therefore would remain HBsAg(+) persistently. Females, however, would be more likely to recognize HBsAg as "foreign" and produce anti-HBs. This would result in the observed predominance of males among chronic carriers of HBV in dialysis patients and other populations. In kidney transplant patients, tolerance to HBsAg in kidney graft recipients would result in tolerance (that is, longer survival) of male tissues, whereas anti-HBs in a recipient would react with male antigens on renal allografts, resulting in early rejection of grafts from male donors.

Similarly, we can speculate that tolerance to HBsAg [reflected in the maintenance of HBsAg(+):anti-HBs(−) status] in pregnant women would result in lack of sensitization against male tissues developing within them, and therefore good survival of male fetuses. Anti-HBs in women, however, could react with male antigens and perhaps hinder fertilization by sperm bearing a Y chromosome or increase the probability of spontaneous abortion of male fetuses. HBsAg(+) males would have HBsAg in their semen which, conceivably, could protect Y-bearing sperm from the effects of anti-HBs or other "anti-male" antibodies in their spouses' reproductive tracts (*52*). The effect of fetal loss in HBsAg(+) women could be explained by unhindered replication of HBV in male fetuses, and this could result in a greater loss of male than female embryos.

The cross-reactivity hypothesis cannot explain all the observations from the Greek study. If the effects of HBsAg and anti-HBs were the only factors modifying sex ratio, HBsAg(+) couples would have more sons than anti-HBs(+) couples (*53*). However, the observation that, even among parents married more than 15 years, HBsAg(+) couples had the same number of sons but fewer daughters per family as compared to anti-HBs(+) couples suggests that human behavior is affected by hepatitis B infection. In this Greek community most younger women preferred small families and practiced some form of birth control. Also, in some parts of Greece a preference for sons (as observed in many other societies) has been reported (*6*). It is possible that parents chose to limit family size only after bearing a desired number of sons. If this were so, couples where both parents were HBsAg(−) and the mother was anti-HBs(+) might give birth to several daughters before achieving the desired number of sons while HBsAg(+) couples would have the desired number of sons early in marriage and, as a result, restrict the number of subsequent births and therefore the total number of daughters born. The sex ratio of offspring of HBsAg(−) couples with anti-HBs(−) mothers would be unaffected by this preference since these couples express neither of the factors (HBsAg, anti-HBs) affecting sex ratio. If these explanations are valid, then in this community biological and social factors interact to influence the secondary sex ratio.

Conclusions

We have observed an association between the types of response to hepatitis B infection in parents and the sex ratio of their offspring. In either parent HBsAg was associated with a high sex ratio of live births, while anti-HBs(+) in mothers was associated with a low sex ratio. Fetal loss in HBsAg(+) mothers was also related to a lower sex ratio. Other variables thought to affect sex ratio, such as paternal and maternal ages (or number of years of marriage) and total number of pregnancies, were not significantly related when considered in the context of HBV response and fetal loss.

Evidence from studies of sex differences in response to infection with HBV, and survival of transplanted kidneys in recipients with different responses to HBV, as well as the study of sex ratio reported in this article led to the hypothesis that there is cross-reactivity between HBsAg and a male-associated antigen. This hypothesis requires both experimental and epidemiological testing.

Very few biological factors that affect sex ratio have been identified. Studies of the kind reported here should be conducted on other populations (*54*), and the effects of additional infectious agents and biological factors on sex ratio should be evaluated.

References and Notes

1. P. M. Visaria, *Eugen. Q.* **14**, 132 (1967).
2. A. Scheinfeld, *Sci. Am.* **198**, 22 (Feb. 1958).
3. W. F. Bodmer and A. W. F. Edwards, *Ann. Hum. Genet.* **24**, 239 (1960).
4. C. Stern, *Principles of Human Genetics* (Freeman, San Francisco, ed. 3, 1973), pp. 529–551. In many countries, including the United States, there is still an excess of males at reproductive age. The sex ratio in a population at this time depends on specific mortality figures.
5. The selective advantage of a particular sex ratio at birth, therefore, depends upon the stabilization of this later sex ratio.
6. J. E. Hesser, thesis, University of Pennsylvania (1974). These differences cannot be explained by biases in reporting or by differences in fetal mortality (*1*).
7. Among the areas with populations reported to have sex ratios that deviate from the norm are Chile (103.0), Hong Kong (109.1), Aden (117.0), Korea (116.0), Gambia (116.2), Greece (113.0), and the Republic of South Africa (people of Asian origin only) (101.2) (*1*, *6*).
8. B. MacMahon and T. F. Pugh, *Am. J. Hum. Genet.* **6**, 284 (1954).
9. W. R. Lyster, *Hum. Biol.* **40**, 63 (1968); *ibid.* **42**, 670 (1970).
10. N. A. Chagnon, *Yanomamo: The Fierce People* (Holt, Rinehart & Winston, New York, 1968).
11. L. A. Goodman, *Ann. Hum. Genet.* **25**, 75 (1961).
12. L. D. Sanghvi, *Nature (London)* **168**, 1077 (1951).
13. C. E. Jackson, J. D. Mann, W. J. Schull, *ibid.* **222**, 445 (1969).
14. J. D. Erickson, *Ann. Hum. Genet.* **40**, 205 (1976).
15. D. F. Poulson and B. Sakaguchi, *Science* **133**, 1489 (1961).
16. B. Sakaguchi and D. F. Poulson, *Genetics* **48**, 841 (1963).
17. The expression of the "sex ratio" condition also appears to depend on the genotypes of both the host and the infectious agent (*16*).
18. J. E. Hesser, J. Economidou, B. S. Blumberg, *Hum. Biol.* **47**, 415 (1975).
19. J. E. Hesser, B. S. Blumberg, J. S. Drew, *ibid.* **48**, 73 (1976).
20. W. T. London, J. S. Drew, E. D. Lustbader, B. G. Werner, B. S. Blumberg, *Kidney Int.* **12**, 51 (1977).
21. B. S. Blumberg, B. Larouze, W. T. London, B.

Werner, J. E. Hisser, I. Millman, G. Saimot, M. Payet, *Am J. Pathol.* **81**, 669 (1975).
22. C. Bruyns, G. Urbain-Vansanten, C. Planard, C. DeVos-Cloeteus, J. Urbain, *Proc. Natl. Acad. Sci. U.S.A.* **73**, 2462 (1976).
23. K. Nishioka, *in Proceedings of a Symposium on Viral Hepatitis, 1975* (Slack, Thorofare, N.J., 1975), p. 322.
24. S. Mazzur, B. S. Blumberg, J. S. Friedlaender, *Nature (London)* **247**, 41 (1974); B. S. Blumberg, *Bull. Acad. Med. Toronto* **45**, 45 (1972).
25. J. S. Robertson and A. V. Sheard, *Lancet* **1973-I**, 532 (1973).
26. S. Mazzur and T. M. Watson, *Nature (London)* **250**, 60 (1974).
27. This study was conducted by J. E. Hesser from our laboratory in collaboration with our Greek colleagues, I. Economidou, S. Hadziyannis, and others.
28. A similar association has been observed in French families [P. Cazal, J.-M. Lemaire, M. Robinet-Levy, *Rev. Fr. Transfus. Immunohematol.* **19**, 577 (1976)].
29. Serums were tested for HBsAg by radioimmunoassay using a modification of the method of Ling and Overby, immunodiffusion, reaction electrophoresis, and passive hemagglutination inhibition by the Hepanosticon (Organon) method. Anti-HBs was determined by passive hemagglutination. Sex ratios were compared by the two-by-two chi-squared test, numbers of sons and daughters by the Mann-Whitney U statistic, and linear least-squares fits by analysis of covariance [C. M. Ling and L. R. Overby, *J. Immunol.* **109**, 834 (1972)].
30. There are some differences between the couples reported by Hesser *et al.* (*18, 19*) and those analyzed in this study. We excluded the following: three couples in which the anti-HBs status of the HBsAg(+) parent was uncertain (five sons, one daughter), and eight couples in which both the father and mother were HBsAg(−) but the anti-HBs information was incomplete (13 sons, 4 daughters). We added the following: one couple in which the father was HBsAg(+):anti-HBs(−) and the mother was not tested (two sons, no daughters), eight childless couples in which both parents were HBsAg(−), and 11 couples in which both parents were HBsAg(−) and one parent was anti-HBs(+) (29 sons, 22 daughters). This last group had been excluded by Hesser *et al.* (*18, 19*) for lack of data other than sex of offspring. Because of incomplete information, 147 families were excluded by both Hesser *et al.* and by us.
31. The HBsAg(+) category includes couples in which one parent was HBsAg(+):anti-HBs(−) regardless of the test results of the other parent.
32. There are different antigenic subtypes of HBsAg, which may occur simultaneously in one population but rarely in one individual. The presence of HBsAg and anti-HBs in one person probably represents antigen of one subtype and antibody to another.
33. B. S. Blumberg, L. Melartin, R. A. Guinto, B. Werner, *Am. J. Hum. Genet.* **18**, 594 (1966).
34. We have made similar observations on an additional population from Mali, West Africa. The fathers of these families were not studied, however.
35. The data on parental ages and pregnancy and birth orders were available for ~ 90 percent of the 633 children reported.
36. N. Mantel and W. Haenszel, *J. Natl. Cancer Inst.* **22**, 719 (1959).
37. J. E. Grizzle, C. F. Steinmer, G. G. Koch, *Biometrics* **25**, 489 (1969).
38. This analysis involved a smaller sample (~ 86 percent of the original 633 children) than the previous analyses since families with incomplete information in any variable were excluded from analysis. In families with HBsAg in one parent and anti-HBs in the other, the anti-HBs was counted as being neither present nor absent (value = 0), since the effect of HBsAg in one parent masked any effect of anti-HBs in the other. A plot of the number of pregnancies suggested a breakpoint which contrasted two or fewer pregnancies with three or more. "Years of marriage" had a correlation of greater than 0.9 with both father's age and mother's age, and therefore, could serve as a surrogate for either variable.
39. A formal goodness-of-fit test is not possible since the definitions of the "HBV response" variable and the "fetal loss" variable were suggested by the data.
40. B. S. Blumberg, L. Melartin, M. LeChat, R. A. Guinto, *Lancet* **1967-II**, 1973 (1967); J. P. Soulier, A. M. Courouce-Pauty, D. Benamom-Djiane, *Vox Sang.* **19**, 345 (1970); E. Terrier, M. Simonneau, B. Jaulmes, *ibid.*, p. 352; K. Okochi, M. Mayumi, Y. Haguino, N. Saito, *ibid.*, p. 332; P. Lous, P. Skinhoj, H. Olsen, *ibid.*, p. 379; M. Leski, C. Grivaux, A. M. Courouce-Pauty, *ibid.*, p. 359; M. Goodman, R. L. Wainwright, H. F. Weir, J. C. Gall, *Pediatrics* **48**, 907 (1971); A. Klinman, N. R. Reid, C. Lilly, J. Morrison, *N. Engl. J. Med.* **285**, 783 (1971); W. Szmuness, A. M. Prince, G. F. Etling, R. Pick, *J. Infect. Dis.* **126**, 498 (1972); B. S. Blumberg, A. I. Sutnick, W. T. London, L. Melartin, *Arch. Intern. Med.* **130**, 227 (1972); W. Szmuness, A. Prince, B. Brotman, R. Hirsch, *J. Infect. Dis.* **127**, 17 (1973); L. J. Farrow, S. G. Lamb, N. F. Coghill, R. L. Lindon, J. Preece, A. J. Zuckerman, J. S. Stewart, *Br. Med. J.* **3**, 83 (1974); W. Szmuness, R. L. Hirsch, A. M. Prince, R. M. Levin, E. J. Harley, H. Ikram, *J. Infect. Dis.* **131**, 111 (1975).
41. M. J. Tong, S-C. Sun, B. T. Schaeffer, N-K. Chang, K-J. Lo, *Ann. Intern. Med.* **75**, 687 (1971).
42. C. L. Vogel, P. P. Anthony, F. Sadikali, L. F. Barker, M. R. Peterson, *J. Nat. Cancer Inst.* **48**, 1583 (1972).
43. B. Larouze, W. T. London, G. Saimot, B. G. Werner, E. D. Lustbader, M. Payet, B. S. Blumberg, *Lancet* **1976-II**, 534 (1976). Male-to-female ratios for primary hepatocellular carcinoma are 8:1 in Taiwan (*41*) and 4:1 in Uganda (*42*).
44. N. R. Shulman, *Am. J. Med.* **49**, 669 (1970); B. H. Bulkley, W. D. Heizer, S. E. Goldfinger, K. J. Isselbacher, *Lancet* **1970-II**, 1323 (1970).
45. S. Sherlock, *Resident and Staff Physician* (July 1977), p. 42.
46. Approximately 75 percent of lupoid chronic hepatitis occurs in women (*45*), while 80 percent or more HBsAg(+) chronic hepatitis occurs in men (unpublished data from Korea).
47. S. Mazzur and N. Jones, *J. Infect. Dis.* **133**, 331 (1976).
48. W. T. London and J. S. Drew, *Proc. Natl. Acad. Sci. U.S.A.* **74**, 2561 (1977). Patients were monitored monthly for the presence of HBsAg and anti-HBs in their serums for long periods of time.
49. W. T. London, J. S. Drew, B. S. Blumberg, R. A. Grossman, P. J. Lyons, *N. Engl. J. Med.* **296**, 241 (1977); J. S. Drew, W. T. London, E. D. Lustbader, B. S. Blumberg, *Birth Defects Orig. Art. Ser.*, in press. In these data, no recipients had preformed antibody to HLA prior to transplantation.
50. Most of these grafts were from cadaver donors, but the association of duration of graft survival with responses to HBV infection was independent of whether the donors were alive and related or whether the donors were cadavers. Although the early rejection of cadaver kidneys by anti-HBs(+) recipients has been observed by others, the specific association with grafts from male donors has not yet been confirmed.
51. All three studies involve populations in which the major HBsAg antigenic subtype is **ay** rather than **ad**. There is some indication from studies in the Solomon Islands (*17*) of a relation between the **ad** subtype and an alteration of secondary sex ratio in the opposite direction. In this way the genotypes of both the host and the infectious agent would be important in determining the expression of this sex ratio effect, as seen in the *Drosophila* "sex ratio" condition.
52. J. Heathcote, C. H. Cameron, D. S. Dane, *Lancet* **1974-I**, 71 (1974).
53. This appeared to be the case in the population from Mali, West Africa.
54. Preliminary results of sex ratio studies in Africa, Papua New Guinea, and Greenland are similar to those from the Plati study; HBsAg is associated with higher sex ratios, while anti-HBs is associated with lower ones.
55. The sex ratio is the number of males per 100 females.
56. B. J. Winer, *Statistical Principles in Experimental Design* (McGraw-Hill, New York, 1962), pp. 578–594.
57. Supported by NIH grants CA-06551, RR-05539, and CA-06927 and by an appropriation from the Commonwealth of Pennsylvania. We thank Dr. Ioanna Economidou, director of the Hellenic Red Cross Blood Transfusion Center, Dr. Stephanos Hadziyannis, and the Hellenic Red Cross for their work in gathering and recording the Greek data, and the members of the Division of Clinical Research for their counsel and technical assistance.

NEWS AND COMMENT

Fuel Reprocessing Still the Focus of U.S. Nonproliferation Policy

While still a candidate seeking his party's presidential nomination, Jimmy Carter made nuclear nonproliferation a campaign issue by calling for U.S. initiatives to dissuade France and Germany from exporting nuclear reprocessing plants. Since he was elected to the presidency, Carter has continued to press a nonproliferation policy concentrated on preventing the spread of commercial nuclear technology which would make "weapons-usable" plutonium more readily available.

A major thrust of U.S. policy has been to delay the rise of a "plutonium economy" at least until safer international arrangements for the management of plutonium can be achieved. Carter set the major lines of his policy in April of 1977 when he announced his decision that the United States would defer development of the Clinch River breeder reactor and completion of the nuclear fuel reprocessing facility at Barnwell, South Carolina. Domestic nuclear energy policy would emphasize a "once through" cycle using enriched uranium in thermal reactors and the indefinite storage of reactor wastes. Administration policy is based on estimates that uranium supplies will be adequate to the year 2000 and beyond and that new technologies will improve the efficiency of the thermal reactors.

Carter also recognized the doubts of other countries about U.S. nuclear strategy and concerns about their own "energy security" and called for a 2-year cooperative study of ways to manage the nuclear fuel cycle that would minimize proliferation dangers. Carter won sup-

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