Letters to the Editor

THE HETEROZYGOTE ADVANTAGE IN PHENYLKETONURIA

To the Editor: Patients with typical ("classical") phenylketonuria (PKU), if untreated, generally suffer from mental retardation so severe as to effectively prevent reproduction; that is, the PKU gene for all practical purposes causes a recessive lethal character. The frequency of the PKU gene in many regions is accordingly very low, but it is unexpectedly high in the Irish [1–3], the West Scottish [2, 4], the Slavs [2, 5], the Yemenite Jews [6], and those descended from these peoples. The most probable explanation is that, in these ethnic groups, the heterozygote for PKU is at some advantage over the normal homozygote, that is, he or she is protected against some environmental hazard [7–9]. It was found that, in Ireland and West Scotland, mothers of children with PKU (i.e., obligate heterozygotes) had fewer spontaneous abortions than matched controls, who, presumably, did not carry the gene [8]. Ascertainment bias had been avoided [10], and the difference between the spontaneous abortion rates in heterozygous and normal women was statistically significant [8].

The only obvious biochemical or physiological difference between normal (wild-type) homozygotes and PKU heterozygotes is a higher concentration of phenylalanine in the blood and tissues of the latter; for example, fasting concentrations of 0.818 ± 0.19 and 1.333 ± 0.23 mg phenylalanine per dl in normals and heterozygotes, respectively [11]. Although the differential rates of spontaneous abortion appeared to establish a clear heterozygote advantage and amply explained the high frequency of the PKU gene in Ireland and West Scotland [9, 12], it was difficult to relate this advantage to the difference in blood phenylalanine concentrations or to suggest how this concentration could affect the tendency to abort.

Ochratoxin A is a mycotoxin produced by several species of *Aspergillus* and *Penicillium* infesting stored grains of various kinds, beans, and other foods [13]. Feed contaminated with ochratoxin A has caused outbreaks of disease in animals (e.g., in pigs in Ireland [14]), and ochratoxin A has been implicated in causing a form of human nephropathy endemic in Eastern Europe [15]. In doses sublethal or harmless to the mother, ochratoxin A can cross the placenta and cause fetal death [16]. Ochratoxin A, an *N*-acyl derivative of phenylalanine, acts by competing with phenylalanine for phenylalanyl-tRNA synthetase, thus bringing protein synthesis to a halt. Doses of phenylalanine sufficient to raise the blood phenylalanine concentration reduce or reverse the toxicity of ochratoxin A [17].

The mild, wet climate of Ireland and West Scotland tends to encourage the growth of molds. Both Ireland and West Scotland have suffered repeated famines and periods of poor nutrition over many centuries. In times of famine or economic hardship, food, prepared from moldy grain, etc., which would otherwise be avoided, tends to be eaten; such food is likely to contain ochratoxin A. A pregnant woman eating such food may miscarry, but if she is heterozygous for PKU the higher concentration of phenylalanine in her blood would tend to protect the fetus. It is suggested that this may be the mechanism by which, in Ireland and West Scotland, women heterozygous for PKU are relatively protected against spontaneous abortion. The high PKU gene frequency in the Slav countries or among the Yemenite Jews may have a similar explanation.

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REFERENCES

1. JERVIS GA: The genetics of phenylpyruvic oligophrenia. *J Ment Sci* 85:719–762, 1939
2. CARTER CO, WOOLF LI: The birthplaces of parents and grandparents of a series of patients with phenylketonuria in southeast England. *Ann Hum Genet* 25:57–64, 1961
3. CAHALANE SF: Phenylketonuria: mass screening of newborns in Ireland. *Arch Dis Child* 43:141–144, 1968
4. LINDSAY G: Scottish experiences of screening for one disorder: phenylketonuria, in *Errors of Phenylalanine, Thyroxine and Testosterone Metabolism,* edited by HAMILTON W, HUDSON FP, Edinburgh, Livingstone, 1970, pp 8–9
5. THALHAMMER O, BRANDON GR, CABALSKA B, ET AL.: Frequency of inborn errors of metabolism, especially PKU, in some representative newborn screening centers around the world: a collaboration study. *Humangenetik* 30:273–286, 1975
6. COHEN BE, SZEINBERG A, BOICHIS A, BODANYI E: Phenylketonuria in Yemenite Jews. *Pediatrics* 32:1069–1073, 1963
7. WOOLF LI: Genetics of phenylalaninemia, in *Phenylketonuria,* edited by BICKEL H, HUDSON FP, WOOLF LI, Stuttgart, Thieme, 1971, pp 103–108
8. WOOLF LI, MCBEAN MS, WOOLF FM, CAHALANE SF: Phenylketonuria as a balanced polymorphism; the nature of the heterozygote advantage. *Ann Hum Genet* 38:461–469, 1975
9. WOOLF LI: A study of the cause of the high incidence of phenylketonuria in Ireland and West Scotland. *J Irish Med Assoc* 69:398–400, 1976
10. TEN KATE LP: On estimating the actual rate of foetal loss in families with an autosomal recessive disorder and Woolf's data on PKU. *Ann Hum Genet* 41:463–464, 1977
11. WOOLF LI, CRANSTON WC, GOODWIN BL: Genetics of phenylketonuria. *Nature* 213:882–885, 1967
12. WOOLF LI: The high frequency of phenylketonuria in Ireland and Western Scotland. *J Inher Metab Dis* 1:101–103, 1978

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13. World Health Organization: *Environmental Health Criteria 11: Mycotoxins.* Geneva, World Health Organization, 1979, pp 88–91
14. Buckley HG: Fungal nephrotoxicity in swine. *Irish Vet J* 25:194–196, 1971
15. Krogh P, Hald B, Plestina R, Ceavic S: Balkan (endemic) nephropathy and food-borne ochratoxin A: preliminary results of a survey of foodstuffs. *Acta Pathol Microbiol Scand, Sect B* 85:238–240, 1977
16. Brown MH, Szczech GM, Purmalis BP: Teratogenic and toxic effects of ochratoxin A in rats. *Toxicol Appl Pharmacol* 37:331–338, 1976
17. Creppy EE, Sclegel M, Roschenthaler R, Dirheimer G: Phenylalanine prevents acute poisoning by ochratoxin A in mice. *Toxicol Lett* 6:77–80, 1980

SECONDARY SEX-RATIO VARIATION

To the Editor: Strong evidence is presented by Ruder [1] that paternal age, independent of any other variables such as parity or maternal age, influences the percentage of male births, at least among whites in the U.S.A. Her research does not, however, address the question as to whether this correlation between age of father and sex ratio of offspring is a statistical one to be observed only for the sum total of all fathers, or whether it will hold also for individual fathers. As the father of one or two sons ages, is there an increase in the probability that his next child will be female, or is it rather that men who father only sons or mostly sons are younger when they reproduce than are fathers of only or mostly daughters?

On a rather small sample of German families, this author [2] found that if the first child is born within the first 18 months after the wedding the percentage of sons among the first born is as high as 55.3%, whereas the percentage of sons among first children born more than 18 months after the wedding is only 49.8%; the difference of 5.5% was statistically significant. In 1963, Renkonen et al. [3] verified this finding for a much larger set of births from Finland. Thus, fathers whose first child was male should, on the average, be about 9 months younger than fathers whose first child was female at the birth of this first child. If this differential in the speed of reproduction applies to later births also, then in families with more sons than daughters, the fathers would be younger at all births. Since most births in such families are male, this could explain most, if not all, of the findings by Ruder [1].

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REFERENCES

1. Ruder A: Parental-age and birth-order effect: the human secondary sex ratio. *Am J Hum Genet* 37:362–372, 1985
2. Bernstein ME: A genetic explanation of the wartime increase in the secondary sex ratio. *Am J Hum Genet* 10:68–70, 1958
3. Renkonen KO, Lehtovaara R: The time interval from the wedding to the birth of the first child. *Ann Med Exp Fenn* 41:560–564, 1963

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