On Agglutination Phenomena of Normal Human Blood
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German Title:
Uber Agglutinationserscheinungen Normalen Menschlichen Blutes

Periodical Published in:
Wiener Klinische Wochenschrift 1901, 14: 1132-1134

Some time ago I observed and reported[1] that blood serum of normal human beings is often capable of agglutinating red blood corpuscles of other healthy individuals. At that time I had the impression that this clumping property of the blood serum against foreign blood corpuscles was particularly evident in some cases of illness and I thought that it could be related to the great dissolving power of pathological sera for normal corpuscles, discovered much earlier by Maragliano,[2] since agglutinating ability and dissolving power do indeed often, but not always, change in parallel. The circumstance that it is not heating, but rather the addition of salt up to an amount equivalent of the normal that increases the dissolving power of sera, speaks against equating Maragliano's reactions with the hemolytic reactions of the blood sera so often studied at present. Maragliano himself differentiates his observations from Landois' phenomenon—hemolysis due to serum from a different species—in that in his case the hemoglobin is not only dissolved but also destroyed. A real difference between my observations and Maragliano's is that in Maragliano's case the serum acts also on corpuscles which come from the same individual and that the reaction is obtained only with abnormal blood. My observations, however, show differences of a rather striking kind between blood serum and corpuscles of different apparently entirely healthy human beings.

[1] Centralblatt fur Bakteriologie, XXVII. February 1900. 10:361.

[2] XI Congress fur innere Medizin. Leipzig. 1822.

From Shattock's description and illustrations[3] his observations undoubtedly are pertinent here even though he detected the reaction only in febrile cases and missed it in normal blood. Shattock attributes the reaction to increased coagulability and rouleaux formation of febrile blood.

The agglutination of human blood by human serum to be discussed further here is called isoagglutination according to Ehrlich and Morgenroth's[4] method of notation. Shortly after the publication of my paper these two authors described experiments in which they succeeded in producing isol-ysins and isoagglutinins, that is, sera acting on corpuscles of the same species, by injection of blood of similar kind. Due to the variety of situations among the individual experimental animals these very thorough experiments confirm the not presupposed presence of clearly demonstrable blood differences within an animal species.

In Ehrlich and Morgenroth's work the phenomena of isolysis receive an accurate review from the standpoint of Ehrlich's theory.

Since the appearance of the communications by Shattock and by me, several investigators have been occupied with the behavior of isoagglutination in man. The criticism of those works which consider the reaction specific for a certain disease results per se from its presence in healthy persons. Other works recorded observations on the intensity and frequency of the reaction in cases of illness.

Donath[6] found the phenomenon more frequently in different forms of anemia than in healthy persons, but not every time. Ascoli[7] observed the phenomenon in healthy individuals, but in greater intensity in sick persons. Like other authors, he got the result that the reaction is frequent in sick persons and only exceptional in healthy ones. My data contradict thisfinding.[8]

Since I have expressed myself very briefly in the above-mentioned communication, I will mention in the following the results obtained in some recent experiments. The tables are self-explanatory. About equal amounts of serum and approximately 5% blood suspension were mixed in 0.6%saline solution and observed in hanging drops or in test tubes (the plus sign denotes agglutination).

[3] Jour. Pathol. and Bacteriology. February, 1900.
[4] Berliner klinische Wochenschrift. 1900.
[5] For the literature see Eisenberg. Wiener klinische Wochenschrift. 1901:42.
[6] Wiener klinische Wochenschrift. 1900: 22.
[7] Münchener medizinische Wochenschrift. 1901: 1229.
[8] Although Eisenberg attacks the data of my work, he mentions the work in bibliography but not with a single word in the text.

Table I. Concerning the Blood of Six Apparently Healthy Men

Sera	Blood corpuscles of:					
	Dr St	Dr. Plecn	Dr. Sturl	Dr Erdh	Zar.	Landst.
Dr St	−	+	+	+	+	−
Dr. Plecn	−	−	+	+	−	−
Dr. Sturl	−	+	−	−	+	−
Dr Erdh	−	+	−	−	+	−
Zar.	−	−	+	+	−	−
Landst.	−	+	+	+	+	−

Table II. Regarding the Blood of Six Apparently Healthy Puerperae

Sera	Blood corpuscles of:					
	Seil.	Linsm.	Lust.	Mittelb.	Tomsch.	Graupn.
Seil.....	−	−	+	−	−	+
Linsm.....	+	−	+	+	+	+
Lust.....	+	−	−	+	+	−
Mittelb.....	−	−	+	−	−	+
Tomsch.....	−	−	+	−	−	+
Graupn.....	+	−	−	+	+	−

Table III. Concerning the Blood of Five Puererae and Six Placentae (Umbilical Cord Blood)

Sera	Blood corpuscles of:					
	Trautm.	Linsm.	Seil.	Freib.	Graupn.	Mittelb.
Lust.....	+	+	−	−	−	+
Tomsch....	−	−	+	−	−	−
Mittelb.....	−	−	+	−	−	−
Seil.....	−	−	+	−	−	−
Linsm.....	+	+	+	−	−	+

A fourth, similar, table dealing with the sera of Table II, combined with the corpuscles of Table I and several other sera, e.g., from two persons with hemophilia and purpura, showed completely comparable regularities and could therefore be omitted. In the investigation of ten other normal persons(in 42 combinations of the same) the situations were similar. The experiments demonstrate that my data require no correction. All 22 examined sera from healthy persons gave the reaction. The result obviously would have been different had I not used a number of different corpuscles for the test.

Halban,[9] Ascoli and, finally, Eisenberg, called attention to a different resistance of the blood corpuscles against the reaction. This is also evident from the tables presented. In addition, however, a remarkable regularity appeared in the behavior of the 22 blood specimens examined. If one excludes the fetal placental blood, which did not produce agglutination—Halban also found that fetal blood rarely produces hemagglutination—from some of the blood serum examinations, in most cases the sera could be divided into three groups:

In several cases (group A) the serum reacted on the corpuscles of another group (B), but not on those of group A, whereas the A corpuscles are again influenced in the same manner by serum B. In the third group (G) the serum agglutinates the corpuscles of A and B, while the C corpuscles are not affected by sera of A and B.

In ordinary speech, it can be said that in these cases at least two different kinds of agglutinins are present: some in A, others in B and both together in C. The corpuscles are naturally to be considered as insensitive for the agglutinins which are present in the same serum.

It is not to be denied that the affirmation of the presence of few different agglutinins in the examined cases sounds rather remarkable, even though somewhat similar situations were found in Ehrlich and Morgenroth's experiments, and that it would be more satisfactory to find another explanation by continued observations.

It is now natural to look for these regularities in pathological cases. Eisenberg traces the formation of agglutinins back to the resorption of constituents of red blood corpuscles. This idea is not entirely new; it was already advanced by Halban and Ascoli as a possible solution. I did not mention this explanation at that time because I had not succeeded in producing in animals the ability for isoagglutination by injection of their own corpuscles in solution.

[9] Wiener klinische Wochenschrift. 1900: 24.

As I believe, Ehrlich also did not report positive results in this direction; to be sure, Ascoli had positive, but not constant, findings. Halban pointed out the difficulties in the interpretation mentioned. Especially, the formation of the naturally occurring hemagglutinins and that of the normal agglutinins that act on bacteria must perhaps be explained in different ways.

Moreover, my investigations show that the different sera do not act identically with respect to agglutination. If one believes, therefore, that they owe their agglutination ability to a kind of autoimmunization through resorption of cell constituents, then one must again assume individual differences to obtain the different sera. In fact, the blood corpuscles also behave differently in the fetal blood (see Table III). Assuming that differences of sera or corpuscles exist, one can understand with the same ease or difficulty agglutination within the species as that through serum from another species. In spite of this the explanation just mentioned cannot be excluded by any means. Indeed, if the nonrefuted experiments of Ascoli are correct, then the physiological destruction of the body tissues must, in general, be considered a source of formation of the active substances of the serum.

To exclude the assumption that perhaps past disease processes are of importance, I regarded investigations on the blood of children and animals utilizable. Halban's investigations do not support such a connection.

The described agglutination can also be produced with serum which has been dried and then dissolved. I did this successfully with a solution from a drop of blood which had been dried on linen and preserved for 14 days. Thus the reaction may possibly be suitable for forensic purposes of identification in some cases, or, better, for the detection of the nonidentity of blood specimens, if, as is possible, rapid fluctuations of the property do not occur, thus making them useless. To be sure, on the second test the six sera in Table I exhibited the same behavior as the specimens taken 9 days earlier.[10]

Finally, it must be mentioned that the reported observations allow us to explain the variable results in therapeutic transfusions of human blood.

[10] Dr. Richter in collaboration with me intends to test the usefulness of the indicated method.