its life, but also fail to produce serum-neutralizing antibodies in such mice against the homologous poliomyelitic viruses and against Theiler's virus. Moreover, antipoliomyelitic sera of human and monkey origin that are capable of neutralizing homologous and other strains of poliomyelitic virus fail to inactivate Theiler's virus. Conversely, serum from mice harboring Theiler's virus does not neutralize the poliomyelitic viruses. On the other hand, serum from normal mice of certain adult age has antiviral bodies against Theiler's virus. In this latter relation, a similarity exists between the virus of Theiler's disease—a natural malady of mice—and that of poliomyelitis of man in that neutralizing antibodies against the latter virus develop with time in man in the absence of clinically apparent disease. It has not as yet been determined, however, whether in man, as in the mouse, there exists the almost universal and prolonged[1, 2] carrier-state—in the intestines or perhaps elsewhere in the host.

11676 P

Isoimmunization in Pregnancy and the Varieties of Isoagglutinins Observed.*

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The production of immune isoagglutinins following repeated transfusions, although of common occurrence in some animal species, is very rare in man. The first instance of this sort in man was described by Landsteiner, Levine, and Janes.[1]

Levine and Stetson[2] described a case in which an intra-group agglutinin was responsible for severe post-transfusion symptoms, with anuria after the first transfusion. This occurred in a woman who, after retaining a dead fetus for a period of about 2 months, finally delivered a macerated fetus. In view of the activity of the agglutinin at 37° C and because of its gradual disappearance, it was believed that the antibody developed as a result of immunization, and it was suggested that the products of the retained dead fetus served as the

* This investigation has been aided by a grant from the Blood Transfusion Betterment Association of New York City.

1 Landsteiner, K., Levine, P., and Janes, M. L., PROC. SOC. EXP. BIOL. AND MED., 1928, **25**, 572.

2 Levine, P., and Stetson, R. E., *J. Am. Med. Assn.*, 1939, **113**, 126.

antigenic stimulus. This suggestion seemed plausible because the cells of the husband, of the same blood group, (who was the donor) were sensitive to the action of the agglutinin. Presumably, the fetus inherited from the father a dominant agglutinogen which was absent in the tissues of the mother, who could thus be immunized.

Our own recent experience and other cases from the literature[3] indicate that the isoimmunization-hypothesis may hold also in certain cases of pregnancy with complications other than the retention of the dead fetus. In each of the cases cited, atypical agglutinins could be demonstrated in the absence of a history of repeated blood transfusions.

In 5 cases[4] there was a history of varying degrees of toxic symptoms during the pregnancy (in 2 of which macerated fetuses were delivered). In one of these cases, the patient had some fever, and rupture of the membranes occurred a few days before delivery, which was normal but followed by a post-partum endometritis. In 3 patients[5] the agglutinins were observed following abortion, one of them of the septic variety. One patient, whose eighth pregnancy resulted in premature separation of the placenta, had stillbirths in the 4 preceding pregnancies.[6] In 2 of the remaining 3 cases there were histories of repeated miscarriages but the present pregnancies, apparently normal, had to be terminated by Caesarian section.† In one case the pregnancy was normal except for morning vomiting during the last six weeks; due to lack of progress in labor the delivery was by Caesarian section.[7]

More intensive study of a larger series of cases is required before any interpretation of these complications can be given in terms of the hypothesis of isoimmunization, but there does appear to be a correlation of the complications with the incidence of atypical agglutinins, and one can speculate as to their relationship.

In the seven cases from which data are available the atypical antibody acted on the cells of the father, who was compatible according

[3] Wiener, A. S., and Peters, H. R., *Annals Int. Med.*, 1940, **13**, 2306.

[4] Four of these cases are from our series, one of which will be published with Dr. S. Polayes; the fifth case was reported by Smith and Haman, *Calif. and West. Med.*, 1934, **41**, 157. This patient had toxic symptoms in each of her four pregnancies.

[5] One of these cases was reported by Parr and Krischner, *J. Am. Med. Assn.*, 1932, **98**, 47; another by Johnson and Conway, *Am. J. Obst. and Gynec.*, 1933, **26**, 255; the third case is one of our own.

[6] Zacho, A., *Hospitalstid.*, 1935, **78**, 225; *Z. f. Rassenphysiol.*, 1936, **8**, 1.

[7] Culbertson, C. G., and Ratcliffe, A. W., *Am. J. Med. Sc.*, 1936, **192**, 471; further data were obtained by personal communication.

† These cases will be published with Dr. L. Burnham.

to the blood groups, a fact which lends considerable support to the hypothesis that, under certain conditions still to be determined, the mother may be immunized by the fetus or the fetal parts of the placenta. In only 2 of these cases were the incompatibilities detected prior to the transfusion; in the remaining cases the transfusions were attempted with resulting shock and in 3 instances the outcome was fatal. Of the 10 cases transfused, 8 showed distinct clinical symptoms and signs of hemolysis of transfused blood (jaundice and varying degree of anuria).

Another interesting feature presented in the author's own cases is the variety of isoagglutinins observed. In 4 of the 7 cases the atypical antibody was characterized by a greater degree of activity at 37° C than at lower temperatures. Consequently, the only previously reported case of Zacho[6] can no longer be considered unique. It therefore seems desirable to designate agglutinins of this sort as "warm-agglutinins". In one of our cases the atypical agglutinin reacted at only 20° C and not at 37°. In the 2 remaining cases the isoagglutinin reacted equally well at 37° and at 20°; in one of these, hemolytic reactions were obtained which ran parallel to the results of agglutination with inactivated serum.

It is of further interest that the specificity of one serum containing warm-agglutinins corresponded to the anti-Rh of Landsteiner and Wiener.[8]cf[3] This observation was made in tests done jointly with Dr. Wiener.

The clinical and immunological aspects of these cases will be more fully described elsewhere. The material is presented because of the several varieties of isoagglutinins observed and because of the general biological significance of the concept that the mother may be immunized by the fetus.[9]

Finally, attention is called to the analogy of the immunization of

[8] This blood factor, demonstrated by means of anti-rhesus blood immune sera, was described by Landsteiner and Wiener, PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 223.

[9] Indirect evidence for the immunization of the mother by the fetus was furnished by Jonsson, who showed that the anti-A and anti-B content of mothers belonging to group O was specifically determined by the blood groups of the infants, provided they were in groups A or B respectively. (*Acta Path. et Microbiol. Scand.*, 1936, **13**, 424.) Some years previously, Hirszfeld speculated at length on the relationship of heterospecific pregnancy and complications in the mother and infant. (*Konstitutionsserologie and Blutgruppenforschung*, 1928, Springer, Berlin.) The relationship of blood differences in mother and child to the etiology of eclampsia was discussed by Dienst (*Zentralb. f. Gynäk.*, 1905, **29**, 353), Ottenberg (*J. Am. Med. Assn.*, 1923, **81**, 295) and others.

the mother by the products of conception and the production of isoagglutinins in rats and mice receiving transplants of certain tumors.[10, 11]

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Atypical Warm Isoagglutinins.

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Zacho[1] reported an instance of premature separation of the placenta with a transfusion-accident, attributable to an atypical isoagglutinin active on the donor's cells. This agglutinin had the unique property of greater activity at 37° C than at lower temperature. Although Zacho's case was the first and only published instance of this sort, it is likely that hitherto antibodies of this character may have been overlooked. In support of this, case reports are presented of 5 patients whose blood recently investigated were found to contain such agglutinins. A brief discussion of the properties and the origin of these agglutinins forms the basis of this communication.

One of these cases was observed in a patient† (B.M.) transfused 6 times because of bleeding from a duodenal ulcer. Apparently, this agglutinin was induced as a result of the antigenic stimulus of repeated transfusions. No such history could be elicited in the remaining 4 instances, nor in the case of Zacho, all of which were observed in women suffering from a variety of complications of pregnancy.

In one patient (G.B.) who gave a history of 2 miscarriages, the present pregnancy was complicated by death of the fetus during labor. A second patient (H.H.) had 3 consecutive miscarriages and in the present pregnancy delivery was by Caesarian section because of uterine inertia. A third patient (D.D.) who suffered from persistent vomiting from the fourth to the seventh months had fever

10 Gorer, P. A., *J. Path. and Bact.*, 1937, **44**, 691.

11 Lumsden, *Am. J. Cancer*, 1938, **32**, 395.

* Aided by a grant from the Blood Transfusion Betterment Association of New York City.

1 Zacho, A., *Z. f. Rassen phys.*, 1936, **8**, 1.

† B. M. is a patient of Dr. Abell, Louisville, Kentucky. The study of this blood was made possible by Dr. D. C. Bull.