Table 1. ACTIVATION OF BLOOD-CLOTTING FACTORS BY SOME PHENYL DERIVATIVES

Compound	Blood-clotting factor I	VIII	IX	XII
Phenylethylene	+	+	+	+
Benzyl benzoate	+	+	+	+
2-Phenyl ethanol	−	−	−	−
Phenyl acetaldehyde	+	−	−	−
o-Hydroxydiphenyl	+	−	−	−
Cinnamic acid	−	−	−	−
Triphenyl ethylene	−	−	−	−
Ellagic acid	+*	−	−	+

* This action of ellagic acid was slightly reduced by citrate.
−, No appreciable effect.
+, Activates the respective factor.

stages of blood coagulation[5]. It is thus of interest to determine the blood-clotting factors which are chemically evolved (activated).

The activating effect of a chemical compound was estimated on factor I (fibrinogen) by the increased sensitivity to thrombin; on factor VIII by the increase induced in its concentration in intact blood from a case of von Willebrand's syndrome[6]; on factor IX by the amount adsorbed on aluminium hydroxide in intact blood[7]; and on factor XII by the effect on the blood-clotting time of intact blood in siliconed tubes. The results obtained with some of the phenyl derivatives tested are summarized in Table 1, and it can be seen that the activities of at least four factors are susceptible to certain chemical reagents.

Because thrombosis has been recorded in cases with low concentrations of certain blood-clotting factors[8] and because it has been demonstrated that high concentrations of clotting factors are liable to produce hypo-coagulability rather than hyper-coagulability of blood[9], I conclude that the *in vivo* evolvement of blood-clotting factors is more important than their concentration in the pathogenesis of thrombosis. I also suggest that the participation of a chemical compound in the induction of thrombosis is highly probable. Accordingly, I am at present testing other reagents in an endeavour to determine the chemical structural group responsible for promoting the formation of abnormal clots.

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Cell Surfaces, Blood Groups and Micro-organisms

WE have described the *in vitro* alteration of the blood group I receptor of the red cell by mycoplasma, and stated that the effect was greater on group A cells than on group O cells[1]. We also noted that *Clostridium* filtrates which had been reported by other workers to destroy the specific I determinant were more active against group A than against group O cells[2]. For these reasons we used group A_1I red cells in our final test system which employed the gamma macroglobulin fraction from a group A_2 patient who was I negative as our agglutinating reagent. Feizi and Darrell have now reported their failure to find an effect of mycoplasma on the receptors for I. Unfortunately, they used group OI cells instead of group AI cells in their test system[3].

The serological evidence for reactivity association between the ABO blood group and agglutination by anti-I reagents is established beyond doubt. The anti-I (Steg) of Race and Sanger gave a higher score against group O cells than against A cells[4]. Tippett *et al.* found an anti-I which reacted more strongly against A_1 than A_2 or O cells; absorption with O cells or simple dilution resulted in a pseudo anti-A_1 which detected a joint product of the I and A_1 genes[5].

The circle has now been closed with the discovery of a serum which required the presence of both the B and I determinants for reactivity[6]. Blood group specific substances and gangliosides which inhibit anti-A and anti-B also inhibit anti-I[7,8] and could be another cause of discrepancy, for the sera of Feizi were used after neutralization with group B substance[9].

Rosenfield *et al.*[10] and Gold[11] have described a whole spectrum of agglutinins which differ in their relative effects depending on the presence or absence of combinations of O and I and its reciprocal agglutinogen, i. Any single reagent[12] cannot be expected to yield results identical with all other anti-I reagents and this has been shown to be particularly true when there is only partial lack of I[9]. In one attempt to measure the agglutinability of red cells from patients with acute leukaemia, not decreased I but increased i was reported[13]. We cannot duplicate this with our anti-i reagents, but are not surprised, because titration scores are far from an ideal method of quantitating agglutinability[14]. Thermal amplitude of an agglutinin is again a different test from titre and results in a clear difference in specificity of the same molecule[15]. The changes in I in leukaemia which we reported have been seen by others and correlated with the simultaneous loss of A[14,16].

Feizi and Darrell point out the difficulty in the concept of a blocked anti-I antigen stimulating the production of anti-I[3]. This is, of course, why we postulated that the antigen was degraded, rather than blocked, by mycoplasma. Experimental support for this postulate has now been given by Tonder and Harboe[15]. Careful serological work with anti-I led them to conclude that the aetiological antigen resembled an antigen on the surface of rabbit red cells more closely than the antigen on human red cells.

The genetic pathways leading to the production of joint products of the ABO and I genes are still unknown. The specific chemical determinants of I and i specificity on the surface of blood cells are also unknown. Haemagglutination is a most sensitive test for detecting membrane changes and the part of the cell surface which identifies agglutinogen specificity must be of very small mass.

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