difference between the molecular ion and the peaks in the spectrum with the composition of the amino acids.

Work is in progress on the MS-902/Argus 500 system recently installed at the University of Liverpool to extend the scope of amino acid sequence determination of peptides by mass spectroscopy. This system is capable of recording a complete high-resolution spectrum in 25s and immediately producing a paper tape of the accurate masses.

This rapid scanning capability may, in principle, be utilized to obtain sequential spectra of mixtures

(R. A. W. Johnstone & D. W. Payling, personal communication), and hence in the case of peptide derivatives to obtain amino acid sequences of the individual components.

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IMMUNOGLOBULIN DISCUSSION GROUP COLLOQUIUM ON 'GENES AND ANTIBODIES'

Gene Expression of Immunoglobulins

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Genetic Control of the Antibody Response

By E. S. LENNOX. (*The Salk Institute, San Diego, Calif. 92112, U.S.A.*)

It should be possible by finding suitable mutants to reveal steps in the pathway of the immune response and perhaps to decide whether the many antibody specificities arise by a somatic generation of diversity. To this end, we have screened many strains of inbred mice for their ability to make antibodies against several strains of influenza virus. Several differences have been found among the mouse strains, and genetic crosses have been made to elucidate the genetic control. In addition, there are very big differences of response among individuals of the same inbred strain.

Some of the findings are as follows:

(1) Strain DBA-2 responds to injection of virus WSE by making only macroglobulin (immunoglobulin M) antibody. In response to other virus strains it does make immunoglobulin G in addition. This defect in specific immunoglobulin G production is controlled by a single gene or close cluster of genes. On second injection strain DBA-2 does make immunoglobulin G antibodies, and hence the block in primary response is at some regulatory step.

(2) Response of F₁ hybrids between two strains that respond poorly is significantly better than either parent. This would seem to indicate multi-genic control of the immune response, a hardly surprising result.

The possible uses and limitations of these kinds of experiments will be discussed.

Genetics of Human Immunoglobulins

By J. B. NATVIG. (*Research Institute of Immunology and Rheumatology, Rikshospitalet University Hospital, Oslo, Norway*)

The four γ G and two γ A heavy chain subclasses show different antigenic and biochemical structures related both to the Fc and Fd parts of the heavy chains. In addition, studies on Gm and Am (Kunkel, Smith, Joslin, Natvig & Litwin, 1969; Vyas & Fudenberg, 1969) genetic markers show that these γ G and γ A subclasses are related to genes of at least six different cistrons. Sensitive haemagglutination inhibition systems have become available for studying antigens that are subclass specific, as well as others shared by some, but not all, subclasses. Many of these antigens, particularly those studied for γ G, are isotypes present in all normal sera. For example, 'non a' and 'non g' (Natvig, Kunkel & Joslin, 1969) are shared by three and two subclasses respectively. However, although present in all γ G2 and γ G3 proteins, 'non a' is only found in Gm(a-) γ G1 proteins. Thus within γ G1 'non a' is antithetic to Gm(a). Further, its distribution completely matches that of the previously described 'non a' peptide (Frangione, Franklin, Fudenberg & Koshland, 1966). 'Non g' is present in all γ G2 proteins, but only in Gm(g-) γ G3-globulins. Thus within γ G3 'non g' is antithetic to Gm(g).

In contrast with these isotypes, the allotypes are present only in some sera and are confined to certain proteins within one particular subclass. Heavy-chain allotypes are known for four subclasses: γ G1, γ G2, γ G3 and γ A2. Most of these markers reside in the Fc portion, but two Fd markers, Gm(f) and Gm(z), are known. The 'non a' and 'non g' markers, the Fd and Fc subclass-specific antigens and the Gm and the Am allotypes have proved useful for studying γ -globulin structure and synthesis. Their

exact localization within the immunoglobulin fragments and chains is therefore of importance. Recent work in co-operation with Dr M. Turner and Dr H. Bennich on the pFc' fragment has added to the further localization of some of these markers within the Fc fragment (M. W. Turner, J. B. Natvig & H. Bennich, unpublished work). Gm(a), 'non a' and Gm(b⁰) are present within the pFc' fragment of the respective subclasses. In contrast, Gm(g) 'non g', Gm(n) and Gm(b¹) were not detected in the pFc' fragment and were probably related to structures nearer to the N-terminal part of the Fc portion.

These markers are also employed in studying immunoglobulin genes. The structural homologies, and the very close genetic linkages found by using the Gm and Am markers indicate that the γ G and the γ A subclass cistrons have developed through relatively recent duplications, due to unequal crossing-over. If this is so, one would expect to find evidence of unequal crossing-over, giving rise to deletions, duplications and hybridizations of the γ -globulin heavy-chain genes. In fact a number of gene complexes as well as single genes have been described that may be explained as result of crossing-over. There are several examples of probable crossing-over events appearing in various population groups. Further, evidence for products of deletions and duplications has been found both in major Gm-Am gene complexes and in isolated polypeptide chains. One particular case of a hybrid γ G heavy chain consisting of γ G1 Fc and γ G3 Fab (Kunkel, Natvig & Joslin, 1969) is an example of a gene deletion and hybridization due to an unequal homologous crossing-over.

The markers mentioned above are probably all part of the constant portion of the heavy chain. Further, for the light chain no genetic markers have so far been definitely localized to the variable portion. However, some reaction patterns with human anti- γ -globulin antibodies of the 'anti-antibody' type are related to the Gm allotypes. These 'anti-antibodies' cannot be inhibited by large excess of native γ G-globulin or F(ab')₂ fragments thereof. In contrast, they react easily with whole γ G-globulin or F(ab')₂ fragments altered through certain immunological reactions, particularly anti-Rh reactions. Since the 'anti-antibody' specificity is related to heavy-chain Gm allotypes and also to the antibody activity of the reactant γ G molecules, the antigenic determinants are likely to be in the variable part of the Fd fragment. Thus allotypic markers related to the Gm system may exist in the variable part of the γ G heavy chain.

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Genetic Markers of Rabbit Immunoglobulins

By J. M. WILKINSON. (*Department of Biochemistry, University of Birmingham, Edgbaston, Birmingham 15, U.K.*)

The occurrence of allotypes in rabbit immunoglobulins was first demonstrated by Oudin in 1956, when he showed that immunization of rabbits with purified antibody from some, but not all, other rabbits gave rise to precipitating antisera and that the antigenic specificities so detected were inherited in a simple Mendelian fashion (see Oudin, 1966). Since that time a considerable body of work has demonstrated the presence of more than 20 allotypic specificities on both heavy and light chains and in all three major classes of rabbit immunoglobulins. The most surprising finding has been that of Todd (1963) and Feinstein (1963), who showed that the α group determinants A1, A2 and A3 of the γ -chain are also shared by the α - and μ -chains, implying that, if the specificities are determined by primary structure, all three chains must have some sequence in common.

Sequence studies on such a heterogeneous population of proteins have been slow to catch up with the antigenic analysis, but it has been clear for some time from the amino acid analysis data for the whole chains and their fragments (Koshland, 1967; Prahl & Porter, 1968) that the differences in allotypic specificity could be correlated with differences in composition. The sequences responsible for the α and β group specificities and the γ -chain alleles A11 and A12 (Mandy & Todd, 1968) have been further investigated. Of these only the A11-A12 pair show a simple relation to sequence, there being a good correlation between a methionine-for-threonine replacement at position 226 in the γ -chain and the specificities A11 and A12 respectively (Prahl, Mandy & Todd, 1969).

The C-terminal sequence of the κ -chains, which carry the β group specificities, has been investigated by Appella, Rejnek & Reisfeld (1969). They have shown several differences between the sequence of the last seven amino acids in chains carrying A4, A5 and A6 specificities, and this has been confirmed by Frangione (1969), who also reported differences in the composition of the peptides containing the intrachain disulphide bonds. There seem thus to be multiple amino acid differences between the chains, as suggested by the amino acid composition, and this is surprising in view of the constancy of the C-terminal half of the human light chains.

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