

## BLOOD GROUP MYTHOLOGY: PRESENT STATUS \*

ALEXANDER S. WIENER †

Serological Laboratory, Office of the Chief Medical Examiner of New York City, and Department of Forensic Medicine, University Medical School, New York, N.Y., USA

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*The discovery of a great multiplicity of previously unknown facts and principles has served to develop the field of blood grouping into an important complex science. The formidable task of mastering the now highly complex field of blood grouping has been facilitated by the availability of a comprehensive text on almost all aspects of the subject, which is now in its sixth edition. This invaluable source book is widely used by advanced workers in the field as well as by beginners, and is treated as the bible on the subject to the exclusion of all other texts. However, the so-called bible has serious scientific faults in that important basic principles are ignored, and certain important basic facts are distorted or misrepresented. Fortunately, other texts are available which are free of these faults, and the use of a single book as the sole source of knowledge concerning the subject has by implication given rise to the myth that the book in question is infallible and may be used alone to the exclusion of all other sources of information. The purpose of the present review has been, not to detract from the well recognized merits of the important "blood group bible", but to point out its limitations, and to point out the existence of other sources which, while not as comprehensive, are free of mythology. If this review serves to remind the readers to consult other sources in addition to the blood group bible, it will have served its purpose, and this may lead to further advances in the field of blood grouping as well as help do away with the thriving field of blood group mythology.*

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The modern world is composed of a society characterized on the one hand by outstanding advances in science and technology, and on the other hand by anachronistic paradoxes, and by superstitious beliefs and mythology. For example, contrasting with the advances in the science of astronomy made possible by advances in radioastronomy, electronics and computer sciences, there has been an increase in the popularity of astrology, such that even in our modern sophisticated society millions of Americans are devotees or believers, as evidenced by the column on the subject which appears in 1300 daily newspapers and which one can consult for one's daily horoscope. The situation has become so serious that a group of 168 scientists, including 18 Nobel prize winners, have recently issued a statement pointing out that it is simply a mistake to imagine that forces exerted by stars and planets at the moment of birth can in any way shape our future. Despite this, it has been estimated that in the United States today there are 10,000 professional astrologists who make a living by writing,

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teaching and acting as consultants about the stars, and astrology courses are even being offered in some colleges.

This paradoxical situation is by no means unique for astronomy and astrology, but characteristic of almost all aspects of modern society and science, including blood grouping. In fact, I was confronted with the problem of blood group mythology as long ago as 1928, when while still a medical student I first entered the field of blood grouping. In my very first published paper, when mentioning the discovery of the A-B-O blood groups, I naively cited a report from the current Japanese literature claiming that such tests were in vogue as early as the 12th and 13th century in China and Japan. After my article appeared, at Dr. Landsteiner's suggestion, I consulted a source book from the Surgeon General's library in Washington, D.C., which explained the basis for this fantastic claim. In the book, the following test of blood relationship was described. The fingers of the two individuals in question were punctured, and the blood allowed to fall into a basin of water; if the bloods flowed together the two persons were indeed related, while if the drops flowed apart they were not. This then was how blood grouping was done in ancient China and Japan! It is of interest to note that the same book asserted that if, at the autopsy of a woman, a section of the pubic bone proved to be pure white, the woman in question was a virgin; if a single blue spot was found she was a virtuous woman, but if numerous blue spots were present the woman was a prostitute. No sooner had I completed my study of the source book from the Surgeon General's Office, then I prepared a note of correction which was published in the same journal as my original article (Wiener 1929). There has been no further mention in any publication of blood grouping tests in ancient Japan or China, so that apparently this was one blood grouping myth that was quickly laid to rest once and for all time. This early experience alerted me to the danger of relying on secondary sources for information, without consulting the original sources. Also, during my studies on the science of blood grouping, I have over the years kept a weather eye open for other examples of blood grouping mythology. I regret to report that such examples are numerous and easy to find, and I have therefore made this problem the subject of a number of my publications. Since the matter can be of considerable importance, and has indeed been responsible for serious misconceptions and errors, when I was invited to speak before this assembly, I decided that the present status of blood group mythology would be a worthwhile and timely subject for discussion.

To begin with, every journal, even the most distinguished medical and scientific journal, from time to time publishes material that is fallacious, or even absurd. This occurs even in journals which subject every article submitted for publication to the scrutiny of referees, supposedly highly qualified in the field in question. Unfortunately, referees are human and fallible, so that on the one hand they sometimes approve articles containing patent nonsense, while on the other hand they may reject sound reports which contain findings they find difficult to accept because of the novelty of the findings or because they conflict with the referees' own preconceived pet ideas. There is no difficulty in finding even in the most distinguished journals, articles reporting observations that are false or even outrageous. As an example may be cited the article on "Group Specific Appearance of Plasma Clots", published in the distinguished journal, *Blood*, in 1950 (Stark and Stivel 1950). According to the two authors of that report, recalcified plasma allowed to clot in a bottle retracts and the shape of the retracted clot was claimed by the authors to be group specific. In fact, those authors claimed that the shape of the clot depended on the A-B-O blood group and subgroup

of A, and they tabulated 955 plasma clot tests all of which they claimed they had correctly grouped for A-B-0 in this way and 140 of group A and group AB, all correctly subgrouped by their plasma clot test. The authors were unable to suggest any reasonable explanation for the phenomenon they had discovered. Of course, the article and the claims it contains are outrageous, and evidently this was recognized by readers of the journal, because to my knowledge the article has never been cited and never even been referred to, except by me in my search for blood group mythology. This, then, is a curious report containing absurd claims that suffered a neonatal death, so that it did not survive long enough to become a permanent part of blood group mythology.

In the same category as the plasma clot article belongs the claim that every one of 28 patients with Dupuytren contracture proved to be type  $Rh_1Rh_2$  (cited by Wiener 1954). Again this fantastic claim has evidently been ignored by readers of the scientific literature, except by me in my culling of the literature. The author of the article in question is said to have testified in court on the basis of his report that Dupuytren's contracture is not a compensable occupational disease but genetically determined. On the other hand, Dr. R. T. Simmons, who had Dupuytren's contracture, told me some time before his death that he was *not* type  $Rh_1Rh_2$ . At any rate, the report has not been cited to my knowledge, so that this is another fantastic claim that died before it could be permanently incorporated into the body of blood group mythology.

In a different category are the reports claiming associations between the A-B-0 blood groups and particular diseases. This aspect of blood group mythology has a long, venerable history, dating back more than 50 years, and it remains viable and healthy even at the present time. Shortly after I first met Dr. Landsteiner, I undertook the preparation of a monograph on blood groups. He encouraged me with this enterprise by reading and correcting the manuscript materials and proofs with me, and I learned a good deal from Dr. Landsteiner as a result. At the time, knowledge of blood grouping was limited mainly to the four A-B-0 blood groups, subgroups of A and AB, the three M-N types and the agglutinin P. Yet this proved to be a complex undertaking for me and the book finally produced, which was released in 1935, had 18 chapters and 220 pages (Wiener 1935). One of the chapters dealt with blood groups and disease, at a time when the Rh factor had not yet been discovered, so that the importance of maternofetal incompatibility, though suspected, had not yet been proved. For attempts to determine associations and disease, investigators used the simplest method possible, they determined the distribution of the four A-B-0 groups in a series of patients with a particular disease and compared this with the distribution in a control series of normal individuals. The diseases for investigation appeared to have been selected without rhyme or reason and included (at the time when the first edition of my book appeared) malaria, syphilis, migraine, dementia praecox, epilepsy, feeble-mindedness, general paresis, dental caries, skin diseases, bone and joint tuberculosis, duration of life, etc. Strangely enough no similar attempts were made to study possible associations between diseases and the three M-N types. Though the studies made no sense to me, they were included with reservations in my book (4 pages were devoted to the subject) for the sake of completeness (Wiener 1935). In the book I pointed out the mutual contradictions among the reports, so that when an association was found by one author this could not be confirmed by others, or this was minimal in degree and readily explained by bias in selection of cases, or to stratification when dealing with a mixed population, or to the fact that the so-called series of controls was not comparable in racial derivation to the series of affected individuals.

Despite these fallacies, investigations on the distribution of the A-B-0 blood groups in disease continued, probably because this was an easy kind of “research” for individuals lacking better ideas. However, while great progress was being made regarding other aspects of blood grouping, notably my discovery with Karl Landsteiner of the Rh-Hr blood types, and their role in the pathogenesis of intragroup hemolytic transfusion reactions and of erythroblastosis fetalis, research on blood groups and disease continued without making any real progress. Thus, the discussion of blood groups and disease in the third edition (1943) of my book on Blood Groups and Transfusion showed virtually no change in the presentation of the subject, except for a table showing that no associations exist between the three M-N types and a variety of diseases. The vacuum that resulted when no further editions of my own book were issued was filled by Race and Sanger’s *Blood Groups and Man*. The first two editions of that book made no reference to the topic blood groups and diseases, but this changed after Aird’s reports appeared claiming associations between group A and carcinoma of the stomach, group O and duodenal ulcer, gastric ulcer, cancer of the stomach, pernicious anemia, diabetes mellitus, cancer of the colon and rectum, cancer of the breast, for all but three of which significant associations were claimed (duodenal ulcer  $\chi^2 = 192.06$ , cancer of the stomach  $\chi^2 = 39.6$ , pernicious anemia  $\chi^2 = 16.0$  and diabetes mellitus  $\chi^2 = 9.2$ ). This discussion was expanded to 20 pages in the fourth edition (1962) of the Race-Sanger book, but mysteriously was omitted in the fifth edition (1968). It is again omitted in the new sixth edition (1975).

A much more extensive treatment of the studies on blood groups and diseases can be found in Prokop and Uhlenbruck’s *Human Blood and Serum Groups*. In that 891 page volume, as many as 34 large pages are devoted to the subject. While the studies on duodenal ulcer are given special prominence, no reasonable mechanism could be suggested why being group O or a nonsecretor should predispose one to such a disease. However, rationale apparently has played little or no role in the studies on blood groups and disease, if one may judge from Buckwalter’s claim of an association between blood group A and fracture of femur (Buckwalter et al. 1956). (This statement must be qualified; I am blood group A and *did* sustain a fracture of my femur when I undertook to join my grandchildren in ice-skating. Perhaps I should have paid more attention to Buckwalter’s report). However, a plausible rationale has been suggested for possible associations between A-B-0 blood groups and particular infectious disease. As has been shown, notably by Springer and his collaborators, many microorganisms have A-like, B-like, and H-like antigens on their surfaces (Springer and Horton 1969). In view of the canalization of the immune response — i.e., in general, the body does not readily produce antibodies to its own constituents; for example, a group B individual could be expected to be less capable of defense against bacteria having B-like antigens. Despite the attractive nature of this idea, unfortunately, not a single proved example of association between blood groups and infectious diseases has yet been established (Springer and Wiener 1962).

The extremes to which the idea of associations between blood groups and disease has been carried are well exemplified by Leone Bourdel’s 200 page book on *Groupes Sanguins et Tempéraments* (Bourdel 1960). On page 19 of this book, in a table on the relation between blood and temperament, we learn that group A persons are harmonic, group O melodic, group B rhythmic, while group AB persons are H-M-R or complex. The book is also embellished with tables giving the A-B-0 blood groups of persons of various professions, namely, creative workers, research investigators, military chiefs, educators, dentists, etc. On a more sophi-

sticated level, associations are worked out for the cephalic index, and even the M-N types and Rh factor come in for discussion. This book, then, is recommended to those who know their A-B-0 blood group and wish to know whether they have selected the correct profession for their lifework. Certainly this is more "scientific" than depending on astrology and horoscopes!

Studies on blood groups and diseases appear to have been of particular interest to geneticists, although it is not entirely clear to me how such studies could advance the science of genetics. In fact, R. B. McConnell's *The Genetics of Gastro-Intestinal Disorders* (1966) devotes much space and many elaborate tables to that subject. With regard to carcinoma of the stomach, the author remarks (p. 57): "In all, 71 separate series of carcinoma patients and their controls have been published. In no less than 55 of these series a significant increase in the frequency of group A was found. In 14 series there was little difference from the controls and in only 2 series was there a considerable deficiency of group A". These discrepancies among the reports apparently do not disturb the author of the book who decides there is an association between blood group A and carcinoma of the stomach, thus settling this scientific problem simply by taking a vote. The author fails to explain why, according to the results in the table, for those living in Vienna (patients and controls both 44% group A) one's blood group has no effect at all, while in Cremona the frequency of group A is almost twice as high (84.7%) in the carcinoma patients as in the controls (46.9%). Apparently if one belongs to group A, one can live safely in Vienna, but if one dwells in Cremona, one takes one's life in one's hands.

Interest in studies on blood groups and disease was encouraged by the pronouncement of famous biometricians (Fisher and Ford) that "no gene is neutral in selection". This assertion was made in the face of abundant evidence of the existence of neutral genes, i.e., the multiple alleles of numerous systems of blood and serum groups, eye color, hair color, fingerprint patterns, etc. To explain the persistence of such polymorphisms, hybrid vigor, i.e., superiority of heterozygotes over homozygotes has been invoked. For example, the prevalence of the semi-lethal sickle cell gene in Africans has been ascribed to the claimed greater resistance to malaria of individuals heterozygous for the gene (Allison 1954). In the first edition of their book, Race and Sanger cited the reported excessive proportion (greater than 50%) of type MN children in MN  $\times$  MN families as a prime example of heterozygous advantage. However, in our own extensive studies on the heredity of the M-N types over several decades, the proportion of type MN children from MN  $\times$  MN matings did not differ significantly from 50%, so I have pointed out that the excess reported by other workers was probably due to the use of underabsorbed antisera. In a recent publication, Race now accepts my explanation as correct. As for the supposed advantage of heterozygosity, in the case of erythroblastosis fetalis (both in Rh or A-B-0 hemolytic disease), the heterozygous baby is at a disadvantage — which is the opposite of what is required by the concept of heterozygous advantage.

The affinity of geneticists for studies on blood groups and disease is evident from the large amount of space that has been devoted to such articles especially in British journals dealing with human heredity, while in December 1964, also the American Journal of Human Genetics found space for an article on "Blood Groups and Personality Traits". This reached its zenith with the appearance in 1972 of Vol 1/4, *Blutgruppen, Human Genetik, Ein kurzes Handbuch* (in order to obtain it for my library, I paid \$ 115 for it). More than half of the book is devoted to the discussion of studies on associations between blood groups and dis-

ease. In this very large volume, also, the discussion is again virtually restricted to the four A-B-0 blood groups, and the remaining multiplicity of blood groups is ignored. As many as 170 pages are devoted merely to tables, apparently produced on a computer, listing the published findings in detail for disease such as Ca of the stomach, Ca of the pancreas, Ca of the esophagus, Ca of the cervix, Ca of the body of uterus, Ca of the ovary, mammary carcinoma, choriocarcinoma, Ca of the larynx, Ca of the bronchi, Ca of the urinary bladder, chronic leukemia, myoma of the uterus, acoustic neuroma, astrocytoma, adenoma of the hypophysis, brain tumors, ependymoma, duodenal ulcer, ulcer of the stomach, ulcerative colitis, pernicious anemia, diabetes mellitus, coronary artery disease, cholecystitis, eosinophilia, atrophic rhinitis, hepatitis and hepatoma, thromboembolic diseases, toxemia of pregnancy, chronic eczema, and many other diseases. I leave it to my readers to decide whether the \$ 115 I paid for this book was a worthwhile investment.

While most of the reports of associations between A-B-0 blood groups and disease apparently are no longer being taken seriously, the claims that group 0 persons, especially, A-B-H nonsecretors, are more susceptible to duodenal ulcer, while group A persons are more likely to get carcinoma of the stomach, continue to be cited, so that those two assertions appear to be firmly fixed in the literature of blood group mythology. Nevertheless, for the sake of fairness, it must be pointed out that studies on associations between blood groups and disease are not totally without rationale. To be sure, in general, the genes responsible for the blood group differences appear mainly to be neutral genes. Thus, just as it is immaterial whether one's iris is gray or brown in color, so it similarly does not appear to matter whether one is group A or group B. However, if the iris is devoid of *all* pigment, as in albino persons, a genetically determined type, serious damage to one's vision can result from the absence of protective pigment. Similarly, in Rh null individuals, the absence of *all* Rh-Hr antigens from the red cell envelope can result in hemolytic anemia.

A reverse situation exists in the case of the Duffy types. In this case, according to a recent report, the Duffy agglutinogens (Fy<sup>a</sup> or Fy<sup>b</sup>) act as a receptor for malarial parasites, enabling the microorganisms to invade the red cells, while red cells of type Fy(a-b-) are not readily parasitized. Thus, the type Fy(a-b-), which is absent or rare in whites, is prevalent among Blacks in Africa presumably because of the selective advantage of this blood type for resistance against malaria. Another example is provided by the receptors on the red cells to which myxoviruses such as influenza viruses become attached. These receptors appear to be closely associated with, if not identical with, the M-N agglutinogens, as has been shown by Springer, since enzymes which destroy the receptors for myxoviruses simultaneously destroy the agglutinogens M and N on the red cell surface.

Another important example of the significance of red cell agglutinogens has been found in sheep (Rasmusen and Hall 1966) whose red cells can be divided into two types according to their potassium content, namely, HK (high potassium) and LK (low potassium). The two potassium types are dependent on which of two agglutinogens, transmitted by corresponding allelic genes, is present on the red cell envelope. While a parallel situation apparently does not exist for man, a close correlation has been found in man between A-B-0 group and secretor type and the presence in the plasma of alkaline phosphatase isozymes (Schreffler 1965).

Thus, studies on blood groups in disease are in part rational scientifically and in part mythology, so that they can be classified as a kind of "fringe" science comparable to chiropractic, parapsychology (ESP), megavitamin therapy, faddist diets with so called "organic"

foods, reducing diets in which “ calories don’t count ”, sightings of UFO (unidentified flying objects), hypnotism, and now acupuncture. With regard to UFO, when Einstein was asked his opinion, he said, “ No doubt these people are seeing *something*, exactly what I do not know, and I’m not curious to find out ”. The modern enthusiasm for acupuncture constitutes a step backward instead of forward for medical science. It appears to have been forgotten that at one time, before surgical anesthesia had been discovered and perfected, many surgeons made use of the consultative services of hypnotists. In particular, Dr. Mesmer, who was frowned on by other members of the medical profession because they could not duplicate his results, made a good livelihood in this way, since he did succeed in rendering some patients insensible to surgical pain. However, when true anesthesia was introduced, the less dependable hypnosis was abandoned, so that acupuncture, which appears to be successful only when the operator and the subject are both absolutely convinced it will work, represents a return to the use of Mesmerism in a different guise. The precise mapping of acupuncture points appears to be merely mumbo jumbo, since objective study has proved that whether or not acupuncture succeeds is quite independent of the exact points of insertion of the needles.

Another aspect of blood grouping which is plagued by mythology is forensic serology. Once blood has dried, it is difficult or impossible to test it reliably for blood groups other than the four A-B-0 blood groups, and not including the subgroups of A. I have been forced to this conclusion by my experience with tests on thousands of dried stains of blood and secretions, from homicide and rape cases, in my capacity as City Serologist in the Office of the Chief Medical Examiner of New York City, since 1938. The reason for this should be apparent — since the red cells are destroyed their agglutinin content must be determined by indirect absorption or neutralization methods instead of simple, direct agglutination tests. For absorption tests the antisera used must be highly diluted (titer only 4 to 6 units, as against 50 to 100 units for ordinary blood grouping), so that the margin for error is very narrow. Moreover, due to incompleteness of absorption when stains are dilute or denatured, all grades of reactions can be encountered instead of the sharp difference between positive and negative reactions characteristic of direct blood grouping to which blood bank technicians are accustomed. Limitations of material, so that tests cannot be repeated, and contamination with sweat and bacteria on dirty clothing create additional problems, so that unless adequate control stains of known groups, testing of “ unstained ” substrate are included, and readings are taken blind, errors are bound to occur. Tests for agglutinogens should be supplemented and complemented by tests for isoagglutinins, but because of limitations of materials this is not always possible. For stains on nonabsorbent surfaces like knives and glasses, the most sensitive and rewarding method is Lattes’ coverslip method for isoagglutinins on blood crusts, while tests for isoagglutinins on extracts of stains on cloth give the most sensitive results by my acacia method. Even so, the majority of dried blood stains give ambiguous reactions, so that a reliable definitive A-B-0 grouping result is possible for only a minority of dried blood stains submitted for examination.

This situation is of course far from ideal, and many newcomers to the field have attempted to introduce new methods of testing that they claim can always determine the A-B-0 blood group of dried blood stains. Among these, the most widely used are the mixed agglutination method and the absorption-elution method. While both of these methods appear to be sound in theory, and both are valuable research tools, they do not lend themselves to the blind technique and often give false results. The results in practice are erratic, and while

some sort of reaction is obtained in every test, more often than not this result is wrong or misleading. Obviously, therefore, the mixed agglutination and absorption-elution methods are not sufficiently reliable for use by forensic serologists. Unfortunately, the methods are nevertheless being widely used, with disastrous results as in the following case which occurred in Washington, D.C.

A young woman was found in her apartment, suspended from a curtain rod, and an apparent suicide. However, investigation by the F.B.I. and by the medical examiner showed no evidence of the strangulation by the rope, but with finger marks instead, and sperm cells in the vagina indicating rape. Finger prints found in the apartment proved to be those of the janitor, who had a bad criminal record of previous rapes and murder, so the janitor was arrested. The defense attorney, a public defender, consulted with a forensic serologist who claimed that a stain of semen on a towel found at the scene of the crime came from a group AB, or group A or group B individuals, based on tests carried out by the absorption-elution method. This finding, if correct, would tend to exonerate the prisoner because he belonged to group O. However, when I was consulted by the District Attorney, I found not only that the stain indeed contained semen but also strongly inhibited anti-H lectin, but not anti-A and anti-B sera, so that it clearly had to come from a group O man. The defense's serology expert testified to her false findings, but her testimony was overcome by my own results, and the janitor was convicted. However, later the other "expert" had saliva of the prisoner mailed to her in her laboratory in Texas and reported the man to be a nonsecretor. It turned out that the so-called expert was so ignorant of the elements of forensic serology that she had failed to caution the shipper of the saliva to boil it immediately after collection to destroy blood group enzymes and bacteria. My own test on a properly collected and shipped boiled saliva sample proved the prisoner to be a group O secretor, as expected, and the criminal is now in prison paying the penalty for the crime he committed.

Despite this and similar blunders, the absorption-elution method continues to be used. Apparently it is attractive because it always *seems* to give a result, though the result is wrong more often than not. The so-called expert for the defense in the case above has been teaching the absorption-elution test and has even been included on the program of this AABB meeting, proving that the myth of the absorption-elution test still survives. In fact, in a recent issue of a Japanese Journal of Forensic Medicine, an investigator reported his application of the absorption-elution method for determining the blood group of very small pieces of hair, nails, teeth and cancellous bone. As in the report on plasma clot blood grouping already described, this worker claims to have grouped correctly hundreds of fragments of hair, nail, etc. — without, however, any mention of the use of the blind test. — Thus, the myth of the absorption-elution test for forensic serology appears to be a hardy and healthy one, unless my presentation here is more effective than I expect it will be, judging from the reception given to my previous articles on blood group mythology.

As another example of the perseverance of blood grouping myths I mention the claimed anti-M lectin from *Iberis amara* seeds. Since lectins of anti-N specificity have actually been found, it seemed plausible that anti-M lectins could also exist. However, when the discoverer of anti-M lectin sent me first extracts of the seeds, and then later the seeds themselves, I was unable to detect any evidence of any anti-M activity. My experience has been shared by other workers, but despite this the myth of anti-M lectin survives and can be found cited even in books published in 1975.

Here we cite also the claim by workers (Simonović and Stefanović 1961) in Bulgaria that by injecting over the period of several years Rh-positive red cells into a plant, *Begonia punctata*, they had succeeded in inducing the production by the plant of anti-Rh (titer 16 units) that could be used for typing human blood. This report was excitedly quoted in the literature

until Jenkins et al. (1961) tested extracts of the injected plant and found them to contain human serum, which was evidently the source of the anti-Rh antibodies in the plant extracts. Another myth with more serious repercussion is that of little d. Even at the present time that hardy myth survives. On forms released by the U.S. Department of Immigration for reporting the results of blood grouping tests, the serologist is required to place check marks in one of a series of four small boxes marked O, A, B and AB, in one of a series of three boxes marked M, N and MN, and check marks also in as many boxes as necessary among six boxes marked C, D, E, c, d, and e. Thus, this scheme makes no provision for reporting type MN<sub>2</sub>, which is not uncommon among Chinese. In addition, it presumes the existence of anti-d sera, and renders impossible the reporting of any of the niceties of the Rh-Hr system, especially for carriers of the genes  $R^z$  and  $r^y$ .

The many myths involving the Rh-Hr system have been discussed in detail in my previous articles (Wiener 1955, 1960) so that only the highlights need be mentioned here. At the basis of all these myths is a blood grouping myth that few recognize as such, namely, that there exists only a single comprehensive and up to date text on the subject, one which need not be named because it is so well known to all of you and is now in its sixth edition. This book is used and cited like a bible, even though blood grouping is not a religion but a science. Unfortunately, the book is characterized by its failure to present basic principles of the subject correctly, by its misquotations of the literature and by distortions of fact. It therefore remains a mystery why it still continues to be cited as if it were the sole reliable reference on blood grouping, when other books which are free from such blood grouping myths are available. Judging from the way the misinformation and myths contained in this blood group "bible" are quoted over and over again, and even further elaborated and embellished, the bible has earned the appellation as the *Source Book of Blood Mythology*, because it is responsible for many of the myths that I have discussed, and which continue to hamper progress in the thorough understanding of the subject of blood grouping.

A major cause for the myths, to be found in the notorious blood group bible, is the failure to recognize the difference between agglutinogens (intrinsic attributes of the red cell envelope) and their serological specificities (extrinsic attributes of the agglutinin molecule); the latter are conveniently also known as blood factors. The CDEcde notations are based on the simple (actually, naive) assumption of a one-to-one-to-one correspondence among antibodies, agglutinogens and genes. Thus each serological specificity becomes a gene so that, for example, what I interpret as an agglutinin Rh<sub>1</sub> determined by a corresponding allelic gene  $R^1$ , and having the serological specificities Rh<sub>0</sub>(D), rh'(C), and hr''(e) is interpreted instead as representing a complex of three agglutinogen molecules C, D and e, or three separate determinants on the red cell surface determined by a tightly linked triplet of genes  $DCe$ , and the concept of so-called gene cistrons with subloci in a specific order is invoked. As more and more Rh-Hr specificities were discovered these were readily absorbed under my own concept of serological specificities as additional extrinsic attributes of the agglutinin molecule; in fact, the number of serological specificities corresponding to a single agglutinin is theoretically *unlimited* or *infinite*. At the same time, in contrast, the C-D-E mythologists have been compelled to postulate more and more determinants, so that eventually an infinite number of them will have to be crowded into a single agglutinin molecule of finite size. Simultaneously, the number of subloci on the gene cistron had to be increased, and one ambitious and imaginative investigator has even drawn a figure of the Rh-Hr gene complex with as many as 20 subloci arranged in a particular order. (Unfortu-

nately, using my own microscope I continue to discern only a single gene locus for the Rh-Hr alleles).

An essential characteristic of blood group mythologists and other mythologists is their ability to disregard facts which conflict with their preconceived ideas. Thus, when new facts are unearthed that do not match established dogma, true scientists invent new hypotheses to match the facts; not so, for mythologists — they simply distort or ignore the facts to match their ideas which are kept intact. A case in point is little d. Based on the demonstrated existence of  $rh'(C)$  and its contrasting factor  $hr'(c)$ , Fisher predicted the existence of contrasting factors for  $Rh_o(D)$ , namely, little d, and for  $rh''(C)$ , namely, little e ( $hr''$ ). The discovery of little e was actually reported, and there have also been reports by impressionable workers of the discovery of little d. These latter claims I proved to be wrong, and I also pointed out that not merely a single kind of little e existed since there are multiple cognate specificities of  $hr''$ , such as  $hr^s$  and  $hr^b$ , as described by M. Shapiro. Thus, of Fisher's two predictions, one — little d — has never been fulfilled, while the other prediction did not go far enough since at least three antibodies, not merely one, have been found, any of which could fit the requirements for Fisher's single anti-e. The fact that Fisher's predictions were thus totally incorrect, however, has caused his protagonists no apparent embarrassment. In fact, Race and Sanger continue to write even in the sixth, 1975, edition of their book, "Now that the groups seem so clear, it must be difficult to realize how obscure they appeared before Fisher illuminated them. Such successful prediction must be rare in biology". This citation demonstrates that, unlike scientists who modify their theories when new facts are unearthed which do not conform with their previous ideas, mythologists do the opposite — they alter the facts to make them fit their preconceived ideas. The facts here are that R. A. Fisher was a distinguished mathematician who never did a blood grouping test in his life, and that may be why not one of his ideas about Rh-Hr was original or correct, as proved by the experience and findings of the past three decades.

As for the assertion that the facts regarding Rh-Hr appeared "obscure" before Fisher "illuminated" them, that is totally false. The serology, genetics and nomenclature of the Rh-Hr types were all worked out by me in detail, as early as 1943. In particular, my theory of inheritance by multiple allelic genes, each allele determining a corresponding agglutinin with multiple (theoretically unlimited in number) serological specificities, has stood the test of time, and is being more and more widely accepted and used. My concept of an unlimited number of Rh-Hr specificities is being constantly confirmed as more and more of the Rh-Hr antisera thus anticipated by me of different specificities are found, 35 by the latest count, while Fisher's much more modest prediction of only two such antibodies, anti-d and anti-e, has proved to be entirely incorrect. Yet the blood group mythologists continue to cite the so-called Fisher predictions and synthesis, and in one recent book (1975) even appears the claim, "So far, five of the six antibodies predicted by Fisher have been discovered, the exception being anti-d". In this way the blood group mythology regarding Fisher's predictions and synthesis continues to be promulgated and even improved upon by raising the number of antibodies said to be predicted by him from two to six.

Another myth to which the Race-Sanger book devotes considerable space is the so-called LW factor — for which more than four pages are used as compared with the five pages in the same book for the complete discussion of the real, clinically and genetically important Kidd blood group system. The antibody anti-LW was first reported by Levine in 1967, who said he found it in the serum of guinea pigs immunized with the red cells of rhesus monkeys.

The LW agglutinin was described as a very high frequency antigen, and LW negative individuals who can be either Rh positive or Rh negative, are extremely rare. Thus, LW has nothing to do with Rh, but since it was discovered by the same method that Landsteiner and Wiener discovered the Rh factor, Levine named the agglutinin he had discovered as LW, in "honor of" Landsteiner and Wiener. Later, paralleling the history of Landsteiner and Wiener's Rh (or rhesus) factor, human LW-negative individuals were encountered whose sera contained antibodies similar in specificity to Levine rhesus LW antiserum. In their book, Race and Sanger pointed out that tests by de Veber et al. on 10,552 unselected Canadian donors showed *not one* to be LW negative, indicating that LW is indeed a very high frequency antigen. In contrast to this as many as 6 of 45 individuals mentioned in Landsteiner and Wiener's first report of their discovery of the Rh (or rhesus factor) were negative. It seems impossible therefore to confuse Levine's LW with Landsteiner's and Wiener's Rh, but Race and Sanger manage to do so anyhow in their book, thus contributing another myth to the already overburdened field of blood group mythology. Interested readers can find a clear and detailed explanation of the reactions of Levine's anti-LW sera produced in guinea pigs in the excellent book of A. G. Erskine (1973). (Also see Wiener 1970).

The nomenclature which I have developed for the Rh-Hr system is simple and compact — all the Rh-Hr symbols are meaningful and, as all scientific symbols should be, are terse mnemonics. Thus, the nomenclature is easy to understand and master — because, like a silent teacher, good scientific symbols give their users insight into the subject. Moreover, by the use of this nomenclature, all the findings regarding the Rh-Hr types are readily and neatly tabulated because the symbols for phenotypes and genotypes, and the symbols for agglutinogens and their serological specificities are sharply distinguished, and, most important, the symbols for the phenotypes and genotypes lend themselves to a natural, logical arrangement in tables. Thus the seemingly very complex tables synthesizing all the facts regarding the Rh-Hr phenotypes and genotypes are readily understood and mastered when my nomenclature is used, and need not be memorized, because all the tables can readily be reconstructed by simple logic as each reaction and symbol falls into its natural place in the tables. Not so for the Fisher synthesis. — The C-D-E symbols do not distinguish clearly between phenotypes and genotypes or between antigens and their specificities. Worse they do not lend themselves to a natural, logical order, so that tables of the Rh-Hr types in terms of C-D-E in different editions of the Race-Sanger book all have different unsystematic arrangements, with resulting errors of commission and omission. While my own tables of Rh-Hr can be compared to an English dictionary where each symbol or work is easily located, the Fisher-Race tables of C-D-E are comparable to Chinese or Japanese dictionaries, which lacking an alphabet, have no systematic arrangement of their symbols or "words". For examples of the errors that result from the use of the Fisher-Race CDE symbols, the reader may consult Table 32 on page 186 of the 6th edition of the Race-Sanger book. Red cells having the specificities  $rh'(C)$ ,  $rh''(E)$ ,  $hr'(c)$  and  $hr''(e)$ , but lacking  $Rh_0(D)$ , are said to be of phenotype  $rh_r rh$  in my Rh-Hr terminology, with two possible genotypes,  $r'r''$  and  $r^y r$ , which are both quite rare. The table in the Race-Sanger book, however, gives for this Rh-Hr blood type only the single genotype  $r'r''$  and omits  $r^y r$ , even though my family studies have proved that  $r'r''$  and  $r^y r$  are about equal in frequency. It is noteworthy that Race and Sanger in their book themselves apparently find the C-D-E symbols unequal to the task of representing phenotypes and genotypes, so that they are forced to resort to so-called "shorthand symbols" which are nothing more than transparent, trivial modifications of

my own genotype Rh-Hr symbols, and which, of course, have nothing at all to do with the C-D-E notations.

I shall conclude this review by pointing out again the myth, which, in my opinion, is at the basis of almost all other blood grouping myths. It is noteworthy that when the author of a scientific paper in the field of blood grouping wishes to cite a source book on the subject, the book selected is almost invariably the Race-Sanger *Blood Groups in Man*, now in its sixth edition. Thus, other important sources, such as the encyclopedic book of Prokop and Uhlenbruck, *Human Blood and Serum Groups*, are generally ignored or slighted. The result is that there has arisen the myth that the only reliable and complete text on blood groups is the Race-Sanger book, which is used like a bible, even though blood grouping is a science and not a religion. Unfortunately, the Race-Sanger book is not dependable, because, as has been shown, it distorts and misrepresents important facts, so that it has become instead a sourcebook of blood group mythology. However, there is no doubt that the Race-Sanger book is useful because it contains information not otherwise readily available. Therefore, my purpose here is not to condemn the book, but only to caution those who must use the book, and to point out that for learning the fundamental principles of blood grouping, one can do better by referring to other sources, notably, the book by Erskine (1973). If this message of mine has been successfully transmitted, the further progress of the science of blood grouping will benefit therefrom, and the effort that I have expended in preparing this review will not have been in vain.

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## RIASSUNTO

*Mitologia dei Gruppi Sanguigni*

La scoperta di un gran numero di fatti e principi precedentemente ignorati ha condotto il campo dei gruppi sanguigni a svilupparsi in una disciplina importante e complessa. L'arduo compito di padroneggiare questa materia ormai tanto vasta è stato facilitato dalla disponibilità di un testo che ne tratta quasi tutti gli aspetti e che è ora giunto alla sua sesta edizione. Questo preziosissimo testo è ampiamente usato da ricercatori e studenti ed è considerato come una bibbia che escluda l'uso di altri testi. Tuttavia, questa cosiddetta bibbia presenta gravi errori scientifici in quanto principi fondamentali vengono ignorati ed alcuni fatti importanti vengono distorti. Fortunatamente, esistono altri testi che sono privi di tali errori. L'uso di un testo come unica fonte di informazione sull'argomento ha portato al mito dell'infallibilità di tale testo e del suo uso esclusivo. L'obbiettivo di questa rassegna non è quello di togliere a questa « bibbia dei gruppi sanguigni » i suoi meriti indiscussi, bensì di indicarne i limiti e di ricordare l'esistenza di altre fonti che, benché non altrettanto ampie, sono prive di mitologia. Se questa rassegna riuscirà a far consultare altre fonti, oltre la bibbia dei gruppi sanguigni, essa sarà servita al suo scopo e ciò potrà condurre ad ulteriori progressi nel campo dei gruppi sanguigni eliminandone i miti.

## RÉSUMÉ

*Mythologie des Groupes Sanguins*

La découverte d'un grand nombre de faits et principes précédemment ignorés a conduit le secteur des groupes sanguins à se développer dans une discipline importante et complexe. La lourde tâche de maîtriser cette vaste matière a été facilitée par l'existence d'un texte qui en traite presque tous les aspects et qui se trouve maintenant à sa sixième édition. Ce texte bien précieux est utilisé par les experts et les moins experts comme s'il s'agissait d'une bible, à l'exclusion de tout autre texte. Mais cette « bible » présente des erreurs scientifiques, des principes fondamentaux y étant ignorés et des faits importants déformés. Heureusement, d'autres textes existent qui ne présentent pas de ces fautes. L'usage d'un texte comme source unique d'information a conduit au mythe de son infailibilité. Le but de cette revue n'est pas d'enlever à cette « bible des groupes sanguins » ses mérites indiscutables, mais d'en indiquer les limites et de rappeler l'existence d'autres textes qui, tout en n'étant pas aussi complets, sont libres de mythologie. Cette revue aura atteint son but si d'autres textes seront consultés à côté de la bible des groupes sanguins, ce qui pourra conduire à d'autres progrès dans la discipline des groupes sanguins en éliminant les mythes qui la caractérisent.

## ZUSAMMENFASSUNG

*Die Mythologie der Blutgruppen*

Die Entdeckung zahlreicher zuvor unbekannter Prinzipien und Tatsachen hat dazu beigetragen, daß sich das Gebiet der Blutgruppen zu einem wichtigen und vielseitigen Forschungsfeld entwickelt hat. Um diesen nunmehr so komplex gewordenen Fachstoff beherrschen zu können, verfügen wir über ein Lehrbuch, das fast alle seine Aspekte behandelt und bereits bei der 6. Auflage angelangt ist. Forscher und Studenten verwenden dieses kostbare Werk weitgehendst und betrachten es gleichsam als eine Bibel, die die Konsultation anderer Texte überflüssig macht. Diese sogenannte Bibel weist aber schwerwiegende wissenschaftliche Fehler auf, weil darin grundsätzliche Prinzipien übergangen und andere wesentliche Tatsachen verdreht werden. Zum Glück gibt es noch andere Werke ohne solche Fehler. Die Tatsache, daß dieser Text als einzige Informationsquelle über das Gebiet benutzte wurde, verschaffte ihm den Mythos der Unfehlbarkeit und seiner exklusiven Anwendung. Die vorliegende Übersicht möchte dieser Bibel der Blutgruppen ihre unumstrittenen Verdienste nicht nehmen, sondern nur ihre Grenzen anzeigen und daran erinnern, daß noch andere Quellen existieren, die zwar weniger weitläufig, aber von keinem Mythos umgeben sind. Wenn infolge dieser Übersicht andere Quellen außer der Blutgruppen-Bibel konsultiert würden, so hätte sie schon ihren Zweck erreicht, d.h. ohne jeden Mythos zu weiterem Fortschritt auf dem Gebiet der Blutgruppen zu führen.

Dr. Alexander S. Wiener, 64 Rutland Road, Brooklyn, N.Y. 11225, USA.