ABO Blood Groups and the Hardy-Weinberg Equilibrium

It is now 50 years since Bernstein's classic demonstration (*1*) that the two-locus interpretation of the genetic basis of the ABO blood groups made by von Dungern and Hirszfeld (*2*) was inconsistent with the population frequencies of the ABO phenotypes, and that the hypothesis of three alleles at a single locus fit those frequencies much better. The algebra involved in this analysis has been reproduced in all major genetics texts and has been taught to countless numbers of students as a convincing illustration of the power of the Hardy-Weinberg formulation in differentiating between alternative genetic systems. It may therefore not be inappropriate to point out that the first part of his analysis does not demand the use of the Hardy-Weinberg equilibrium expression for allele frequencies ($p^2 + 2pq + q^2$) at all, but is, in fact, independent of the allele frequencies at a specific locus.

We are concerned here only with that part of his argument which deals with the assumption of two independent loci, an A and a B locus, as the genetic basis for the ABO groups. The set of equations relating the frequencies of the A, B, AB, and O phenotypes with the corresponding genotypes and allele frequencies, as they appear in Bernstein's original paper and copied, with minor modifications, in standard textbooks on genetics, is as follows.

Genotype	Probability	
	Group O	
aabb	$(1-p)^2(1-q)^2$	$= \bar{p}^2 \cdot \bar{q}^2$
	Group B	
aaBB	$(1-p)^2q^2$	$= \bar{p}^2 \cdot (1-\bar{q}^2)$
aaBb	$2(1-p)^2q(1-q)$	
	Group A	
AAbb	$p^2(1-q)^2$	$= (1-\bar{p}^2)\bar{q}^2$
Aabb	$2p(1-p)(1-q)^2$	
	Group AB	
AABB	$p^2 \cdot q^2$	$= (1-\bar{p}^2)(1-\bar{q}^2)$
AaBB	$2 \cdot p(1-p)q^2$	
AABb	$2p^2q(1-q)$	
AaBb	$2p(1-p) \cdot 2q(1-q)$	

By inspection, $\bar{O} \times \overline{AB} = \bar{A} \times \bar{B}$. Also since $\bar{A} + \overline{AB} = 1 - \bar{p}^2$ and $\bar{B} + \overline{AB} = 1 - \bar{q}^2$, then $(\bar{A} + \overline{AB}) \cdot (\bar{B} + \overline{AB}) = \overline{AB}$. (A bar over a term indicates "the frequency of" that term.)

The preceding implies that the equation $(\bar{A} + \overline{AB})(\bar{B} + \overline{AB}) = \overline{AB}$ is a necessary relationship of the phenotypic frequencies revealed only after the application of the Hardy-Weinberg rule for the distribution of alleles in homozygotes and heterozygotes. However, a second glance at the equation suggests something quite different. What that equation states is that if there are two sets of alternative properties, A (and not-A) and B (and not-B), with the sets independent of each other, then the probability of A and B occurring simultaneously is the probability of A times the probability of B. This is obviously the statement of the elementary rule of probability and, as such, should not require the algebraic manipulation of the gene frequencies for its derivation. In fact, it does not. That this relationship is independent of allele frequencies may be easily verified by substituting nonequilibrium values for the homozygotes and heterozygotes at each locus. As long as the two loci are combined randomly, the simple relationship must hold.

Similarly, an alternative relationship, $\bar{O} \times \overline{AB} = \bar{A} \times \bar{B}$, suggested by the same method, is independent of gene frequencies and is simply obtained if not-A not-B is substituted for O, A not-B for A, and B not-A for B.

A little thought will convince one that not only must these relationships hold for this particular genetic theory, that of the two loci, but for any genetic hypothesis, no matter how simple or contrived, so long as A and B are independent. As a matter of fact, such tests for independence would be valid even if the characteristics were not genetically determined.

Bernstein was a mathematician with considerable facility in handling genetic formulations; this is well illustrated by his subsequent demonstration, in the same work, of the surprisingly good fit of the three-allele hypothesis with population data, as well as by his other contributions (*3, 4*). We might wonder, then, why he chose to present the argument against the two-locus hypothesis in this cumbersome way. It is possible, but not likely, that he overlooked the significance of his final equation for the two-locus case, that $p(A) \times p(B) = p(AB)$. Perhaps he recognized the predilection of geneticists for algebraic formulations and felt that they would be more convinced of the validity of his argument if he expressed it with detailed (and unnecessary) algebra. Or could it be that he possessed a rare sense of humor and was playing a practical joke on biologists? If so, it has worn well.

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References and Notes

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2. E. von Dungern and L. Hirszfeld, *Z. Immunitaetsforsch. Exp. Ther.* **8**, 526 (1911).
3. F. Bernstein, *Z. Induk. Abstamm. Vererbungsl.* **54**, 400 (1930).
4. ———, *ibid.* **57**, 113 (1931).
5. I thank Professor F. H. Sobels of the University of Leiden for making facilities available for relaxed contemplation during a sabbatical leave.

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"Serotonin Depression"—A Biochemical Subgroup Within the Affective Disorders?

Abstract. *The distribution of 5-hydroxyindoleacetic acid (5-HIAA) concentrations in the cerebrospinal fluid of 68 depressed patients was bimodal. Twenty-nine percent of the patients were in the lower mode, with a concentration of 5-HIAA below 15 nanograms per milliliter. Although there were no differences in overall severity of depression between the two modes, there was a significant correlation between the concentration of 5-HIAA and severity of depression in the lower, but not in the upper, mode. The finding suggests the existence of a biochemical subgroup of depressive disorder, characterized by a disturbance of serotonin turnover.*

Evidence of a disturbance of serotonin turnover in the depressive disorders has accumulated over recent years, but the findings in the field are contradictory (*1*). Low (*2*) but also normal (*3*) concentrations of serotonin have been found in brains from suicide victims. Tryptophan, the precursor of serotonin, is claimed by some authors (*4*) to have antidepressant effects, while others (*5*) have found it to be of doubtful value. Low (*6*) but also normal (*7*) concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) from depressed patients have been reported.

We have developed a highly sensitive and specific mass fragmentographic method (*8*), which has been used to determine 5-HIAA in CSF from 43 depressed patients (*9*). The distribution of the metabolite appeared to be bimodal. This suggested the existence of two biochemically different types of depression, which might explain some of the divergences between earlier findings.

A further 25 patients have now been studied. In this second sample a more extensive rating of psychopathology was used; otherwise, the basic study design remained essentially the same. Only patients