HIRSZFELD* AND THE ABO BLOOD GROUPS

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The importance of Ludwik Hirszfeld's contributions to our knowledge of the ABO blood group system has been affirmed in various ways: by Karl Landsteiner (1931) in his Nobel Address, by Hirszfeld's election to the Presidency of the Blood Group Section of the Second International Congress of Blood Transfusion (Paris, 1937), and by the naming in his memory of the Hirszfeld Microbiological Institute in Wroclaw (Milgrom, 1954). Despite this, however, one very important part of his work on the blood groups still awaits appreciation and even recognition—namely, his early, explicit awareness of the relevance of the *ABO* genes to natural selection. Accordingly, an attempt is made in this communication to draw together his various comments on the subject, under headings of Climate, Age and Sex, Social Class, Disease, and Race.

CLIMATE

In 1900 Mendel's principles of heredity, unappreciated since 1866, were published afresh in the three main languages of science—in French by de Vries (1900a, b), in German by de Vries (1900c), Correns (1900a, b, c), and Tschermak (1900), and in English by Bateson (1900, 1901)—but as late as 1909 Bateson had to report that "Of Mendelian inheritance of normal characteristics *in man* there is as yet but little evidence" (author's *italics*). Almost immediately after this, however, von Dungern and Hirszfeld (1910, 1911) were able to show, from a study of the families of the teaching staff at Heidelberg University, that the principles of Mendelism apply to the normal human serological characteristics discovered by Landsteiner (1900, 1901) 10 years before, characteristics which they proceeded to name the blood groups AB, A, B, and O.† Eight

years later Hirszfeld and his wife (1919a, b, c) recorded the ABO blood group incidence in 8,000 soldiers and refugees on the Macedonian Front, and the hair colour of 1,000 French and British soldiers. No correlations were found between hair colour and the blood groups but, broadly speaking, the results showed a fall in the incidence of blood group A from Western Europe to India, and of blood group B from India to Western Europe.

The Hirszfelds concluded that the most likely cause of this East-to-West reciprocity was that a mainly *A* race and a mainly *B* race had developed, by mutation from *O*, in the West and East respectively, and had since become mixed by migration or conquest and subsequent intermarriage. But before they reached this conclusion the Hirszfelds put forward a much more interesting suggestion: "A is more suitable for increased resistance of the organism to disease in a temperate climate, while B is more suitable in a hot climate". The perceptiveness of this remark is seen from an authoritative statement made forty years later by Sheppard (1959a):

"In the long run selection due to changes in the external environment will alter the gene pool and therefore the selective value for the different blood group genotypes. . . . There is, however, some evidence that the environment can, on occasion, play a more direct role in altering the selective values of the various allelomorphs of the *ABO* locus. . . . In every thorough investigation of polymorphism maintained by selection it has been shown that the selective values of the phenotypes change markedly from place to place and from time to time. Thus if the ABO blood groups are maintained by selection it would be unreasonable to postulate that the selection pressures are the same everywhere." (See also Sheppard, 1959b.)

* This is the Polish spelling. Early publications use the German spelling Hirschfeld (see References).

† Their paper of 1910 has recently been translated into English—see *Transfusion* (1962), 2, 70—as one of the "Historical Milestones" series.

Furthermore, if the Hirszfels' environmental hypothesis were well-founded, one would expect the high Indian incidence of B, which was one of the pillars of that hypothesis, to be characteristic not only of the Indian (Caucasoid) race but also of the Mongolian race, and this is found to be so. Indeed, Mourant (1954) has drawn attention to the remarkable fact that the regions in which the incidence of B is highest of all in both races are those in which their territories adjoin, and he even suggests that this phenomenon may indicate environmental selection. Buettner-Janusch (1959) goes still further along the same lines by pointing out that the Hirszfels' East-to-West fall in the ratio of B to A "follows certain relatively consistent changes in altitude and environment", and Huxley (1960) has suggested, on general grounds, that "Well-defined clines inexplicable by ABO gene-diffusion are a possibility to be borne in mind". In fact the view is now widely held that one of the functions of a morphic system like that of the ABO genes may be to extend the environmental range of the species in which it occurs (Huxley, 1955), and that, in the words of Dobzhansky (1955), "Genetic variability is a means whereby Mendelian populations master environmental diversity". See also Levene (1953), Waddington (1957), and Dobzhansky (1960).

AGE AND SEX

Though the Hirszfels at once rejected their own hypothesis that "A is more suitable for increased resistance of the organism to disease in a temperate climate, while B is more suitable in a hot climate", the basic idea exemplified in it—i.e. that the ABO genes have selective value—very soon became a familiar and productive one. As well as leading to many investigations, especially in Finland, of the relationship of the blood groups to particular diseases it also prompted investigations of the relationship of the blood groups to longevity. Thus a series of 1,000 *post mortem* subjects in Munich (Oppenheim and Voigt, 1926; Lützel and Dormanns, 1929) led the authors to suggest that B individuals might have, on average, the longest life-span, and Hirszfeld (1928) considered the same possibility on the basis of a series of 3,000 old people living in Copenhagen (Thomsen, 1927; Hansen, 1928).

Meanwhile, at the other end of the age-scale, Hirszfeld and Zborowski (1925) had blood-grouped 264 newborn babies and their mothers. They found that the male-to-female ratio was very much higher for the babies of AB mothers than for those of non-AB mothers—i.e. 2.87 (23 : 8) compared to

1.04 (119 : 104)—and they declared that "if this finding were confirmed it would have far-reaching theoretical significance". Unfortunately, however, no reference to Hirszfeld and Zborowski's observation was made in the monographs of Snyder (1929), Lattes (1929), Steffan (1932), Schiff (1933), and Wiener (1935), or in the lengthy reviews of Levine (1928), Witebsky (1932), and Holzer (1935), and the matter lay undisturbed for 26 years.* Eventually the subject was brought to life again by Sanghvi (1951), who, in a series of 2,200 New York and Bombay babies, found a significantly higher male-to-female ratio for O babies of O mothers than for A babies of A mothers—a finding confirmed by several large series in 1954–59 (Allan, 1959). This ironically suggests that, if Hirszfeld and Zborowski had enlarged their series of newborn babies to even as much as half the size of the Hirszfels' own 1919 series of 8,000 adults, they might have anticipated Sanghvi's finding and failed to confirm their own. As it is, their own finding has now been partly confirmed on fairly large numbers, for in the aggregate of all known series of white babies so far reported (Allan, 1959) the ratio of male to female babies is significantly higher for the babies of AB mothers than for those of non-AB mothers—i.e. 1.26 (667 : 531) compared to 1.08 (16,130 : 14,982).

In this connexion it is interesting that Hirszfeld and Zborowski (1926) also found a shortage of group O female offspring from the mating class *O fathers by A mothers* and a shortage of group A female offspring from the mating class *A fathers by O mothers*, and also that this finding has nearly always been misrepresented (Obituary Notice, 1954; Allan, 1954).

SOCIAL CLASS

Though the Hirszfels rejected their own hypothesis that the A and B genes might have different selective values under different climatic conditions, Hirszfeld suggested 9 years later (1928) that the selective values of the ABO genes might differ in the different social classes, with their varying environmental stresses. Thus, in commenting on the results of his blood grouping of 1,200 Warsaw school-children, he remarked that "the table shows a rather higher percentage of group B children in the State schools. How easy it would be to relate this circumstance to some disease or other with a mainly working-class incidence!" Whether or not the exclamation mark means that this time Hirszfeld

* Oppenheim and Voigt may have known of the finding, for Hirszfeld (1926) writes of their having told him in conversation that in their series of 500 Munich *post mortem* cases there were only four AB males compared to fourteen AB females.

was writing only half-seriously, the fact is that he was giving here a particular illustration of a hypothesis advanced 23 years afterwards by Darlington (1951) and tested in two different ways in recent years—namely, by Dawson (1958), with not conclusively negative findings, in a comparison of the occupations of 10,000 Dublin blood donors, and by Haga (1959), with rather more suggestive results, in a comparison of foetal loss in two environmentally-different Japanese communities. Darlington's hypothesis was advanced at a Symposium arranged by the Royal Anthropological Institute which led to the establishment of the Nuffield Blood Group Centre.

DISEASE

Among those who made the studies referred to above, of the ABO blood groups in relation to particular diseases, was Hirsfeld himself, who instigated the blood grouping, in his Warsaw laboratory, of 300 tuberculosis cases, 1,700 syphilis cases, 1,200 Schick test cases, and 1,200 Dick test cases. Moreover, the fact that all these series gave non-significant or negative results did not deter him from putting forward (Hirsfeld, 1926) an idea now supported by Vogel, Pettenkofer, and Helmbold (1960) on evidence subsequently discussed by Fraser Roberts (1962) and Springer and Wiener (1962)—the idea that the existence and distribution of normal antibodies, including anti-A and anti-B, might help to elucidate epidemiological history (see also Eichner, Finn, and Krevans, 1963).

In addition Hirsfeld must also have studied closely the results of other people's work in this field, as is seen from his comment on a report by Buchanan and Higley (1921) on a series of 2,400 patients of varying national origin, with a variety of diseases, blood-grouped at the Mayo Clinic in 1917–21. Fraser Roberts (1957) has shown that, in assessing their results, Buchanan and Higley gave undue weight to the geographical variations in ABO blood group distribution which the Hirsfelds had recorded in 1919, with the result that they failed to appreciate that their peptic ulcer series contained a real excess of group O. But though the significance of their figures escaped the notice of Buchanan and Higley themselves, and also of others, with the result that it was not confirmed for 35 years (Aird, Bentall, Mehigan, and Roberts, 1954), it did not escape the notice of Hirsfeld, as is clear from his comment 5 years later (Hirsfeld, 1926):

"Buchanan and Higley exclude the possibility of significant associations between the blood groups and diseases . . . but what strikes one is their astonishing

excess of group O patients with chronic ulcer or gall-bladder disease. It is possible that obscure metabolic anomalies may be involved here."

The fact that almost all the diseases so far known to be, or suspected of being, associated with blood groups are diseases of the alimentary tract (Fraser Roberts, 1957, 1959) gives special point to Hirsfeld's coupling of Buchanan and Higley's figures for gall-bladder disease with their chronic ulcer figures.

That Hirsfeld was able to recognize, from a series of only 172 cases, the now-established association between peptic ulcer and blood group O was due to the magnitude of the association between group O and duodenal ulcer. On average, group O individuals are about 1·36 times as likely as group A individuals to have a duodenal ulcer (Fraser Roberts, 1957), a fact which highlights, in human terms, the statement of Ford (1960):

"One of the big advances in quite recent times is the discovery that selection-pressures are enormously greater in nature than we had any concept of. When Fisher wrote "The Genetical Theory of Natural Selection" (1930) he envisaged advantageous selection-pressures in natural populations of up to about 1 per cent. To-day we know that in such populations selection-pressures of up to 50 per cent. are quite usual."

RACE

Not only, however, was Hirsfeld keenly aware of the possibility of associations between the ABO blood groups and particular diseases. He further believed that such associations might differ in different races, and it is notable that a beginning has very recently been made on comparative studies by which this hypothesis can be tested (Buckwalter, Kark, and Knowler, 1961; Bronte-Stewart, Botha, and Krut, 1962; Desai and Creger, 1962). Thus in a passage on the anthropological uses of the blood groups Hirsfeld (1926) wrote:

"Associations between [a blood group] and predisposition or immunity to disease can arise in two ways—from secondary selective processes (vorgängen) or from the action of neighbouring genes. . . . We might postulate the appearance in many individuals in a particular population of a mutation in the vicinity of the *A* or *B* gene conferring special survival value in relation to diphtheria . . . whereas a different population can be envisaged in which this mutation would not appear. . . . I do not doubt that the blood groups can help to solve the deepest problems of anthropology."

That Hirsfeld's illustration of the manner in which the ABO blood group genes may interact with other genes was linked to a wholly fallacious

idea does not substantially detract from his clear recognition that the genes do indeed interact, and that they may do so in different ways, *for genetic reasons*, in different races. Nor is it a long step from the passage quoted above to the most dynamic of contemporary hypotheses with regard to the world distribution of the blood groups—the hypothesis of Ford (1942, 1945) that the blood group genes may act, and be acted upon, in different ways and degrees in different races, *as a result of racial differences in the modifying genes*, and that these racially-determined variations in the effects of the ABO genes are the cause of the racial variations in ABO blood group distribution (Cf. Brues, 1954).

In this connexion it is interesting that the West-East fall in the incidence of A which the Hirszfels established is now known to be much more true of the A_2 than of the A_1 gene. (The existence of the sub-groups of A was discovered in 1911 by von Dungern and Hirszfeld.) In aboriginal populations A_2 is relatively common in Europe and Africa, a great deal less common in India, and rare or absent in Eastern Asia, Australasia, and America (Mourant, Kopeć, and Domaniewska-Sobczak, 1958; Kirk, 1961). By contrast the frequency of the A_1 gene is relatively high in a broad and almost uninterrupted band running *south-east* from Northern Canada and Greenland over Europe and Western Siberia to Mongolia, China, Japan, Polynesia, and Australasia. The frequency of the B gene is relatively high in a broad and almost uninterrupted band running *south-west* from North-West Alaska and Northern Siberia over the whole of Asia, Eastern Europe, and the Near East to Africa and Madagascar. The frequency of the O gene is as high as 60–100 per cent. almost everywhere except where the broad bands of high B and high A_1 frequency intersect like an enormous St. Andrew's Cross—i.e. on the land-mass from the Adriatic, Baltic, and Barents Seas to the Sea of Japan and the Bay of Bengal—a world-wide abundance which the finding of Sanghvi (1951) with regard to sex-ratio at birth in relation to blood group (*vide supra*) might eventually help to explain. For details and maps see Mourant and others (1958).

In the light of this world distribution of the A genes it is not surprising that Hirszfeld (1938) took public issue with the German Society of Blood Group Research for characterizing the blood group A as Nordic, and for condoning the use of the blood groups in the interests of political demography. What is surprising is that, despite this protest, a copy of his "Konstitutionsserologie und Blutgruppenforschung" (1928) should have remained, throughout the Nazi régime, on the shelves of the Prussian State Library.

DISCUSSION

From the above it is clear that Hirszfeld and his colleagues, besides having shown that the blood groups are (1) determined genetically and (2) distributed differently in different human races, were also the first to suggest that the genes by which the blood groups are determined are subject to natural selection, and the first to explore this basic idea in cardinal directions. It is also clear that in so doing Hirszfeld was able to recognize an important finding which has now been fully confirmed—namely, the strong association of blood group O with peptic ulcer—while he himself made an observation which has now been partly confirmed—namely, a high sex ratio in babies of AB mothers. And it is clear that he was aware of the importance of these observations.

Yet Hirszfeld omitted to follow up these observations, and this omission may well have been far-reaching in its effects. The timely broadening of the field of human genetics which might have resulted from (say) a more general and effective recognition of the importance of the figures of Buchanan and Higley (1921) on peptic ulcer may be gauged from the contemporary (1919) edition of Thomson's "Heredity", or, for that matter, the 1929 edition of Gates's "Heredity in Man". Even as late as 1950 Dobzhansky could say that "The action of natural selection on man has been almost completely ignored", and that "next to nothing has been done to reveal the adaptive significance of human genetic traits"—see also Buettner-Janusch (1959)—and few things did more to put this right than the confirmation of Buchanan and Higley's figures 4 years later by Aird and his colleagues (1954). A beginning along these lines had, in fact, been made, in respect of some polygenic characters, before the First World War (*e.g.* Carr Saunders, 1912), but the subject was then lost sight of. Perhaps it fell between the two stools of the Mendelian-Pearsonian controversy.

But Hirszfeld's failure to follow up the paths he uncovered was not only deeply disappointing; it is also very puzzling. (Even *Les groupes sanguins* (1938), with its autobiographical passages, yields no clue.) The durability and liveliness of his interest in the subject is attested by its recurrence in his writings over a period of many years. And though his administrative and editorial duties were increasing—he was Director of the Warsaw Serum Institute from 1920 to 1931, and from then to 1939 he was concurrently a Warsaw University Professor and the Director of the Department of Bacteriology and Experimental Medicine in the Polish National Institute of Hygiene—his authoritative position would have enabled him to delegate the testing of his ideas. It is

unlikely, too, that a man who lectured secretly in the Ghetto was deficient in perseverance.

There are, however, three other less improbable causes—respectively theoretical, practical, and personal—though which of these, or which combination of them, may have been active can only be guessed.

The first possibility is that Hirszfeld's belief that the ABO blood group genes are physiologically active, not inert, may have been undermined, in course of time, by the lack of a real theoretical basis for it. Sheppard (1958) believes that "had more people been familiar with the principles of polymorphism, some of these facts"—i.e., the various associations found since 1953 between the blood groups and disease—"would have been discovered and investigated long ago." This may indeed be true of the generality, but Hirszfeld, for his part, was writing before the principles of polymorphism had been established, and accordingly the hypothetical roots of his unproductivity must be looked for further back—as far back even, perhaps, as the period discussed in the following passage from a paper by Fisher (1936), "Has Mendel's Work been Re-discovered?"

"Had Mendel's new facts and methods come to the knowledge of Francis Galton the experimental analysis of heredity might well have been established 25 years earlier than it was in fact; but minds equally receptive were certainly rare. . . . The journal in which Mendel's work was published was not a very obscure one, and seems to have been widely distributed. In London, according to Bateson, it was received by the Royal Society and the Linnaean Society."*

This prolonged neglect of Mendel (1866, 1870)—a neglect which was to cause him "intense disappointment" (Fisher, 1930)—meant that his principles of heredity were unknown even to his young compatriot Landsteiner when, in 1900, at the zenith of Viennese medical world-supremacy, he discovered the ABO blood groups. Moreover, the contrast thus made plain between the retarded state of genetics and the advanced state of immunology, especially in Central Europe, in 1900 could not have been sharper, or have affected more deeply the course of blood group research in the next 50 years. Hirszfeld alone of the early blood group workers appears to have been accustomed to think of the blood groups in a genetic way as well as immunologically, but even in the 1920s he was thinking in the dark, for a parallel more fundamental result of the lost generation of genetic investigation was the delay till 1930

in the development of a theory of evolutionary genetics—the theory embodied in Fisher's "Genetical Theory of Natural Selection", with its synthesis of Darwinism and Mendelism. Nor did the fact that the 1920s were the hour before the dawn make any real difference, for Fisher's book was, apparently, so far ahead of its time that neither a German nor a French translation was made of it. (A contributory cause of this omission in Germany was, perhaps, the fact that the nazis came to power (1933) so soon after the book had been published in Britain.) Thus the volume in which alone Hirszfeld would have found the *rationale* of his ideas of the 1920s, and thereby, quite probably, the stimulus to test them systematically during the 1930s, is most unlikely to have come within his ken in the years up to 1939, and still less likely to have done so at any time afterwards. Doubtless Hirszfeld was familiar, after 1935, with the ABO blood group *vade mecum* of the English-speaking world—Wiener's "Blood Groups and Blood Transfusion" (1935), a volume notable for its scholarliness—but in this no mention was made of "The Genetical Theory of Natural Selection".

The second possibility is that the cause of Hirszfeld's failure to follow up the paths he uncovered was a practical one, arising from the fact that he was writing at a time when even the idea of large-scale grouping of hospital patients, expectant mothers, or newborn babies was far in the future. In the light of this fact he may well have thought it impracticable to try to amass the very large numbers of cases—"numbers", as Fraser Roberts (1957) has said, "to be counted in thousands rather than hundreds"—which he doubtless foresaw would be needed for adequate confirmation of findings in this particular field of study, or even for "infirmation", to use a term of Bacon (1604) revived by Nicod (1924). This possibility is the stronger in that, as Brass (1960) has said, Hirszfeld's general statistical outlook between the two world wars may, in any event, have been that of the then predominant Pearsonian school of biometry, with its belief in the invariable need for, and value of, largeness of sample.

There remains the possibility that the cause of Hirszfeld's failure to follow up his observations was, in fact, neither theoretical nor practical but emotional—that his evidently genial, prolific, intuitive personality (Milgrom, 1960) made him, within this field, mistakenly, content to remain a sower.

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NOTE ADDED IN PROOF

The section on Race contains quotations of certain passages from one of Hirszfeld's papers. A recent re-translation of these and related passages suggests that I may have previously read more into them than Hirszfeld himself had in mind.