

RECENT ADVANCES IN MEDICAL GENETICS

LAURENCE H. SNYDER,

Professor of Medical Genetics, Department of Medicine, and Chairman of the
Department of Zoology and Entomology, The Ohio State University

The most spectacular, if not the most important advance in medical genetics in recent years has been the unraveling of the complexities of the blood agglutinogens. Fourteen such agglutinogens are now known, and a fifteenth is postulated and will doubtless soon be described. These antigens in various combinations form the so-called human blood groups and types. Not many years ago we spoke of four blood groups. Today we know 5,760, and we will soon be able to distinguish 8,640, when the last of the three Hr antigens is identified.

The various medical and medico-legal problems centering around the blood groups are fundamentally problems of medical genetics, and can be solved only by modern medical genetic methods. The individual agglutinogens are inherited as dominant factors, some of them related as alleles of a series, others independent of each other in inheritance. In the A-B series there are now eight groups, by virtue of three sorts of A antigen. They are as follows: O, A¹, A², A³, B, A¹B, A²B, A³B. In the M-N series there are five types, namely, M, N¹, N², MN¹, MN². Since any one of the eight in the A-B series could be any one of the five in the M-N series, there are 8×5 , or 40 groups in these two series combined. In the P. series there are four types, P¹, P², P¹P², and P-. This makes 40×4 , or 160 groups. Since any one of these may contain antigens in water-soluble form (secretors) or in alcohol-soluble form (non-secretors), there are now 160×2 , 320 groups. The recently-discovered Rh antigens are combined into eight types, Rh^o, Rh¹, Rh¹¹, Th^{o1}, Rh^{o11}, Rh^{1 11}, Rh^{o1 11} and Rh-. These, added to the list, make 320×8 , or 2,560.

The newest of the agglutinogens are the Hr factors. These are not independent of the Rh antigens, but are reciprocally related to them, so that we must redescribe the Rh group by adding an Hr designation to them. At present we can identify Hr¹ and Hr¹¹, and no doubt soon will have identified Hr^o. Using all three Hr factors, there are 27 Rh-Hr groups. Multiplying these 27 by the 320 groups which we identified without the Rh-Hr antigens, we have 320×27 , or 8,640 human blood groups.

These groups are all of use in medico-legal cases of disputed paternity, and in the identification of individuals, but only the A-B series and the Rh-Hr series are of practical importance in transfusions. The A-B groups are involved in transfusions because certain individuals contain natural antibodies against agglutinogens A and B. The Rh-Hr groups are of importance for another reason, for, although no natural antibodies against these antigens are ever present as far as we know, antibodies can be produced against them when they reach the blood stream of a person lacking them. Thus in multiple transfusions Rh- blood must be given to an Rh- person.

The most important application of the Rh antigens is in pregnancies where an Rh- woman carries an Rh+ fetus. Here the antigen of the fetus may pass through the placenta into the mother, immunizing the mother. The resulting antibodies may return through the placenta and unite with the Rh antigen of the embryo, causing one or another of the manifestations of erythroblastosis (Levine, 1943; Wiener, 1943, 1945).

The Rh antigen of the embryo is of course inherited from the father in these cases. The father is, therefore, Rh+. He may be homozygous (pure) for the Rh factor, or he may be heterozygous and carry the gene for Rh-. In the first instance all his children will be Rh+, in the second, only half. As a rule the first Rh+ pregnancy serves merely to immunize the mother, while a second or later Rh+ pregnancy stimulates the further rapid production of antibodies, which may then affect the embryo. Occasionally a first Rh+ child is affected, and we have some evidence in our laboratory that these affected first-born children show spina bifida and other gross abnormalities. In some instances affected first-born children may be the result of a previous transfusion given to the mother.

When we determine by genetic methods how often by chance an Rh- woman would be expected to marry an Rh+ man and to produce an Rh+ child, we run into some interesting facts. In a population such as that of the United States we would expect 28.8% of all children born to have one or another Rh antigen which the mother does not have. If all such cases are potentially erythroblastotic, we should expect the incidence of erythroblastosis to be 28.8%. However, the frequency of clinically diagnosed cases has never approached this figure. The recorded incidence is about one in 200 births, or about one-half of one percent. Obviously the difference between 28.8% and one-half of one percent is a discrepancy which must be explained.

First of all it has been observed that of the three Rh antigens, only Rh^o is of any great importance in producing symptoms. There have been a very few cases reported of effects due to immunization with Rhⁱ or Rhⁱⁱ, but the number is relatively insignificant. We may confine our attention, then to Rh^o. When we compute how often a child will be expected to have Rh^o when the mother lacks it, we find the answer is 8.7%. This is much closer to the observed half of one percent, but still far enough away to demand further investigation.

Next we recall that first-born children are seldom affected. In our American population about 31% of children are first-born. Eliminating these from our calculations, we would expect 6% of children to have Rh^o, to be born of mothers lacking Rh^o, and to be second- or later-born in the family. This further closes the gap between the expected and the observed incidence of symptoms due to Rh immunization, but still leaves a discrepancy.

Looking further, we see that the cases of erythroblastosis are not distributed randomly among the Rh- mothers, but are grouped into specific families. This suggests that the Rh^o antigen may permeate the placenta only in certain Rh- mothers, or that perhaps only certain Rh- women are capable of producing potent antibodies. It may be that both these things account for the fact that not as many cases of erythroblastosis are found as can potentially occur.

Another intriguing possibility suggests itself, and the exploration of this possi-

bility has led to suggestive results. It is conceivable that in some instances where the antigen immunizes the mother, and the antibody in turn reaches the fetal circulation, that the effects on the fetus are different from those usually recognized as classical erythroblastosis.

Following the lead of Yannett and Liebermann, we have investigated the possibility that Rh immunization might in some instances result in feeble-mindedness. Our results confirm this, and we tentatively suggest that this finding raises the incidence of effects from one-half of one percent to one percent, thus closing the gap further.

Still another genetic factor may be involved in the recent discovery by Wiener that immunization may result in either of two kinds of antibodies, univalent or bivalent. The manifestations may depend upon the kind of antibody produced.

In addition to the practical applications of the blood agglutinogens, which have taken up an undue proportion of this review, applications in prevention, in diagnosis, and in genetic prognosis have developed from modern medical genetic research. For examples of these, see Snyder, 1946.

Fundamental research on which such practical applications are built has progressed rapidly in recent years. The basic relations of the mutant gene in man have been thoroughly investigated. A new type of hereditary transmission, incomplete sex-linkage, has been added to the longer-known types (Haldane, 1942), and this has made possible the first chromosome maps for man.

Recent studies with the electroencephalograph by Lennox and his co-workers have shown that cerebral dysrhythmia is inherited as a dominant factor, and may be used in predicting the occurrence of epilepsy in families. The genetic aspects of human cancer have been thoroughly reviewed and documented by Blank (1944).

The biochemistry of several human anomalies has been worked out, and tied in with genic action. Thus a single gene controls the production of an enzyme which, when present, brings about a certain reaction, but when absent, fails to bring about the reaction. Mutations in single genes thus bring about, through failure to produce the appropriate enzyme, albinism, phenylketonuria, alcaptonuria, Von Gierke's disease, and other errors of metabolism. The enzyme, its point of action, and its genetic determiner can now be exactly specified (Haldane, 1942; Beadle, 1945).

Lethal factors have been investigated, and various rare human anomalies which were long thought to be simple dominant factors have been shown to be lethal in the homozygous condition (cf. Snyder and Doan, 1944). These dyscrasias include telangiectasia, minor brachydactyly, sebaceous cysts, spina bifida and Pelger's anomaly.

For a comprehensive review of the recent advances in fundamental research underlying medical genetics, see Muller, Little and Snyder (1946). For text books on medical genetics, there are recent editions available by Roberts (1940), Davenport, Keeler, Slye and Macklin (1940), Snyder (1941), Ford (1942), Gates, Snyder and Hooton (1943) and Bauer (1945).

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