# Inherited Complement Deficiencies

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# Inherited complement deficiencies

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Isolated genetic deficiencies of individual components of the complement system have been described in man for all the components of the classical pathway and the membrane attack complex as well as for Factor I, Factor H and properdin. It is only for Factor B and Factor D of the alternative pathway that homozygous deficiency states are not so far known.

Complement deficiency states provide the most direct way of looking at the role of the complement system *in vivo* and emphasize the importance of complement in resistance to bacterial infection and in particular to infection with *Neisseria*. This association is not unexpected since *in vitro* studies have shown complement to be an efficient enhancer of phagocytosis and inflammation. The particularly frequent occurrence of neisserial infection may be ascribed to the ability of these organisms to survive in phagocytic cells so that the plasma cytolytic activity provided by complement is needed to kill them.

On the other hand the strong association between complement deficiencies and immune-complex diseases – especially systemic lupus erythematosus – was unexpected and seems paradoxical in view of the large part played by complement in the pathogenesis of immune complex mediated tissue damage. The paradox can be explained in part by the necessity for an intact complement system in the solubilization and the proper handling of immune complexes. It is also likely that complement deficiency can allow the persistence of low virulence organisms that produce disease solely by an immune complex mechanism.

Recently described deficiencies of complement receptors and their effects *in vivo* are described.

## INTRODUCTION

The history of the complement system differs from that of, for example, blood clotting, in that the system was largely worked out without the use of deficient plasmas to define its components. Nevertheless it would be wrong to believe that the study of complement deficiencies had made no contribution to our understanding of the complement system. Perhaps the most striking example was the contribution that the recognition of the first Factor I-deficient patient made to the unravelling of the mechanism of the alternative complement pathway. This work however is now quite old and is being reviewed elsewhere (Lachmann 1984).

## C8 DEFICIENCY

A more recent example is provided by C8 deficiency. C8 has been known for some time to comprise three polypeptide chains. More recently it has been shown by Steckel *et al.* (1980) that two of these chains – the α chain and the γ chain – are covalently linked by disulphide bonds whereas the β chain is separate. C8 deficiency was first described by Petersen *et al.* (1976) and was found in the first family to show some evidence of HLA linkage though this could not be confirmed either in this or in subsequent families with similar deficiency.

[ 141 ]

The patients described by Petersen had no obvious C8 molecule detected antigenically in their plasma and no C8 activity. A number of subjects with an apparently identical deficiency are known, see table 1. A further and distinct type of C8 deficiency was described by Tedesco; originally at the European Complement Workshop in 1976 but first published by Tedesco *et al.* (1980). Tedesco and his colleagues described two Italian siblings with deficient C8 activity and readily detectable dysfunctional C8 protein in their circulation. Again it was shown that a number of other pedigrees existed quite independently that had an apparently identical deficiency. The dysfunctional protein in this second group of patients was demonstrated to be the $\alpha$–$\gamma$ subunit of C8. It was shown by Tedesco and his colleagues (1983) that when the two types of deficient serum are mixed together, full haemolytic activity was restored and, furthermore, that the sera without the obvious dysfunctional protein were capable of fixing on to EC567 an activity that subsequently allows the C8 $\alpha$–$\gamma$ subunit to react and, in the presence of C9, to be fully haemolytically active. It is therefore clear that the original type of C8 deficiency is C8 $\alpha$–$\gamma$ subunit deficiency and that the sera of these patients contain $\beta$ chains, which are not detected by conventional anti-C8 antisera.

## TABLE 1. C8 DEFICIENCY

With obvious 'dysfunctional protein' which is $\alpha$–$\gamma$ subunit; i.e. $\beta$ chain deficiency

| *ca.* 10 patients | neisserial infection | most |
| | systemic lupus erythematosus | 1 |
| | ? systemic connective tissue disease | 1 |
| | healthy | 1 |

with no obvious 'dysfunctional protein' but ? all have $\beta$ chains in their serum; i.e. $\alpha$–$\gamma$ subunit deficiency

| *ca.* 10 patients | neisserial infection | most |
| | xeroderma pigmentosa | 1 pedigree |
| | healthy | 1 |

Two types of deficiency restore each others haemolytic function.
$\beta$ chain reacts with $\overline{C567}$.
By using one type deficient serum can screen for polymorphism of others.
Both $\alpha$–$\gamma$ and $\beta$ polymorphic and ? unlinked; $\alpha$–$\gamma$ linked to PGM1 on chromosome 1.

The second type of deficiency is $\beta$ chain deficiency with circulating $\alpha$–$\gamma$ subunits. These two subunits are capable of recombining in whole plasma to form a functionally active C8 molecule and the two subcomponents reacts sequentially in the complement sequence, the $\beta$ subunit reacting before the $\alpha$–$\gamma$. By using the two types of deficient serum Marcus *et al.* (1982) were able to show polymorphisms in both subunits, that is, by using the $\beta$ chain deficient serum as detecting agent they could detect on electrophoretic plates the $\beta$ subunit and demonstrate this to be polymorphic, and conversely using $\alpha$–$\gamma$ deficient serum as detecting agent they were able to detect $\alpha$–$\gamma$ polymorphisms. No linkage between the two C8 subcomponents was shown in their studies. It has, however, since been shown that the $\alpha$–$\gamma$ subunit is linked to PGM1 on chromosome 1 (Mevag *et al.* 1984).

It can therefore be concluded that C8 comprises two subcomponents which are not genetically linked, which act sequentially and which can associate in whole serum to form the complete C8 molecule. This state of affairs is analogous to what is know about C1, except that the complex formed between the two C8 subcomponents is much firmer than that formed between C1q and C1r–C1s. Therefore, C8 should be considered not as a single complement component but as a complex of two quite separate molecules and it would be consistent with the nomenclature used for C1 to call them C8q and C8r!

## OTHER DEFICIENCIES

Except in the case of C8 deficiency the existence of well-defined dysfunctional proteins in complement deficiency states is uncommon. In the case of C1 esterase inhibitor deficiency, which is exceptional in that it is the heterozygote that shows disease (hereditary angio-oedema) and where ascertainment is therefore much more frequent, approximately 15 % of the known pedigrees have dysfunctional proteins (Hadjiyannaki & Lachmann 1971) and it is believed that this may be taken as an average figure for random mutations occurring in the structural gene. It seems that about five out of six mutations will cause no product to be formed and one out of six a product that is antigenically cross-reactive and capable of being secreted and having a sufficient half-life to be detected in the plasma, but which is functionally abnormal. In the commoner forms of homozygous complement component deficiencies a very highly dysfunctional molecule which is difficult to detect has been described in the first case of C3 deficiency (Davis *et al.* 1977) and there is one case showing a combined deficiency of C6 and C7 where the C6 molecule is dysfunctional, being about 30 kDa, small and antigenically highly deficient, whereas the C7 molecule is apparently normal (Lachmann *et al.* 1978). The molecular basis of this very unusual combined deficiency is not yet known. The explanation regarded as most plausible at the present time (when DNA probes for C6 and C7 are not yet available) is that these two complement proteins share a primary RNA transcript and that the particular lesion producing the double deficiency produces a deletion from the 5′ end causing small amounts of primary transcript to be formed which is also structurally abnormal in the portion that codes for C6. It would be very intriguing to know if this explanation is correct since the control of synthesis of C6 and C7 are separate and in the acute phase of inflammation C6 synthesis rises much more than C7 synthesis. If therefore the suggestion that they share a single primary transcript is correct this would be evidence of control of protein synthesis at a level subsequent to primary transcription. One well-characterized example of a deficiency with a dysfunctional protein is C1q and this is described by Reid (this symposium). In this case the situation is unusual in that the dysfunctional protein shows really quite marked differences from the normal protein and it is far from obvious how these could be accounted for by a single mutation or a single deletion. The report by Hack *et al.* (1983) that an apparently similar abnormal C1q molecule can be found in some patients with systemic lupus erythematosus who are not C1q deficient, suggests the possibility that this dysfunctional protein could be the product of a separate gene which is not normally transcribed and translated. Again only studies of the genome will clarify this point.

Perhaps the principal information that studies of genetic complement deficiencies have given us, however, is on the role of the complement system *in vivo*. Table 2 gives a recent collection of the cases of complement deficiency reported in the literature with their clinical associations and is from Schifferli & Peters (1983). No such compilation is ever up to date as more cases are reported and as it is clear that with the commoner deficiencies a substantial number of cases are not reported. However, it gives a general picture.

It can be seen that complement deficiency states may be associated with good health over a whole lifetime but are also associated with a small number of particular clinical states. The first of these is infection. This is not unexpected since the adaptive immune system is believed to be largely concerned with protection against infection. Complement deficiency may be associated with the same type of immunity deficiency as is seen in the antibody deficiency

syndrome, infections largely with pyococcal organisms; but there is also a more common and more specific association with neisserial infections. These include meningococcal meningitis and disseminated gonococcal infection. The other major clinical association of complement deficiency is with immune complex disease. Of these diseases systemic lupus erythematosus is the most common, but a wide variety has been reported.

TABLE 2. REPORTED CASES OF COMPLEMENT DEFICIENCIES AND ASSOCIATED DISEASES

| component | number with homozygous deficiency | associated diseases | |
|---|---|---|---|
| | | i.c. disease | infections |
| classical pathway | | | |
| C1q | 15 | 14 | |
| C1r or C1s | 8 | 6 | |
| C4 | 16 | 14 | many pyogenic |
| C2 | 66 | 38 | |
| C1 inhibitor | > 500 | 2% | |
| C3 and alternative pathway | | | |
| C3 | 11 | 8 | 10 pyogenic (+Neisseria) |
| B/D | — | — | — |
| properdin | 3† | — | 2 (+3 died of fulminant infections); Neisseria |
| C3b inact (I) | 5 | 1 | 4 pyogenic |
| β 1H (H) | 2‡ | 1 (h.u.s.) | |
| membrane attached complex | | | |
| C5 | 12 | 1 | 9 |
| C6 | 17 | 2 | 10 Neisseria |
| C7 | 14 | 1 | 6 |
| C8 | 14 | 1 | 8 |
| C9 | many | —§ | |

† Plus three probable cases, died before analysis.
‡ Partial, less than 10%.
§ No disease association.
i.c. disease, systemic lupus erythematosus and s.l.e.-like syndromes, glomerulonephritis, vasculitis.
h.u.s., haemolytic uraemic syndrome.
From Schifferli & Peters (1983).

Since none of these clinical associations are invariable, that is, not all patients with complement deficiency suffer from such diseases, the complement deficiency acts only as a diathesis or predisposing state and it is pertinent to enquire as to the nature of the association.

One possibility that should never be discounted too readily is that there is an element of ascertainment bias in the clinical associations. Once an association has been reported patients with the relevant disease are particularly likely to have their complement titres measured and therefore are particularly liable to be recorded. The approach to this particular problem is to have reliable population data and the incidence of complement deficiency states. This has been curiously difficult to obtain. A number of studies have been performed in the past and these are tabulated in table 3. They are all somewhat unsatisfactory in dealing with unrepresentative populations. For example, blood donors exclude the sick and all children, so that they would

exclude most of the population where one might expect to find complement deficiency. The same is true of our own survey of the Cambridge outpatient population. This excludes the entirely healthy and when the population sampled was analysed it transpired that their mean age was about 60!

TABLE 3. INCIDENCE OF COMPLEMENT DEFICIENCY IN NORMAL POPULATIONS

| source | population | number studied | complement deficiency encountered | nature of deficiency |
|---|---|---|---|---|
| Hassig et al. (1964) | Swiss army recruits | 40000 | 14 | largely low C4 + C2 (no genetic data) |
| Torisu et al. (1970) | Japanese mass medical examination | 42000 | 3 | C4 low (sera inactivate C4) no genetic data |
| F. Stratton (personal communication) | Manchester blood transfusion panel | 15000 | 1 | C2-deficient (no family data) |
| Lachmann et al. (1978) | Cambridge hospital outpatients | 2000 | 1 | C6 + C7 deficient (inherited) |
| | | | 1 | low C1, C4, C2, C1 inhib and C3, hereditary angio-oedema with systemic lupus erythematosus |
| | | | 2 | low C1, C4, C2, C1 inhib I/C + +. Caldwell's syndrome |

There is however one much more recent and much more satisfactory study which has been carried out in Japan in 1983 by Inai & Akagaki (1984) (table 4). In this study not only have blood donors from many regions of Japan been tested, but a large hospital population has been similarly tested, and it is therefore possible to compare a population that excludes the healthy with a population that excludes the sick. The interesting feature of this study is the high incidence of C9 deficiency in Japan. This is ascertained by a C9 level of less than 2% of the

TABLE 4. COMPLEMENT DEFICIENCY AMONG OSAKA BLOOD DONORS

(Inai & Akagaki 1984)

| | no. | homozygote frequency | gene frequency | heterozygote frequency |
|---|---|---|---|---|
| tested | 52175 | | | |
| 'absence' of complement activity | 283 | | | |
| C9 deficient | 55 | 0.105% | 3.25% | 6.28% or c 1/16 |
| C7 deficient | 5 | 0.0096% | 0.98% | 1.94% or c 1/52 |
| C8 deficient | 2 | 0.0038% | 0.62% | 1.23% or c 1/81 |
| C2 deficient | 0 | | | |
| uncharacterized C5 8 deficiency | 5 | | | |
| evidence of complement activation | 198 | | | |
| reason for deficiency unknown | 17 | | | |

C9 deficiency among random Japanese patient group: 48/49577 or 0.097%

N.B.

Average CH50 of C9 deficient blood donors — 12 units

Average CH50 of C9 deficient random patients — within normal range (30–50 units)

Average CH50pg 1 C9 deficient patient with chronic bronchitis and acute phase reaction — 63 units

[ 145 ]

normal level. Homozygous C9 deficiency defined in this way occurs in roughly 1 in 10 000 Japanese people and it is of considerable interest that the incidence is the same in the blood donor population and the patient population. That may be taken as formal evidence that there is no statistically significant association of C9 deficiency with disease in the Japanese population. Nor indeed has C9 deficiency been claimed to have any particular disease associations. It is further intriguing that C9 deficiency is often associated with readily detectable haemolytic activity. Haemolytic activity is less in the C9-deficient blood donors than in the C9-deficient patients; and in patients who may be undergoing an acute phase response, the haemolytic titre may be within normal limits or in one patient even supra-normal. This is somewhat at variance with the findings in artificially C9-depleted serum and an adequate explanation is still awaited. Either elevated C8 levels really can compensate quite substantially for absence of C9 or the very low levels of C9 that are found in the deficient patients may play a major role in producing lysis.

Besides the high incidence of C9 deficiency among the Japanese, it is curious that there is no C2 deficiency described, though this is by far the commonest Caucasian deficiency. The other deficiencies found were largely also in the terminal components. It is worth noting in this large study that, as expected, a relatively modest increase in gene frequency greatly increases the number of homozygotes that are found. It is one of the problems of ascertaining the homozygotes for infrequent genes that relatively small differences in gene frequency have a very substantial effect on the ascertainment. Deficiency of C7 that shows a gene frequency about 1/3 of that of C9 deficiency in Japan but homozygotes will be detected in 1/10 000 as opposed to 1/1000 people and this difference makes a big practical difference in finding homozygotes.

A further approach to ascertainment is to look at whole populations of patients with particular diseases. This has been attempted on several occasions with meningococcal meningitis and the results reported were somewhat at variance (see table 5). In one study

TABLE 5. MENINGOCOCCAL INFECTIONS AND COMPLEMENT DEFICIENCY

| no. of infections | no. of patients | no. of patients with complement defect | type of defect |
|---|---|---|---|
| 1 | 71 | 0 | |
| 2 | 10 | 2 | C8 deficient × 2 |
| 3 | 2 | 1 | C8 deficient |
| 4 | 1 | 1 | Nef with PLD |
| Merino et al. (1983) | | | |
| 1 | 20 | 3 | C6 deficient × 2 |
| | | | C8 deficient × 1 |
| | | | complement activation |
| | | | systemic lupus erythematosus |
| | | | or myeloma |

Ellison et al. (1983)

complement deficiency was found only in people who had had more than one attack of meningococcal meningitis (Merino et al. 1983) whereas in a separate study a quite appreciable incidence of complement deficiency was found even among first cases (Ellison et al. 1983). The complement deficiencies found were not always genetic and acquired complement deficiency as a result of other disease also appears to predispose to repeated meningococcal meningitis. This is strong evidence that the association is physiological and not due to genetic linkage with another disease susceptibility gene.

## THE ASSOCIATION OF IMMUNE COMPLEX DISEASE WITH COMPLEMENT DEFICIENCY

The association of immune complex disease with complement deficiency has always been regarded as surprising since it is known that complement plays a substantial part in the mediation of immune complex damage. There is however no doubt that homozygous complement deficiency particularly of the early acting complement components is a strong risk factor for the development particularly of systemic lupus erythematosus. It is reckoned that about 30 % of the substantial number of homozygous C2 deficient subjects known suffer from systemic lupus erythematosus and the percentage is even higher for C4 deficiency (approximately 14 out of 20 cases (Hauptmann et al. 1984)). However the association is not only with these two HLA encoded complement components, but is found also with C1 deficiency and occasionally with patients with deficiencies of the late acting complement components (see table 2). Although studies have been done looking at populations of patients with systemic lupus erythematosus to establish the frequency of complement deficiency, it has been found that while the incidence of homozygous deficiencies is really quite low, only 1 in the 137 cases studied by Glass et al. (1976), there is a surprisingly high incidence of heterozygous complement deficiency involving either C2 or particularly C4 (Fielder et al. 1983).

In the case of C2 deficiency nearly all recorded cases occur on the background of a single haplotype HLA A10, B18, DR2, BFS, $C4A^4B^2$, $C2^1$ and for this group of patients the possibility cannot be excluded that the predisposing gene for the development of systemic lupus erythematosus is not the complement deficiency gene itself but some tightly linked susceptibility gene elsewhere on the haplotype. This explanation is however less applicable in the case of C4. It is true that much of the heterozygous C4 deficiency seen in the study by Fielder et al. (1983) is on the basis of the haplotype A1, B8, DR3, BFS, $C4A^{Q0}B^1$, $C2^1$ but there are other haplotypes carrying C4 deficiency genes and indeed the homozygous C4 deficiencies do not occur on any consistent HLA haplotype. It therefore looks relatively unlikely that the association can frequently or consistently be due to the presence of a closely linked disease susceptibility gene. Further support for this view comes from the association of systemic lupus erythematosus with hereditary angio-oedema where the C2 and C4 deficiency are secondary to C1 inhibitor deficiency and where the genetic abnormality is not linked to HLA, and also from the association of systemic lupus erythematosus and of other immune complex disease with the presence of nephritic factor, which is an acquired abnormality giving rise to hypocomplementaemia. All these findings strongly suggest that deficit in complement function predisposes to development of these diseases.

The mechanism by which deficiency in complement function produces immune complex disease has attracted much interest. The major mechanism that is now believed to be responsible is a failure, in the absence of an adequately working complement system, to either keep immune complexes soluble as they form or to resolubilize insoluble complexes. Miller & Nussenzweig (1975) first drew attention to the need of an intact alternative pathway to convert preformed insoluble complexes into soluble form and allow them to be removed from C3 receptors on cells. More recently Schifferli & Peters (1983) have shown that when one looks not at the resolubilization of previously insoluble complexes but at the more physiological situation where complexes form in the presence of a complement source, it is indeed the classical pathway that is particularly important in preventing the formation of insoluble complexes *ab initio*. This is entirely consistent with what we know about the activation of different pathways since the

alternative pathway is activated only by immune precipitates and it is the classical pathway that is activated by soluble immune aggregates. An extensive literature on immune complex solubilization has built up (see review by Takahashi & Takahashi 1981) and it does seem most probable that this is an important pathogenetic mechanism. The failure of adequate immune complex solubilization cannot of itself explain the association of systemic lupus erythematosus with deficiency of complement components subsequent to C3 since the membrane attack complex is not believed to play any part in this process. It may turn out that the association with the late acting components with systemic lupus erythematosus is produced by some separate mechanism. A plausible candidate is that an intact complement system, and perhaps an intact membrane attack complex, is necessary for the elimination of micro-organisms (perhaps particularly viruses) which are not themselves primarily pathogenetic but which can give rise to immunological disease by persistently reproducing antigenic material. That disease is caused in this way is known from the studies of lymphocytic choriomeningitis in mice (Oldstone & Dixon, 1969), and hepatitis B virus infection in man, which gives rise to hepatitis by immunological mechanisms. It is also known that in human serum both retroviruses (Welsh *et al.* 1976) and the Epstein–Barr virus (Martin *et al.* 1984) can be lysed by the complement system even in the absence of antibody and other viruses not yet recognized as causes of human disease may behave in the same way. It is therefore not impossible to conceive of a situation where immune complex disease may result from complement deficiency by allowing persistence of a low virulence organism giving a continuing supply of antigen. It is not however possible at present to give a genuine example where this is the case. It is also perhaps worth pointing out that many of the cases of systemic lupus erythematosus associated with the late acting complement component deficiencies have not been fully typed for heterozygous complement deficiency of the early components so that there may be a further risk factor at work.

### Deficiency of complement receptors

#### CR1 deficiency and systemic lupus erythematosus

As already stated no genuine homozygous deficiency states for CR1 are known so far but it has been observed both that there is apparently a structural polymorphism of CR1 demonstrated by molecular mass difference in the proteins (Dykman *et al.* 1983) and that the number of CR1 molecules found on red cells appears to be inherited (Wilson *et al.* 1982). Interestingly enough these two forms of genetic variation appear not to show linkage to each other suggesting that the latter form of variation may not be in the structural gene. It has further been reported that CR1 levels are low on the red cells of patients with systemic lupus erythematosus and it has been suggested that genetically lower CR1 levels are another risk factor in the development of this disease. Work in our own laboratory however (Walport *et al.* 1984) has not confirmed this view. A study of CR1 levels using a monoclonal antibody in a number of families of patients with lupus and others has shown:

(i) that, as found by others, CR1 levels in patients with systemic lupus erythematosus are distinctly low. However,

(ii) the levels in the relatives of patients with systemic lupus erythematosus do not differ significantly from normal and in fact some of the lower values given by relatives of patients with systemic lupus erythematosus are given by spouses rather than by blood relatives (figure 1).

(iii) When families are looked at it can be seen that indeed the tendency to have high or low levels does run in families.
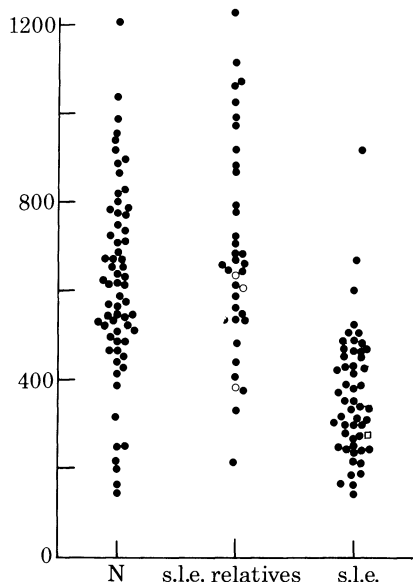
[ 148 ]

FIGURE 1. Erythrocyte CR1 numbers. Open circle, spouse of s.l.e. patient; open square, C2 deficient; partly shaded square, C2 heterozygote. From Walport *et al.* (1984).

However, there is difficulty in fitting this data into the simple model proposed by others, that is, that there is an *H* allele coding for high CR1 levels and an *L* allele coding for low CR1 levels at a single locus. The problem lies in giving values to what is to be considered HH and LL phenotypes. If figures are taken from the population data and the values obtained used in family studies, they do not show adequate inheritance. All this means is that it is necessary to allow a considerable range of values between HH and HL and between HL and LL where the phenotype cannot be predicted confidently from the numbers measured. This unfortunately makes further analysis difficult. Nevertheless we have seen at least one family where a patient with systemic lupus erythematosus with low CR1 levels is clearly the child of two parents who are both at the very top of the distribution range and would have to be HH. This suggests strongly that the low levels in this particular patient with systemic lupus erythematosus are indeed acquired and not genetically determined. Furthermore it has been shown (Ross *et al.* 1984*a*) that when the numbers of molecules of C3dg on a patient's red cells are measured as well as the CR1 levels, in both cases using monoclonal antibodies, there is a strong negative correlation between the number of molecules of C3dg and the molecules of CR1. Since the number of molecules of C3dg on the red cells is a measure of complement activation *in vivo* this again suggests strongly that the low numbers of CR1 seen are also the result of complement activation *in vivo*. It is however not the case that occupancy of the receptor by C3 fragments is responsible for the apparent low number since the monoclonal antibody used binds to receptor even when it is occupied. Whether the low levels of CR1 represent the sequestration from the circulation of cells with high levels of receptor at complement fixation sites or whether it reflects some effect on the synthesis of CR1 in the red cell precursors remains to be determined. It is also of interest that two patients who have homozygous C2 deficiency with systemic lupus erythematosus also have low CR1 levels. This is a further argument against CR1 deficiency being a risk factor as opposed to a consequence of systemic lupus erythematosus. If homozygous C2 deficiency itself is such a strong risk factor then it would not be anticipated that the rather weak risk factor provided by low CR1 levels itself (since some 10 % of the population have apparently low levels) would be necessary or expected in such patients.

[ 149 ]

## CR3 DEFICIENCY

A new deficiency of complement-related protein has been described in the last few years which produces a striking immunity deficiency. The first case was described by Arnaout and his colleagues (1982) as a case of GP150 deficiency, where GP150 is a glycoprotein found on the surface of polymorphs. It was found that the absence of this protein was associated with a failure to react with a number of monoclonal antibodies OKM-1, MAC-1, MO-1, MN-41, which recognize the cell surface complement receptor now called CR3. CR3 is a lectin-like receptor whose specificity as far as complement components goes is wholly for iC3b with which it reacts in the presence of divalent cations and which reaction can be inhibited by *N*-acetyl-D-glucosamine. It is therefore in its reactivity closely similar to bovine conglutinin: a lectin-like serum protein found only in cows which reacts with iC3b in the presence of calcium ions and can be inhibited by *N*-acetyl-D-glucosamine (Lachmann 1967). Also like bovine conglutinin CR3 can react directly with yeast, the carbohydrate group responsible for the combination with CR3 and with conglutinin being shared by yeast cell wall polysaccharides and iC3b. Structurally, however, the two molecules are quite different. Bovine conglutinin is a polymer, the subunit containing collagen, whereas CR3 belongs to a small family of molecules sharing a β chain of 90 kDa and with individually specific α chains. The other two members of this are LFA-1 and a further protein not yet given a name. LFA-1 is present on lymphocytes as well as monocytes and polymorphs whereas CR3 is found only on polymorphs and monocytes.

Three further cases of a deficiency similar to the Boston child were identified by Dr Ronald Thompson in Birmingham and these have been further studied (Ross *et al.* 1984*b*). All of the affected children have infections particularly involving the skin and show a clinical syndrome rather similar to those shown by other children with polymorph defects. Their polymorphs and monocytes show no CR3 activity and most strikingly of all they fail to give any respiratory burst with unopsonized zymosan. However their CR1 and their Fc receptor levels are normal. On testing with monoclonal antibodies to the other proteins of the same group all the children have been found also to lack LFA-1 on their lymphocytes and to have none of the common β chain on lymphocytes, monocytes or polymorphs. It remains to be determined whether the primary deficiency is in the β chain of whether there is deletion of the whole group of α chains. However, it is interesting that their clinical status relates more clearly to the deficiency of their polymorph function than to any problem with the absence of LFA on their lymphocytes since the immunoglobulin levels are normal and there is no obvious defect in T-cell function. It is of particular interest that the deficiency of this lectin-like receptor could have so profound an effect on polymorph function and that this cannot be substituted by the presence of the other receptors. If this failure is in fact substantially due to a failure of CR3 to react with cell-bound complement rather than to ligands occurring on yeast cell walls and perhaps some other similar micro-organisms, then this would be the first indication of a genuine *in vivo* biological function for the carbohydrate group of C3bi. This carbohydrate prosthetic group is in itself very unusual both in being mannose-rich and in that it is concealed in the native molecule and is exposed to reaction with both conglutinin and CR3 only when the C3 is cleaved as far as iC3b. It is also interesting that a similar carbohydrate is not present in C4 which otherwise is so similar.

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