

## Editorial Note

*It is appropriate to dedicate the first issue of TRANSFUSION to the man who laid the foundations for this field of science. 1961 is the diamond jubilee of the publication of the description of "the so-called Landsteiner reaction" in the Wiener Klinische Wochenschrift (14: 1132, 1901). The translation which follows was prepared through the courtesy of Professor A. L. Kappus, Chairman of the Department of Microbiology at the Marquette University School of*

*Medicine. Dr. Kappus made every effort to preserve the flavor of the original article which was made difficult by the involved construction of the academic German in use at the turn of the century. Those who are interested may determine Dr. Landsteiner's blood group by studying his tables. This observation serves to underline the importance of the procedure of "proving the blood groups" by the method introduced by Karl Landsteiner.*

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## On Agglutination of Normal Human Blood

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SOME time ago I observed and reported that serum of normal humans frequently agglutinates red blood cells of other healthy individuals.<sup>1</sup> At that time I was under the impression that this ability of the serum to agglutinate foreign red cells was especially pronounced in some diseases and I believed that this agglutinating ability was related to the strong lytic ability of pathologic sera on normal red cells which was observed by Maragliano<sup>2</sup> many years ago. This concept seemed to be supported by the fact that agglutinating and lytic abilities frequently although not always changed in a parallel fashion. However, the fact that the addition of sodium chloride up to normal concentrations will (although heating will not) destroy this lytic ability of the sera indicates the reactions of Maragliano are not identical to the hemolytic reactions of the blood sera which are being investigated so intensively. Maragliano himself differentiates his observations from the phenomenon of Landois—hemolysis caused by foreign

serum—since in Maragliano's case hemoglobin is not only dissolved but also destroyed. A fundamental difference between my observations and those of Maragliano is that in his case the serum acts also upon the red blood cells of the same individual and that his reaction occurs with pathologic blood only. My observations, however, reveal characteristic differences between blood serum and red blood cells of various apparently healthy persons.

The report and pictures presented by Shattock<sup>3</sup> describe a related phenomenon, although he found the reaction only in febrile diseases and failed to see it with normal blood. Shattock thinks that the reaction is connected with the increased coagulability and rouleaux formation of the febrile blood.

The agglutination of human blood by human serum ought to be called isoagglutination according to the nomenclature of Ehrlich and Morgenroth. Shortly after my publication these two investigators reported

TABLE 1. *Concerning the Blood of Six Apparently Healthy Men*

Sera						
Dr. St. ....	-	+	+	+	+	-
Dr. Plecn. ....	-	-	+	+	-	-
Dr. Sturl. ....	-	+	-	-	+	-
Dr. Erdh. ....	-	+	-	-	+	-
Zar. ....	-	-	+	+	-	-
Landst. ....	-	+	+	+	+	-

  

Rbc's of:	Dr. St.	Dr. Plecn.	Dr. Sturl.	Dr. Erdh.	Zar.	Landst.
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experiments in which they injected blood of the same species and thereby succeeded in preparing isoagglutinins and isolysins, that is, sera which act upon the red blood cells of the same species. These very comprehensive experiments confirm the unexpected existence of clearly demonstrable differences between the bloods within one animal species.

In the paper of Ehrlich and Morgenroth<sup>4</sup> the phenomena of isolysis are discussed in regard to the theoretical concepts presented by Ehrlich.

Since the publication of the reports of Shattock and myself a number of investigators studied isoagglutination in man. The fact that the reaction occurs in the blood of healthy individuals renders those papers valueless which consider the reaction specific for certain diseases.<sup>5</sup> Other papers even report observations concerning the intensity and frequency of the reaction in diseases.

Donath<sup>6</sup> found the reaction more frequently in patients with different forms of anemia than in healthy people, though this was not always the case. Ascoli<sup>7</sup> observed the reaction in healthy individuals but

noted greater intensity in diseased ones. Eisenberg investigated healthy and diseased persons. He, like others, came to the conclusion that the reaction occurs frequently in diseased but only exceptionally in healthy persons. This, however, contradicts my statements.<sup>8</sup>

As I have given only a very brief report in my paper mentioned above I would like to present the results of some recent experiments. The tables need no interpretation. Equal amounts of serum and of 5 per cent red blood cell suspension in 0.6 per cent sodium chloride were mixed and observed in a hanging drop preparation or in the test tube. (The + sign signifies agglutination.)

A fourth similar table concerning the sera of Table 2 mixed with the red blood cells of Table 1 and some other tested sera, for instance those of one case of hemophilia and one case of purpura, presents entirely identical regularities and is therefore omitted. The investigation of another ten normal persons (in 42 combinations) gave similar results.

These experiments prove that I do not

TABLE 2. *Concerning the Blood of Six Apparently Healthy Puerperal Women*

Sera						
Seil. ....	-	-	+	-	-	+
Linsm. ....	+	-	+	+	+	+
Lust. ....	+	-	-	+	+	-
Mittelb. ....	-	-	+	-	-	+
Tomsch. ....	-	-	+	-	-	+
Graupn. ....	+	-	-	+	+	-

  

Rbc's of:	Seil.	Linsm.	Lust.	Mittelb.	Tomsch.	Graupn.
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TABLE 3. *Concerning the Blood of Five Puerperal and Six Placentae (Cord Blood)*

Sera						
Lust. ....	+	+	-	-	-	+
Tomsch. ....	-	-	+	-	-	-
Mittelb. ....	-	-	+	-	-	-
Seil. ....	-	-	+	-	-	-
Linsm. ....	+	+	+	-	-	+

  

Rbc's of:	Trautm.	Linsm.	Seil.	Freib.	Graupn.	Mittelb.
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have to correct my statement. The reaction was given by all of the 22 tested sera from healthy adults. Obviously, this result would not have been obtained if I had not used a number of different red blood cells for the test.

Halban,<sup>9</sup> Ascoli, and finally Eisenberg have already reported on the variable resistance of red blood cells towards the reaction. This is also shown in the above tables. Moreover, there was a peculiar regularity in the reaction of the 22 tested blood specimens. If one disregards some tests with sera from fetal placental blood which do not cause agglutination—Halban also found fetal blood serum rarely agglutinates—the sera may, in most cases, be grouped in three groups.

In a number of cases (Group A) the serum reacts with the red blood cells of another group (B) but not with the red blood cells of Group A; these react with the serum B in an identical way. In the third group C the serum agglutinates the red blood cells of Group A and B but the red blood cells of C are not influenced by the sera of A and B.

Applying the commonly used technical terms it may be said that there exist at least two different types of agglutinins, one in A, another one in B, and both together in C. The red blood cells are inert to the agglutinins which are present in the same serum.

No doubt a report concerning the presence of a few different agglutinins in the cases tested sounds peculiar, although the experiments of Ehrlich and Morgenroth

with isolysins showed quite similar conditions; it might be more satisfactory to find another interpretation by further observation.

It is suggested that attention be paid to these regularities in pathological cases.

Eisenberg thinks that the production of agglutinins is due to the resorption of components of red blood cells. This idea is not new; Halban and Ascoli have already presented it as a possible explanation. I did not formerly refer to it because I did not succeed in producing autoagglutination by injecting animals with their own lysed red blood cells.

I believe that Ehrlich does not report any positive results in that line either; Ascoli on the other hand obtained positive but not constant results. The difficulties of the given interpretation are mentioned by Halban. Perhaps the origin of naturally occurring hemagglutinins and normal agglutinins reacting with bacteria require different explanations.

Furthermore, my experiments show that various sera do not act identically as far as agglutination is concerned. Thus, if one believes that their agglutinating ability is developed in response to some autoimmunization due to resorption of cell components one has also to assume individual differences in order to interpret different sera. Actually, there are differences in different red blood cells and even already in fetal blood. Even if one acknowledges the differences of the sera or the red blood cells, the agglutination within one species is just as easy or as difficult to understand as the

agglutination by a serum from another species.

Nonetheless the presented interpretation cannot be disregarded; it is even the most adequate one if the untested experiments of Ascoli are correct. Then the physiological disintegration of the cells of body tissues might well be responsible for the formation of active serum components.

The experiments with sera from infants and animals are well suited to exclude the influence of pathological processes which may have occurred in the past. Halban's experiments also provide evidence against such a relation.

The agglutination described can be performed with serum which is dried and promptly dissolved; I succeeded in obtaining it with blood dried on cotton cloth and dissolved after fourteen days. Provided rapid changes in the agglutinating ability do not occur the reaction may be suited to establish the identity, or more correctly the non-identity, of a blood specimen. In a second test, the six sera of Table I gave

the same reaction as a fresh specimen obtained nine days previously.<sup>10</sup>

Finally, it might be mentioned that the reported observations may assist in the explanation of various consequences of therapeutical blood transfusions.

### References

1. Centralblatt für Bacteriologie XXVII. 8: 361, v. 10. Februar 1900.
2. XI Congress für innere Medicin. Leipzig 1892.
3. Journ. of Pathol. and Bacteriology. Februar 1900.
4. Berliner klinische Wochenschrift, 1900.
5. Literatur siehe bei Eisenberg, Wiener klinische Wochenschrift, 1901, Nr. 42.
6. Wiener klinische Wochenschrift, 1900, Nr. 22.
7. Münchener medicinische Wochenschrift, 1901, S. 1229.
8. Although Eisenberg attacks my report in his paper, and at the same time confirms it in regard to the blood of patients, he mentions my paper in the bibliography but with no word in his text.
9. Wiener klinische Wochenschrift, 1900, Nr. 24.
10. Dr. Richter and I plan to investigate the reliability of this method.



Obverse and reverse of the Landsteiner Medal issued by the Netherlands Red Cross in 1933.  
(Courtesy of A. S. Wiener, M.D.)