Table III confirms that while Vuorio and Mrs. B. are similar, they are not identical. Group A and O sera, fully absorbed with Mrs. B., still reacted with Vuorio. Mrs. B.'s saliva contained what appears to be a fraction of the normal B antigen and that, as might be expected, corresponds to the antigen on her red cells (table IV, A). The anti-B in Mrs. B.'s serum appears to react with only a fraction of the B substance found in group B secretors (table IV, B).

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Mrs. B., and indeed all her family were most co-operative and we are glad to be able to thank them here.

The kindness of O. and P. Mkel in sending us a generous sample from Mr. Vuorio enabled us to compare him in some detail with Mrs. B.

Our thanks are also due to Miss Dodd for her most interesting range of adsorbed sera and eluates from animal cells.

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A Weak Form of the Blood Group Antigen A: an Inherited Character

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Routine blood-grouping as it is or should be performed today, is in most cases a rather dull exercise, not producing any excitement. If, however, a sample turns up which behaves not as expected and if one can exclude an experimental error, it is always worthwhile to investigate further to find out the cause of this irregular behaviour.

Mrs. E. presented herself at an ante-natal clinic during her first pregnancy and a sample of her blood was one of those which did not conform to our "established" rules. It gave the following reactions:

Table I

Reactions Given by Sample from Mrs. E.

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From this, it can be seen that the cells behaved as expected of Group O cells but the serum contained anti-B only. After the first tests, Dr .Race and Dr. Sanger and myself, we all jumped to (what appeared later) wrong conclusions. I had done tube tests only and felt that this was a further example of Am, whereas Dr. Race and Dr .Sanger, who investigated the cells with their much more sensitive Petri-dish method, thought at first that this was either a case of chimerism or foetal bleeding. A similar picture would also be obtained if a Group A2 patient would be transfused with massive doses of Group O blood. We could quickly eliminate the last possibility and also chimerism as Mrs. E. was not a twin. Dr .Race and Dr. Sanger were able to separate the cells which appeared to be A2 and O respectively and when their antigens were investigated, it was found that both cells were absolutely alike in their antigenic structure, apart, of course, from the agglutinability of the "A" cells by anti-A and the inagglutinability of the "O" cells by the same serum. This, if further proof was needed, made chimerism and foetal bleeding most unlikely. Fortunately, Mrs. E.'s parents and one brother are alive and were good enough to allow us to investigate blood samples. The parents came from different parts of the country and were not related. This investigation produced evidence that we were dealing with an inherited character as the samples from both the mother and the brother of the patient gave identical reactions with those obtained with the sample from Mrs. E.

The identity of the reactions makes it possible to describe them together. The sera of all three people agglutinated Group B cells strongly but Group A cells were left unagglutinated. The cells of the three people were not agglutinated at all in tubes and it did not make any difference whether the cells were suspended in saline, albumin, P.V.P., or treated with enzymes. However, when the cells were mixed with anti-A or anti-A +B (from Group O donors) in Petri dishes (the method described by Race and Sanger), very small agglutinates started to appear after approximately six minutes but no agglutination was seen with anti-B or AB serum. In this test, only approximately 0.5 % of the cells were agglutinated. This estimation was based on a comparison with artificial mixtures of A2 cells and O cells. In all, nine Anti-A, seven Anti-A +B, eight anti-B and two sera from AB persons were used. The position was somewhat different when a very powerful immune anti-A serum from a Group O donor was used in the indirect Coombs test. This immune anti-A was the result of a mis-matched transfusion and the agglutination obtained in the anti-globulin test was general, though the agglutinates here too were small, and in fact smaller than with any other example of A. The immune anti-A used does not contain antibodies against any of the other antigens found on the cells of the three people other than anti-A. This probably shows that the majority of the

cells carried an A antigen of some sort though this A antigen does not seem to be capable of agglutination when the cells are tested in the usual way.

The presence of an A in the red cells was further confirmed by absorption and elution tests with anti-A and anti-A +B. The cells absorbed anti-A but less than Aj, A2, A2B, A3 and Am cells. Artificial mixtures of 10% A2+90% O, and 5% A2 +95 % O, absorbed more anti-A than the test cells. However, these absorbed

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more than the one example we had of AmB and Ax. Anti-B was not absorbed. Human anti-A4 and Dolichos biflorus anti-Aj did not agglutinate the cells on the slides. The cells reacted as strongly in titration tests against anti-H (*Ulex Europaeus*) as A2 or O cells.

Unfortunately, we are unable to state what group the baby was as the cord blood sample could not be investigated and a sample collected when the baby was three weeks old reacted negatively to anti-A and anti-A +B. It is, however, possible that a weak A antigen might not be fully developed at birth. Unfortunately, a later sample was not available.

The possibility that the three people belonged to the Am group was finally excluded when it was found that their saliva contained H but no A or B substance. They all secreted Lea substance.

Fig. 1.

Fig. 1 shows in detail the inheritance of this group. The ABO and Lewis groups of the red cells and the secretor status in the saliva are given and it is clear that the weak A is inherited. We assumed that the gene producing this effect must be a dominant gene and here perhaps it would be appropriate to say what we mean by dominant in blood grouping. The easiest way perhaps to define dominant would be to say that the word is used to mean that a single dose of the gene will express itself in favourable circumstances. These favourable circumstances in our case would be that the genotype does not include an A gene higher in the series than the one which is being studied. Elsewhere it might mean that an appropriate test serum is available to demonstrate the presence of the antigen produced by the gene in question.

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Though a dominant gene in the A1A2BO series would appear to be the simplest explanation and the most likely one, one might argue that the weak A is the result

of the dominant effect of a modifying gene on the expression of a normal A gene. This, however, has not so far been an experience in blood grouping and the simple allelic explanation must be preferred. A recessive modifying gene, however, cannot be assumed in this case as one would have to postulate homozygosity for the mother and heterozygosity for the father for an extremely rare gene. In this connection, it is perhaps permissible to mention the weak B described by Dr. Dunsford and his colleagues^{1,2} who in the final paper assumed this weak B to be the result of modifying genes similar to the gene X postulated for the Am. This would, as pointed out, necessitate the most unlikely assumption of homozygosity of a very rare gene in one parent and heterozygosity for the same gene in the other parent. It is much more likely that the explanation we offer for the weak A of this communication also applies to the weak B of Dunsford and colleagues.

If we look at the family of A's so far described in the literature, whereabouts does Mrs. E.'s A come in?

Table II has been much discussed amongst ourselves but we still feel that it is not quite satisfactory. The A described does not fit into the picture of an A₃. The

Table II

Some Reactions of Various A Phenotypes

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three members of our family are secretors as could be shown by the great amount of H in their saliva but they do not secrete A. Neither is the A they carry identical with the A₄ and A₅ described by Gammelgaard. A₄ and A₅ cells show general agglutination and could not possibly raise the queries our A raised at first. Clearly, the reactions of our A are quite different from the reactions obtained with A_x samples. The latter are firmly agglutinated by anti-A in sera from Group O people, though not by anti-A from Group B people. Our family was not as choosy and their cells could be agglutinated weakly both with anti-A from Group B people and anti-A from Group O people. A_x does in addition seem to be somewhat heterogenous. Fischer and Hahn³ who described it in 1935 were followed by a number of authors who gave to this antigen different names (A₄, A₀, A_z). Some of the examples are clearly inherited as a dominant character but in others, the inherited character is irregular and the presence of modifying genes has been suspected. The A described now is clearly also not due to a modifying gene. People belonging to the Am group secrete plenty of A substance, if they are secretors. Several examples of this subgroup have been described, the first probably by Gammelgaard⁴ in 1942, though he called it A_x in spite of the prior use of this symbol by Fischer and Hahn seven years ago for quite a different antigen. Wiener and Gordon⁵ provided the name Am in 1956 and we have described two further examples in 1957⁶. The A on the red cells in this

subgroup is hardly demonstrable with any method but against this, there is plenty of A in the saliva and the genotype can be determined as was shown in a previous paper.

The Ag again does not fit the picture presented by our family. In 1957, Van Loghem and his colleagues⁷ reported the finding of a very weak kind of A in a patient who before his illness had twice been grouped without comment as an A. It was, therefore, assumed that the weak A, called Ag, was not due to a genetic cause but was the consequence of a blood disease from which the patient was suffering. A very similar case was described in 1957 by Stratton, Renton and Hancock⁸ who showed that their patient had transmitted an Ax gene to his daughter. Both the Dutch and the English patients were non-secretors.'

We ourselves have seen lately a very similar case, again in a patient suffering from myelogenous leukaemia who unfortunately died before a full investigation could be performed. This patient too had been grouped during health as Group A without any comment but in the terminal stage of his illness, no reaction could be obtained with anti-A or anti-A+B. All three people in our family who had the weak A were perfectly healthy and as the Ag has been assumed to be the result of a modification due to illness, this explanation for the A described, clearly does not apply.

Notation of the Members of the A Family

By custom, the alleles at the ABO locus have been given subscript numbers. We probably all know what we mean when we talk about an A₄ or an A₂. Lower down in the scale, A₃ has been fairly well defined and so has A₄ and A₅. But we ran into a difficulty for the still weaker members of the family. If a letter is suggested, it may

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well be that this would have to be changed when the next weaker or slightly stronger member of the family would be discovered. It would not appear to be helpful to give specific names to samples which may represent only different points on a normal distribution curve of antigen strength unless they are distinguished by some qualitative peculiarity or a distinctive property. On the other hand, weak forms of A due to modifications are conveniently described by subscript letters.

The A antigen of the E family does not, as far as we know, correspond with any weak form of A previously reported. For the reasons given above, we hesitate to give this kind of A a symbol which in all likelihood would have to be changed in a year or two. Though we hope that this newest child of the A family will survive, we do not want to add to the rather unlucky premature christening of the A and B weaklings. We have described this form of A in the hope that if similar cases will occur, they may be assembled to start with as curios by enthusiastic collectors and

when and if a greater number of them will be seen together, one might start to sort them out to see the pattern of alleles or genetic and environmental modifications to which the blood groups are subject and which the ABO system indicates so nicely. The time might then come to arrange for a proper and decent christening party for all the members of this rather widespread and interesting though sometimes troublesome and exciting family.

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