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SPECIAL REVIEW ARTICLE

GENETIC BACKGROUND OF CERTAIN IMMUNOLOGICAL PHENOMENA WITH PARTICULAR REFERENCE TO THE SKIN*

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It is well known from clinical experience that there are certain differences in the incidence of development of immunological reactions in various groups of people. Some individuals become strongly sensitive when exposed to even a very little amount of weak sensitizer for a very short time. However, others fail to become sensitized after exposure to a far higher concentration of a strong sensitizer for a relatively long time.

The explanation for this fact can be sought in differences in genetic influences. As early as 1650 Sennertus described the familial incidence of asthma.

The aim of this paper is to review our knowledge of the genetic control of immunological phenomena in both experimental animals and in human subjects. The first part will take the form of a survey of the genetic factors involved in delayed hypersensitivity reactions in experimental animals and of the occurrence of diseases based on immunological phenomena. The second part will deal similarly with humoral antibody formation and the final part with the incidence of diseases associated with auto-immune phenomena.

I. CELL-MEDIATED IMMUNE REACTIONS

There has not been very much work on the problem of the genetic control of delayed hypersensitivity reactions. However, the small amount of work that has been done in this field has been more intensive and concentrated than the work in other fields with the result that more precise conclusions can be drawn about the factors and mechanisms involved.

A. In Experimental Animals

The earliest approach to the problem was by Landsteiner and Jacobs (1935) and Landsteiner and Chase (1937) who worked with simple chemical compounds and noticed that identical treatment leads sometimes to different degrees of hypersensitivity within the same group of guinea pigs, even when kept under the same living conditions (temperature, food etc.). Landsteiner and Chase (1940) tried to breed guinea pigs according to whether they had a high or low susceptibility to experimental sensitization and this work was further extended by Chase (1941). Chase (1941) was able, after a very careful selection, to establish two strains of guinea pigs which differed significantly in their degree of sensitivity, despite the same sensitizing procedure and the same environmental conditions. One group gave, in almost all animals, uniform intense reactions after only a brief course of sensitization by intradermal injections with a total of 0.01 mg dinitrochlorobenzene (DNCB) while the other group responded with only a low grade sensitivity to an even longer course. However, these animals were not complete non-responders and the reactions seen were far from uniform. Sometimes some of the offspring of poor reactors exhibited stronger reactions than either parents. Chase also observed differences in guinea pig strains procured from different breeders.

Breeding experiments with parents, selected for their reactivity to poison ivy, showed again that the degree of susceptibility was hereditary and that groups of good and poor responders can be established. There was a rough accordance between the sensitivities developed to DNCB and poison ivy, but sometimes there was a discrepancy in that a good responder to DNCB would be a poor responder to poison ivy and vice versa. This fact could be explained by different genes, which control the ability of the animals to be sensitized to these different substances. These experiments show very clear proof that there is genetic control

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in the manifestation of hypersensitivity to simple chemical compounds.

After this basic work there was a gap of more than twenty years before the problem of genetic control in delayed hypersensitivity was tackled again. Stone (1962) sensitized Hartley, strain 2 and strain 13 guinea pigs to *M. tuberculosis* and determined the minimal dose necessary for inducing a state of hypersensitivity. In these experiments he found that Hartley guinea pigs were more easily sensitized than the inbred strains 2 and 13 and strain 13 more than strain 2. More recently research into genetic differences in the immune response has turned to the use of synthetic polypeptides. These are simple chemically defined antigens and it is therefore easier to follow more closely the genetic control of the sensitization process. Kantor, Ojeda and Benacerraf (1963) observed that it was possible to immunize only 40% of Hartley strain guinea pigs to the dinitrophenyl (DNP) group linked to polylysine and they assumed that this reflected constitutional differences, presumably genetic, among these randomly bred guinea pigs. Only those guinea pigs capable of reacting to one antigen (DNP-Polylysine) were able to react to the DNP group linked to the immunologically unrelated copolymer of glutamine and lysine. The constitutional difference was therefore thought to operate at a stage before the formation or selection of the immunological specificity. This difference in sensitizability could be due to the presence or absence in guinea pig macrophages of an enzyme capable of splitting lysyl-peptide bonds. Levine, Ojeda and Benacerraf (1963a) extended this study by using four different hapten poly-L-lysine conjugates and found that individual random bred Hartley guinea pigs were either capable of developing an immune response either to all of these compounds or else to none of them at all. The ability to respond immunologically appears therefore to depend not on the structure or the 'degree of foreigness' of the haptenic group but on the ability to metabolise the conjugate in a precise way. In a further study Levine, Ojeda and Benacerraf (1963b) performed breeding experiments and also used inbred strains of guinea pigs. They demonstrated that 82% of 22 offspring of 8 pairs of responder parents were responders, whereas none of the 26 offspring of 9 pairs of non-responders could be sensitized. None of 11 strain 13 guinea pigs and all of 40 strain 2 animals could be sensitized to the hapten poly-L-lysine conjugates. This fact is in favour of the genetic control being by a single Mendelian dominant gene. Levine (1964a) also compared the antigenicity of benzylpenicilloyl-poly-L-lysine (BPO-PLL) conjugates in random bred and inbred strain 2 guinea pigs. Although he did not find any significant differences among these strains, the results of these experiments suggested that the first step of immunization could be the metabolic breakdown of the antigen. This could then be followed by the coupling of antigenic fragments with RNA, which could require an activating enzyme specific for the lysine side chain. Difference in the presence of that enzyme, which may be hereditary, could explain differences in immunizability of the different strains. Further it was found (Levine, 1964b) that certain BPO-polylysines were not antigenic in any of the strains used. Levine and Benacerraf (1964) started with the suggestion that the difference between responder and nonresponder guinea pigs may reside in their abilities to metabolise the poly-L-lysine carrier properly. This might be due to a presence of a single essential metabolic enzyme, which was either responsible for degradation of the PLL carrier or involved in the metabolic process. This in turn could lead to the formation of the specific inducer, bearing the antigenic dominant. They also suggested that in addition to the known requirements for antigenicity (presence of antigenic determinants and ability to be degraded by reticulo-endothelial tissues), the resulting degradation products must undergo specific metabolic steps to induce an immune response. However, these steps have not yet been identified. Nevertheless, it was discovered that the enzymatic digestion of the PLL molecule is not impaired in unresponsive guinea pigs. It was also found (Vassalli, Levine and Benacerraf, unpublished observation) that the uptake of antigen by lymph node macrophages in unresponsive guinea pigs was also unimpaired.

In a further set of experiments Levine and Benacerraf (1965) crossed random bred Hartley guinea pigs, which do not respond to hapten-PLL conjugates, with heterologous responder guinea pigs and found that the off-

spring included at least one nonresponder. Of 31 offspring from 10 pairs of parents consisting of nonresponders and heterologous responders, 14 were responders. This result supports the view that immune response to PLL conjugates is a genetically transmitted autosomal Mendelian dominant controlled by one single gene. A very broad analysis of the genetic control of immune responses was made by Green, Paul and Benacerraf (1966). They suggested two main objections against the hypothesis that the ability to produce immune responses to hapten PLL conjugates in good responders depends on the ability to metabolise the PLL carrier. Firstly, there are no differences between responders and non-responders in the enzymatic digestion of the PLL molecule concerned, and secondly, the uptake of the molecule by lymph node macrophages was not altered in unresponsive guinea pigs. Therefore they suggested that the gene governing antigenicity controls a specific metabolic step prior to the recognition of specificity, which involves the formation of an unidentified inducer of immunogenicity. The alternative possibility is that the gene controls the recognition of the PLL specificity as an antigen. In very carefully performed experiments the authors found that DNP poly-L-lysine which behaved as a complete antigen in responder guinea pigs can behave in nonresponders as a hapten. Guinea pigs genetically unable to recognise the antigenicity of DNP poly-L-lysine respond to immunization with the conjugates of DNP poly-L-lysine to several different albumins. However, they produced humoral antibodies to the DNP group only and did not show delayed hypersensitivity to DNP-PLL. The conjugates of DNP poly-D-lysine to albumin did not appear to be antigenic at all. As the result of these experiments two hypotheses of genetic control were discussed: (1) the 'metabolic gene hypothesis' which assumes a metabolic reaction in the poly-L-lysine prior to recognition of specificity, possibly in the macrophages, and results in the formation of a specific inducer of immunogenicity; (2) the 'specific gene hypothesis' which supposes a specific immunological recognition of poly-L-lysine as a partial antigen/antibody complex capable of reacting with it, whereas there is no gene capable of recognising poly-D-lysine. The results of the experiments of Green *et al.* (1966) are in favour of the 'specific gene hypothesis'.

In continuation of these experiments Green, Vassalli and Benacerraf (1967) discovered that animals which were genetically nonresponders when immunized against DPN-poly-L-lysine complexed with a foreign albumin, produce two types of antibodies one against the DNP-poly-L-lysine hapten and another against antigenic determinants of the conveyor molecule. Each type is produced in separate plasma cells. Schlossman, Yaron, Ben-Efraim and Sober (1965) extended the knowledge of the genetic differences in Hartley, strain 2 and strain 13 guinea pigs on immunization with the series of α,N-DNP-L-lysines. It was possible to sensitize the majority of Hartley guinea pigs to DNP-poly-lysines consisting of seven or more lysine molecules and all strain 2 animals to polypeptides consisting of nine or more L-lysine residues but only 66% of animals to DNP linked to eight lysine residues. DNP linked to shorter chain peptides of L-lysine were not antigenic. DNP-poly-D-lysines were not antigenic at all. An attempt to sensitize strain 13 to any of the copolymers of L-lysine failed completely.

Ben-Efraim, Arnon and Sela (1966) investigated the antigenicity of conjugates of polylysine with peptide chains of tyrosine and glutamic acid or DNP-groups. These were immunogenic in strain 2 guinea pigs but were not able to sensitize strain 13 animals. The same was found to apply to other lysine-containing copolymers, whether linear or multichain. Copolymers devoid of lysine were immunogenic in both strains. It was suggested that strain 13 guinea pigs were unreactive to polylysine and the sole presence of sequences of lysine in otherwise antigenic copolymers make them non-immunogenic for that strain. This was confirmed in experiments using polylysine linked to rabbit serum albumin as antigen where the lysine peptide chain serves as a hapten which was also non-immunogenic in strain 13. This failure of the immune response was thought to be due to clusters of positive charges within the molecule. However, it could have been due to some other, as yet, undefined properties of the molecule or of the animal.

Ben-Efraim and Maurer (1966) attempted to sensitize Hartley, strain 2 and strain 13 guinea pigs and their F_1 hybrids with a series of

random copolymers of amino acids and aggregates of polymers with methylated plasma albumin. The results obtained in these guinea pig strains and mainly the ability of all F_1 hybrids to be sensitized support the hypothesis that the ability to respond immunogenically is genetically controlled and is a dominant Mendelian trait. Oligolysine containing copolymers, glutamic acid-alanine and glutamic acid methylated guinea pig plasma albumin aggregates are immunogenic for strain 2 guinea pigs only and the copolymers glutamic acid-alanine tyrosine and glutamic acid-tyrosine + methylated bovine plasma albumin aggregate were immunogenic in both strains. There were differences in the ability of some strains to show the delayed hypersensitivity reactions and passive cutaneous anaphylaxis (PCA) to different antigens.

Ben-Efraim, Fuchs and Sela (1967) continued these studies and found that some antigens such as linear copolymers of tyrosine, glutamic acid and alanine are immunogenic in both strains 2 and strain 13. Linear and branched copolymers containing lysine are immunogenic in strain 2 only and linear copolymers of tyrosine and glutamic acid are only immunogenic in strain 13. The D-optical isomers were not immunogenic in either strain. The immunogenic responses in F_1 hybrids of the two strains were identical with that of strain 2, suggesting that the genetic determinants of strain 2 are dominant. Polák, Barnes and Turk (1968) studied the genetic control of three different inorganic metal sensitizers, potassium dichromate, beryllium fluoride and mercuric chloride, using Hartley, strain 2 and strain 13 guinea pigs. It was found that only a proportion of outbred Hartley strain guinea pigs could be sensitized with these agents, but unlike the findings of Chase (1941), there was no parallelism in the reactivity of guinea pigs to dichromate and beryllium. Strain 2 guinea pigs could be sensitized to dichromate and beryllium but not to mercury and strain 13 could be sensitized to mercury but not to the other metals. Crossbreeding experiments using sensitivity to beryllium fluoride as a marker in Hartley guinea pigs indicated that the ability to react to a particular metal is inherited as a simple Mendelian dominant trait. Further it would appear that this ability to react to different metals is controlled by different genes. The explanation of the differences of the ability of strain 2 and 13 to be sensitized to different metal compounds is yet not clear and could be similar to that of the synthetic antigens mentioned above.

Despite the fact that the precise mechanism of the genetic control of delayed hypersensitivity cannot yet be explained, the evidence indicates very strongly that the process of sensitization is genetically controlled.

B. In the Human

Despite the fact that the genetic control of delayed hypersensitivity reaction in experimental animals appears now to be beyond any doubt, very little has been done to demonstrate and analyse the genetic factors and their role in human diseases based on delayed hypersensitivity reactions. This is even more surprising, when one considers that contact eczema, one of the main skin diseases due to delayed hypersensitivity, has been investigated from a number of other different approaches, as it is a frequent cause of industrial morbidity. Biberstein (1927) described a case of polyvalent sensitization against different house plants in a mother and her two daughters.

Wedroff and Dolgoff (1935) sensitized 72 patients with eczematous dermatitis and 20 control patients to DNCB. They then tested them with different concentrations of the antigen. In 50 of the patients with eczema the reactions were greater and the degree of sensitivity higher than in controls. This is in favour of the assumption that there is a disposition to become sensitized in a certain but not clearly defined group of people.

Sulzberger and Baer (1938) were able to sensitize five subjects to 1–2–4 trinitrobenzene but only one of this group to 1–3–5 trinitrobenzene. This again suggests the presence of a constitutional factor, which could play a certain role in sensitization at least to weak sensitizers. Landsteiner, Rostenberg and Sulzberger (1939) extended the studies in individual differences in the ability to become sensitized and tried to sensitize a group of 82 persons to both DNCB and paranitroso-dimethylaniline (PNDMA). They were able to divide their subjects into three groups: (1) sensitized to DNCB only, (2) sensitized to PNDMA only, and (3) sensitized to both DNCB and PNDMA. Altogether

50 subjects could be sensitized to both or one of these agents, and 32 subjects could not be sensitized to either. Of the 50 responders 21 reacted to both compounds, 20 to DNCB only and 9 to PNDMA only. DNCB sensitized 50% and PNDMA 36.6% of the persons tested. From the results it is easy to understand why patients affected with recent or active contact dermatitis are more susceptible to sensitization with other simple chemical substances, as has been shown by Sulzberger and Rostenberg (1939). Schwartz (1940) observed a lower frequency of occupational eczema in negroes than in white people and in people with dark hair than in those with blonde hair. Hofbauer (1943) tried to describe more precisely the characteristics of people who are more frequently affected by contact eczema. His description was based on a detailed study of 120 patients with occupational eczema of diverse origin, and of 105 patients with other skin diseases. As a result of this study Hofbauer was of the opinion that the group predisposed to contact dermatitis showed a predominance of blood group A, were mostly leptosomic in body type, vagotonic, with blonde hair and light skin and had an allergic family history. Despite the fact that this study is based on an analysis of two groups of 120 and 105 patients only, it is of great interest that a positive allergic family history was found in 43% of patients with eczema and only in 23% of patients with other skin diseases.

In the introduction to his book on contact dermatitis, Waldbott (1953) described a study of the frequency of this disease in different areas and found that negroes are affected less often than whites. He did not find differences between North American Indians and whites in hypersensitivity to poison ivy but he found that eskimos did not develop sensitivity to poison ivy at all. He also mentioned that allergic patients are more likely to come from allergic families. Hanhart (1953) expressed the same opinion. Niermann (1964) described a pair of twins, who both worked on a farm and both suffered from contact eczema of the hands after contact with milk fat. This was the only positive pair out of 19 twins which he observed with contact eczema. In all the others the eczema occurred in one of the twins only.

Recently Forsbeck, Skog and Ytterborn (1966) tested siblings and children of patients with contact dermatitis to common routine allergens and were able to demonstrate that these persons are more often positive than the controls. They also found a higher frequency of atopic diseases among the families of patients with contact sensitivity. Walker, Smith and Maibach (1967) studied the genetic factors in human allergic contact dermatitis. They found that children whose parents had been sensitized to nitrosodimethylaniline (NDMA) became sensitized at a higher rate than children of non-sensitized parents. Evidence regarding the genetic factors in drug eruptions is controversial, both Albahary (1953) and Lindemayr (1959) did not consider that genetic factors have any influence in drug eruptions. Riehl (1927) however, described the familial occurrence of Salvarsan dermatitis in a father and in his two children, treated for syphilis. Gruetz (1930) also reported a case of Salvarsan allergy in a mother and her daughter. Blumenthal and Jaffy (1933) observed hypersensitivity to both quinine and salvarsan in a mother and her child. Kriegk (1951) described four cases (mother and child; two sisters; three sisters; and a father and daughter) where there was a familial occurrence of Salvarsan dermatitis. This would suggest that the genetic control of Salvarsan dermatitis was similar to that found in dermatitis due to other chemical sensitizing agents. However, Niermann (1964) did not find a concordant occurrence of drug eruptions after the intake of analgesics, sulphonamides and iodine in seven pairs of twins. Samter and Berryman (1958) have tried to explain the genetic differences in disposition to contact eczema and drug eruptions by genetic differences in enzyme activity. People with deficient enzyme activity would be unable to neutralise some antigens and therefore become more easily sensitized. This weakness could be an inherited characteristic (Motulsky, 1957) and related to the inherited enzymatic deficiency of erythrocytes found in negroes (Brown, 1958). This would be consistent with the observations in experimental animals, mentioned above.

In conclusion it could be said that although the genetic control of hypersensitivity to drugs and contact allergy in man is not proved to the same extent as it is in experimental animals, the observations which have been made so far are consistent with this concept.

II. HUMORAL ANTIBODY FORMATION

A great number of skin diseases are based on reactions of a range of antigens with different humoral antibodies and therefore it will be useful to give a survey of the genetic control of humoral antibody production in experimental animals.

A. In Experimental Animals

In 1928 Lewis and Loomis described a difference in haemolytic antibody production by different inbred strains of guinea pigs. Using guinea pigs of strain 2, 13, 32 and 35 they found that animals of strains 35 and 13 produced much more antibody against bovine and sheep red cells than those belonging to strain 2 and 32. Strain 35 proved to be a better antibody producer than strain 13. The authors drew the conclusion that immunological reactivity is an inheritable characteristic.

Gorer (1936a, b) immunized rabbits with erythrocytes of different mouse strains (black, albino and agouti) and showed three different antigenic factors in mouse erythrocytes and a characteristic distribution of these factors in different strains. Antigen II was present in albinos and absent in black mice and its presence was determined by a single dominant gene. In further experiments (1936 b) he found that the pure line of black mice was sharply divisible into two groups by direct agglutination tests. Cross experiments confirmed that the presence of the antigen was controlled by a single determinant gene.

Much later Davidsohn and Stern (1949 a) in their studies on strains of mice with low and high incidences of mammary tumours were able to show that the natural anti-sheep red cells agglutinins were present much more frequently and in much higher titres in C57 black inbred mouse strains with a low incidence of mammary tumours than in C3H, DBA or Marsh-albino strains with a high tumour incidence. Similar differences, however, were not found in the incidence of natural agglutinins against human red cells. In a further experiment (1949 b) differences were found in the ability of these strains to produce immune antibodies (agglutinins and haemolysins) against sheep and human red cells. The highest levels of immune antibodies were found in C57 black mice and lower levels in C3H and DBA mice. The Marsh-albino, Bagg-albino C and Akm strains appeared to develop low titres only. Experiments on the activity of the reticuloendothelial system, using the uptake of congo red, showed that the C57 black strain was more active and more responsive than the five other strains. It was suggested that this ability was probably controlled genetically. In further experiments (Davidsohn and Stern, 1950 a, 1950 b, 1954; Stern and Davidsohn, 1954 and Stern, Brown and Davidsohn, 1956) the same authors found no correlation between the level of natural anti-sheep antibodies and the presence or absence of the milk agent associated with the development of mammary tumours in C3H, A, D_2 and I inbred strains. They were, however, able to demonstrate differences in the presence of the Forssman antigen, which was present in normal and neoplastic tissues of C3H, DBA and C57H black mouse strains, but absent in Marsh-albino, Bagg-albino, Bagg-albino C, Akm, C57 brown and I mice. In an investigation of the natural agglutinins against sheep and chicken red cells in 13 different inbred mouse strains (Davidsohn and Stern, 1954) considerable differences were found in the incidence of the antibodies. However, there was no correlation between the presence of the anti-sheep and anti-chicken antibodies in individual strains. This indicates that the production of anti-sheep antibodies is probably controlled by a different genetic factor than that controlling the production of anti-chicken red cells antibodies. Further, each mouse strain showed a characteristic pattern of distribution of immune antibody titres. The immune responses were not related to the presence of natural haemagglutinins and there was also no correlation between the levels of immune antibodies produced against sheep or chicken red cells. Generally it was found that there was a high response in strains with a low incidence of tumours, and a low response in those with a high incidence. It was concluded (1956) that genetic differences in the ability to produce natural agglutinins are controlled by one or more genetic factors and that the factors associated with a low or absent level of circulating antibody are incompletely dominant.

Dineen (1964) studied the differences in immunological responses to sheep red cells between and within nine inbred strains of mice and found that the differences in the titres of

antibodies produced by different animals within a single strain was only 2.7%. However, the difference in titres in animals of different strains averaged 12.9%. As a result it was assumed that the genetic component was a major source of immunological variation. Sobey and Adams (1955) also investigated immunological responses to sheep red cells in mice. They studied the antibody responses of 228 parents and 456 offspring of albino mice, but the results suffered a large sampling error because of variation in response from generation to generation, the significance of which was not appreciated at the time. Therefore a new approach to this problem was sought by using female mice of the same generation from lines with increased or decreased reactivity to oestrogens (Claringbold Sobey, and Adams, 1957). It was found that the primary antibody response to sheep red cells was genetically controlled, but there was no evidence that the genetic control of the secondary response was related to the control of the primary response. The high oestrogen selection line gave a higher primary antibody response than the low one. However, this difference could only be detected if the antigen was injected by the intraperitoneal route. On the other hand there was a significant difference between the two lines in their secondary response irrespective of the route of administration. The low oestrogen sensitivity line gave a higher secondary response than the high oestrogen sensitivity line. Thus there was no correlation between the intensity of the primary and secondary responses in the two different strains, which shows that there must be different factors governing the primary and secondary antibody responses.

As far as antibodies to soluble antigens are concerned, Fink and Quinn (1953) found genetic variations in the production of circulating antibodies against egg albumin in five inbred mouse strains. Different results were obtained according to the route of injection of the antigen. Strains DBA and C57BL/6 were the best responders to intramuscular injection and strains BALB/C and C57BL/6 to intraperitoneal injection. They found no correlation in the response to two different antigens, egg albumin and pneumococcal polysaccharide. The strains DBA/1, C3H and A/L appeared to respond well to pneumococcal polysaccharide but BALB/C and C57BL/6 responded poorly, showing again as in previous reports that different genetic factors appeared to be involved in the control of the antibody response. Kleczkowska and Kleczkowski in 1939 were able to divide families of rabbits into strong, medium and weak responders according to their immunological reactivity to human serum. They thought this finding was due to the segregation of a single gene.

Sobey (1954) studied the inheritance of antibody response to tobacco mosaic virus in rabbits and found that the ability to produce antibodies to this virus is genetically controlled and it was possible to breed strains with high and low secondary response to this antigen.

Differences were also shown (Sang and Sobey, 1954) in the immune reactivity of rabbits of small Ermine Rex and Flemish Giant strains, to various protein, bacterial or viral antigens. However, they could not demonstrate any genetic control in the response to bovine plasma albumin.

Maurer (1964) immunized four inbred strains of mice (C57BL, C3H, 129 and BALB/C) and random bred animals with copolymers of glutamic acid and lysine ($G_{60}L_{40}$), glutamic acid and alanine ($G_{60}A_{40}$) and glutamic acid, lysine and alanine (GLA). All strains responded to GLA but only C57BL to GL.

Pinchuk and Maurer (1965) studied the ability of seven different strains of mice to form antibodies against a random copolymer of glutamine, lysine and alanine ($G_{67}L_{33}A_6$) and found that this ability is controlled by a dominant Mendelian factor. Three of the strains which he investigated were 100% responders, the others did not respond at all. However, all seven strains could make antibodies to related polymers which had a higher alanine content. Breeding experiments using the progeny of Swiss mice indicated that a similar genetic factor was involved.

McDevitt and Sela (1965, 1967), using synthetic antigens in CBA and C57 mouse strains, demonstrated that although both strains responded equally to bovine serum albumin, they showed tenfold or more differences in the antigen binding capacity of their sera after immunization with poly-(tyr,glu)-poly DL-alanine-polylysine E[T,G)-A-L. Neither strain re-

sponded to the polyglutamic acid determinants, both strains responded to the poly-(phenyl alanine, glutamic acid) determinant. C57 responded well to two different antigens with poly-(tyrosine, glutamic acid) determinants and CBA to poly-(histidine, glutamic acid) (H,G)-A-L determinants. In crossing experiments, F_1 hybrids showed a definite genetic control of antibody response due to a single major genetic factor with one or more modifying factors. This control appeared to be specific for the antigenic determinant. The CBA strain responded to (H,G)-A-L and C57 to (T,G)-A-L. The genetic control of these antigens is dominant and controlled by a number of different genes.

Arquilla and Finn (1963) using inbred strains of guinea pigs and insulin as an antigen, showed that strain 2 guinea pigs are able to produce antibodies to some parts of the bovine insulin molecule, to which strain 13 guinea pigs do not respond. They also assumed that there was a genetic control of antibody production with respect to the determinant groups toward which antibodies are directed.

Weiser, Golub and Hamre (1941) used diluted egg-white as antigen to show differences in white, brown and black mouse strains in the production of precipitins and in the manifestation of anaphylaxis. It was found that the white mouse strain was the best responder, while the black one reacted very poorly. Similar observations have been made with antigens of bacterial and viral origin. McMaster and Hudack (1934) were also able to demonstrate differences in agglutinin titres in a susceptible and a resistant strain of mice immunised with killed cultures of *S. paratyphi B, B. buteridis* and *B. prodigiosus*.

Prigge (1937) studied the range of doses of diphtheria toxoid necessary to protect guinea pigs of various inbred and random bred strains. He found that in one of his inbred strains he needed from 1 to 25 times a standard dose of toxoid to get protection. However, in outbred animals the range of dose necessary to get protection varied from one standard dose of toxoid to 32,000 standard doses. Gorer and Schutze (1938) compared antibody production against H and O antigens of *S. typhi murium* and *S. enteridis* with the development of resistance to these bacteria in a number of mouse strains. Two inbred strains and two outbred strains selected for resistance and susceptibility were studied and differences were found in these four strains. Scheibel (1943) bred two strains of guinea pigs one of which was composed mainly of good producers of diphtheria antitoxin, whereas the members of the other strain were poor producers. After six generations the good strain contained 97.5% good producers of antitoxin and the other had only 11.5% of animals which were good producers. Hereditary influences in the antibody response to diphtheria vaccine in guinea pigs are also described by Holt (1951).

Ipsen (1954) working with tetanus toxoid found that various inbred strains of mice differed in that some strains needed ten to thirty times more antigen than others to produce primary immunity to toxin injected in the unimmunized state. These strains, however, did not differ in their susceptibility to a lethal dose. He found (1959) that differences between individuals of the same strain existed and these differences were not found to be greater in outbred than in inbred strains. The possible explanation of these differences was thought to be due to a variation in the ease and speed with which cells first mature into specific antibody producing cells. However, the rate of multiplication of these cells was not considered to bear a relation to the immunizability of the animals. Sang and Sobey (1954) in their experiments with two rabbit strains (small Ermine Rex and Flemish Giant) and their crossed offspring found that the secondary antibody response to tobacco mosaic virus was genetically controlled and there was a correlation with the genetic control of antibody production to diphtheria toxoid.

In more recent work Sobey and Adams (1961) studied the antibody response to Vi and O antigens, to Rhisobium meliloti and to two strains of influenza virus (MEL and LEE) in mice. They drew the conclusion that one could only detect the genetic control of the immune response to substances containing one antigen only. If more than one antigen was present the genetic control of the production of antibodies against these antigens could be independent and it would be difficult to demonstrate genetic control of the immune response to the substance as a whole.

All the papers reviewed give strong evidence that the formation of humoral antibodies to different antigens in various species of laboratory animals is to some extent controlled genetically. The importance of genetic factors has also been shown in the human, where the emphasis is on studies in families and especially in twins.

B. In the Human

There is a considerable amount of data about the genetic control of the production of different types of antibodies in experimental animals, although a deep analysis of how that genetic control really works is still missing. It is not known, however, at what stage and by what means hereditary mechanisms control antibody production. In humans we are confined to studies of the familial occurrence of different allergic conditions and diseases, and of their occurrence in twins. The only experimental work on hereditary factors in humoral antibody production in humans is that of Carlinfanti (1948). He investigated the anti-A_1, Anti-A_2 and Anti-B hemagglutinin titres in 51 families with 159 children and he found that there was a high degree of correlation between the titres found in parents and in their children.

III. AUTO-IMMUNE PHENOMENA

Auto-immune phenomena have recently been shown to be associated with many diseases both in general medicine and in dermatology. Despite the large amount of work that has been done in this field, very little is known about the genetic control of these phenomena. A good survey of the present stage of our knowledge of the genetic factors involved in the manifestation of auto-immune phenomena in experimental animals and in clinical medicine is in the report of a Symposium on Auto-Immunity and Genetics, held in Glasgow in 1966 (Clin. exp. Immunol. *3:* suppl., 1967).

This paper will give only a brief review of the experimental background of some auto-immune diseases in certain inbred strains of laboratory animals. This will be followed by a discussion of the possible role of genetic factors in the development of some skin diseases, which are associated with auto-immune phenomena. This will be based on studies which have been made of the familial distribution of these diseases and of their occasional occurrence in twins.

A. In Experimental Animals

Some of the earlier reports of the role of genetic factors in auto-immune disease were made by Olitsky, Casals and Tal (1950) and Olitsky and Lee (1953). The authors sensitized different inbred strains of mice with mouse brain tissue homogenised in Freund's complete adjuvant to produce allergic experimental encephalomyelitis. They found that this disease appeared more frequently in one strain, BSVS mice, than in other strains.

Lipton and Freund (1953) who worked with guinea pigs, immunized different inbred guinea pig strains and outbred Hartley guinea pigs with central nervous system tissue in Freund's complete adjuvant in different doses to find out the minimal dose sufficient to produce allergic encephalomyelitis. They found that the dose of mycobacteria necessary for the production of this disease in Hartley guinea pigs was much less than that needed for the other strains. These results were confirmed nine years later by Stone (1962) who showed that Hartley strain guinea pigs are more susceptible to experimental allergic encephalomyelitis than inbred strain 13 guinea pigs, which in turn are more susceptible than strain 2.

Similar results were reported by McMaster, Lerner and Mueller (1965) in experimental allergic thyroiditis. They immunized Hartley and strain 13 guinea pigs with thyroid extracts and estimated the frequency with which allergic thyroiditis developed. The outbred Hartley guinea pigs developed thyroiditis more frequently than strain 13 animals, showing that the Hartley strain is generally more susceptible to auto-immune disease than other strains of guinea pigs. A possible explanation of the differences in response of the different strains is that there might be some genetic differences in their ability to process the auto-antigens.

There are no reports of the genetic control of auto-immune skin diseases in animals. An experimental model for auto-immune phenomena in the skin is much needed at the present time.

In a recent report Holborow and Denman (1967) summarised the spontaneous auto-immune character of NBZ mice based on their own studies, (Holborow, Barnes and Tuffrey, 1965), and those of Bielchowsky, Helyer and Howie (1959), Burnet and Holmes (1963.

1965), Bielchowsky and Bielchowsky (1964) and Howie and Helyer (1965). They drew the conclusion that the development of auto-immune phenomena in this strain is an inherited characteristic and is expressed in the heterozygote, and that more than a single gene must be involved in their manifestation. The autoimmune abnormalities in NZB mice appears thus to be an expression of their genetic constitution.

B. In the Human

Lupus erythematosus, pemphigus vulgaris and pemphigoid have been shown to be associated with the presence of auto-antibodies in the serum. The relation between discoid lupus erythematosus and systemic lupus erythematosus is by no means understood. The fact that transition from discoid lupus erythematosus to systemic lupus erythematosus occurs in only 1% of cases and that the sex ratio of female to male patients differs in the two conditions suggests they may have a different aetiology. Because the genetic predisposition to the two diseases is different the genetics of discoid lupus erythematosus (DLE) should be considered separately. Observations in this as in other skin diseases, are confined to studies of the familial appearance and particularly of the appearance of this disease in twins.

Interest in the familial occurrence of DLE started as early as 1900 when Roth described a case of LE in two sisters and in the child of one of them, and Rona (1901) reported three sisters, two of whom had obvious DLE and the third had a condition which was consistent with, but not typical of DLE. Cohn (1907) published a case of LE in siblings (brother and sister), Sequeira and Balean (1902) in two sisters, Brocq and L'Aubry (1900) in mother and daughter, and Leredde and Pautrier (1902) in two brothers, but Jadassohn (1904) considered these last three cases were not typical. In later studies Truffi (1924) presented three sisters with this illness, Sidlick (1929) two sisters, Michelson (1929) a brother and sister, Veiel (1930) two sisters, a father and daughter, Pautrier and Zorn (1931) two brothers, Greenhouse (1932) and Abramowitz (1932) a brother and sister, Willbrand (1932), Grandy (1933) and Beek (1934) all described DLE appearing in two brothers.

Mashkilleison and Neradow (1936) described eight families in which there was a familial occurrence of LE in 17 patients. These cases formed 12–15% of all cases of LE seen at the Leprosarium in Moscow at that time. They expressed the opinion that there is a hereditary predisposition to LE. In the same report mention was made of the first description of the familial occurrence of LE in a brother and sister by Hutchinson in 1891.

Hirschberger (1936) found five cases of LE in one family, two sisters, their aunt and two daughters of one of the sisters. He considered that DLE was associated with a constitutionally conditioned, heritable reactivity of the skin. Rabeau and Ukrainczyk (1939) described a case of LE in mother and daughter. Lot (1951) described four cases of familial appearance in brother and sister, two brothers, father, daughter and her two sons and in a pair of monozygous twins, and Hopkins in 1952 described the disease in a mother, daughter and a cousin of the mother.

Grünhagen (1952) summarised that up to that time the known cases of familial LE included 21 pairs of siblings, three cases of three brothers and sisters, three cases of fathers and daughters and two cases of mothers and daughters, one case consisted of father, daughter and two sons and another of two sisters, their mother, her sister and a sister of the father. The author also assumed that an important role in this disease was played by a hereditary constitutional factor.

Further cases of the familial appearance of LE have been reported by many other authors including Bondet (1952), Burckhardt (1953), Gate (1953), Marchionini (1953), Dunipe (1956) and others.

Burckhardt noted that 6% of his cases of LE had a familial distribution supporting the opinion that heritable constitutional factors were involved in the disease, but Nagy and Daroczy (1962) found only one case of the familial occurrence of LE in a series of 150 cases of LE seen in the Dermatology Clinic in Debrecen.

The concordant appearance of DLE in twins gives further support for the importance of genetic factors in the development of this disease. Reports of this type have been made by Lot (1951), Grünhagen (1952), Davis and

Gutridge (1951), Steagall, Ash and Fentznes (1962), and Blumenfold, Kaplan, Mills and Clark (1963). However, in none of these cases did the disease develop at the same site, time and form. There are also reports of the discordant occurrence of the disease (Niermann, 1964). Niermann (1966) discussed the data on the familial occurrence of LE in altogether 71 cases of which 41 were cases of chronic discoid LE, 25 of acute DLE and 5 had both acute and chronic forms of the disease. He rejected five other cases, where the diagnosis was based on the finding of LE cells only without skin or other organ lesions and concluded that despite the great number of familial cases and only a few cases of twins, the question of an inherited genetic factor in this disease was still open. Rowell (1967) is of the opinion that in DLE the disease is controlled by a sex-linked dominant gene localised on the X chromosome.

Observations on the familial occurrence of the two other skin diseases associated with auto-immune phenomena are much more scanty.

Feldmann (1936) reported a case of pemphigus vulgaris in two brothers, Greenbaum (1940) in father and son and in two sisters. Miller and Frank (1949) in a man and his two sisters, Maragnani (1959) in three members of one family. Pierini (1956) in siblings, and Bukharovich (1959) in a mother and her daughter. The only report of a case of twins with the concordant occurrence of pemphigus vulgaris was made by Corriciati (1938). Niermann (1966) in a review of his observations could not find enough support to decide whether there was any genetic control of this disease.

There is no report of the familial occurrence of Behcet's syndrome, and other diseases associated with auto-immune phenomena.

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