# THE PATHOPHYSIOLOGY OF THIS COMPLEMENT SYSTEM IN LEPROSY

V D Ramanathan

## INTRODUCTION

The complement system, which consists of a group of proteins and glycoproteins, generally serves to amplify the effects of the interaction of antigen with antibody. In addition, this system, independent of immune mechanisms, can initiate inflammatory responses and function as an important first line of defence. Furthermore, complement plays a cardinal role in metabolising antigen-antibody complexes. More recently, the immunomodulatory effects of several of its components are also being studied.

It is currently held that the elimination of *Mycobacterium leprae* from the human host is mainly through the T-lymphocytes and macrophages and that the complement system is not involved in this process. Nevertheless, in view of the active interaction of *M. leprae* with the complement system and the form&on of large amounts of immune complexes(IC) in leprosy, the importance of this system in modulating certain immunopathogenetic phenomena is being recognized now. In this communication, the current state knowledge in this field will be reviewed and an attempt will be made to identify possible areas of future research where lacunae exist.

## THE COMPLEMENT SYSTEM

This system bears certain resemblances to the coagulation system. Many of the nearly 30 components which comprise this system exist as inactive precursors or zymogens. More than one stimulus is capable of initiating the activation of this system. Like the intrinsic and the extrinsic pathways of the coagulation system, complement can be activated via classical and alternative pathways.

*Components:* The complement system comprises of three groups of molecules. The first group consists of molecules directly involved in the

V D Ramanathan MBBS, PhD
Dept of Pathology
Tuberculosis Research Centre, Chetput
Madras 600 031.

activation. Since unchecked activation will lead to disastrous consequences to the host, a number of control proteins form an essential part of this system. The complement components and/or their activation products exert their effects on a variety of cells through receptors present on their surfaces and these molecules are known as complement receptors. Some of the features of the components and complement receptors are shown in Tables I and II

**Table I. Components of the complement system**

| Components involved in activation | |
|---|---|
| Initial components | |
| C1, C2, C4 | - Classical pathway |
| Initiating factor, properdin, factor D, factor B | - Altcrnativc pathway |
| Amplification components | |
| C3, C5 | |
| Terminal components | |
| C6, C7, C8, C9 | |
| Cofactors and inhibitors | |
| C4 binding protein, factor H | |
| C1 estcrase inhibitor, anaphylatoxin inactivator | |
| C3b inactivator | |

**Table II. Complement receptors**

| Ligand | Receptor | Present on |
|---|---|---|
| C3a, C4a | C3aR | Mast cells, monocytes, neutrophils, basophils, T cells |
| C3b, iC3b, C3c C4b | CR 1 | RBCs, B and T cells monocytes. neutrophils, eosinophils |
| C3d, C3dg iC3b | CR 2 | B Cells, thymocytes, dendritic cells |
| iC3b,C3d | CR3 | monocytes, neurophils, eosinophils, dcndritic cells, R and NK cells. |
| iC3b | CR4 | Monocytes, neutrophils, K and NK cells. |
| C3dg,C3d | CR 5 | Neutrophils, platelets. |

*Activation:* Antigen-antibody complexes are the most studied of the classical pathway activators. Immunoglobulin M and IgG3 are the most potent

activators while other classes and subclasses seem to lack the ability to activate the classical complement pathway. However, the alternative complement pathway can be triggered by IC containing immunoglobulins of all classes. Here the critical feature appears to be that the complex should be present in the form of a precipitate. A variety of microbes including mycobacteria and a number of substances with repeating subunit structures like polysaccharides are capable of initiating the alternative pathway. Once triggered each component acts on the next component and a sequential step-by-step activation takes place. This starts with C1 when the classical pathway is activated and begins with the initiating factor in the case of the alternative pathway. Both pathways have a common sequence from the level of the third component till C9 which is the last component in the sequence. The mechanism of activation is shown schematically in Fig.1.

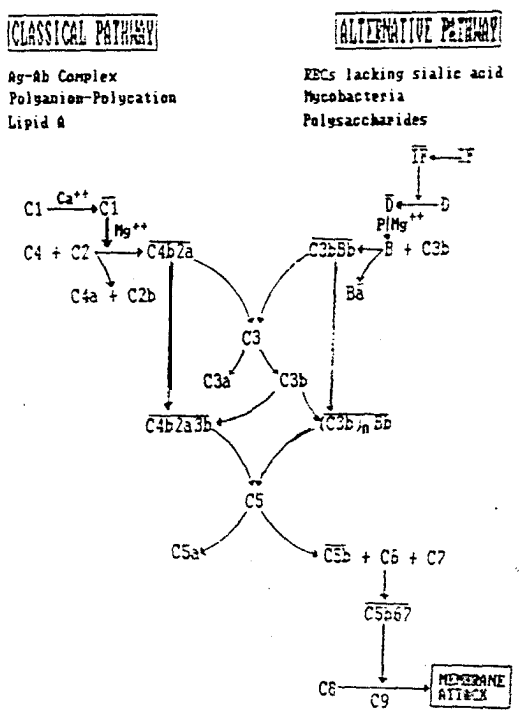


**Fig. 1. The classical and the alternative pathways of complement activtation.**

*Consequences:* When the activation takes place on the surface of a cell, multiple holes are formed and this leads to an osmotic lysis of the cell. In addition, a number of other activation products are formed which exhibit a wide range of

biological effects. A summary of these is given in Table III.

**Table III. Important biological effects of some of the active fragments of the complement system**

| Fragment | Biological action |
|---|---|
| $C3_a$ | Anaphylatoxin, supression of immune response |
| $C4_a$ | Anaphylatoxin |
| $C4_b$ | Immune adherence |
| $C3_b$ | Immune adherence, elimination of IC, modulation of immune response |
| $C_3{}_{dg}$ | Modulation of immune response |
| $C5_a$ | Anaphylatoxin, chemotaxis, enhancement of immune response |
| C7,8,9 | Membrane attack complex |

*Major functions:* One of the earliest observed functions of the complement system is that it is involved in the elimination of microbes. This is achieved by two major mechanisms. The first is through opsonisation at the level of C3 which facilitates the phagocytosis of micobes by neutrophils nad macrophages. The phagocytes then kill the organisms through various microbicidal enzyme systems. The second mechanism is lysis of the organisms with the aid of the membrane attack complex (MAC) formed by the terminal components of the system.

The complement system promotes both acute and chronic inflammation through its active fragments which have anaphylatoxic and chemotactic properties. Further, activation of phagocytes and release of tissue - damaging enzymes also add to the inflammatory potential of the system.

The important role of the complement system in metabolising IC is well recognized now. This is achieved by prevention of immue precipitation through the classical pathway, solubilization of precipitated IC through the alternative pathway or by internalization of complement-reacted IC through the complement receptors.

Complement components and their active fragments appear to function as potent immuomodulators. The generation of B lymphocyte memory cells, alteration of lymphocyte proliferation, stimulation of antibody production, enhancement of antibody-dependent cellular cytotoxicity are some of the

documented effects of complement on the immune system (reviewed in Erdei *et al* 1991).

## THE STATES OF THE COMPLEMENT SYSTEM IN LEPROSY

The involvement of the complement system in diseased individuals is usually assessed by quantitating the blood levels of the components using haemolytic or immunochemical methods. However, a major shortcoming in this approach is the lack of dynamic information provided, and static profiles of the complement system can be misleading. For example, normal levels of a particular component, say C3 could be due to an increased synthesis which is masked by an increased catabolism. Similarly, a decreased level could be either due to lowered synthesis or due to an increased breakdown with normal synthesis.

The ideal way of assessing the complement system is by conducting metabolic turnover studies of the various components. Unfortunately, this is very time consuming and is beyond the reach of the average research worker in leprosy. An alternative method which is advocated involves the quantitation of the breakdown products of complement components (Perrin *et al* 1975). These methods are based on the changes in physiochemical properties and expression of new epitopes consequent to activation of the system. It is believed that a combination of functional and immunochemical estimation using the above mentioned principle is the best way of looking at the functioning of this system.

Although, there are a number of reports of complement profile in leprosy, a vast majority of them give only static information and hence will not be discussed any further. However, awareness of this problem has led investigators to use more dynamic approaches.

Bjorvatn *et al* (1976) reported an increase in both C3d and inferred that there is (a) activation of the complement system, especially during reactional states and (b) a hypercatabolism of C3 with both increased production and breakdown. Subsequently, Saha *et al* (1977;1983) noted an increase in the catabolic fragment factor Ba during ENL reactions, While confirming the activation of this system during the occurrence of ENL reactions, Ramanathan *et al* (1984) reported an increase in C3d in patients with reversal reactions also.

As evidence of involvement of the complement system in leprosy, especially during lepra reactions, mounted, efforts have been directed towards establishing the temporal relationship between the activity of this system and the evolution of reactions. Valentijn *et al* (1982), Saha *et al* (1982) and Ramanathan *et al* (1991) have reported on sequential estimations of the levels of complement

catabolic fragments before, during and following subsidence of lepra reactions. It is clear from these studies that the activation process continues and then declines gradually only after the subsidence of reactions. A similar observation has been made on the involvement of this system in reversal reactions also (Ramanathan *et al* unpublished findings).

Since immunochemical estimations do not necessarily differentiate the functionally active from inactive molecules, haemolytic assays have been performed by a number of workers (Petchclai *et al* 1973; Bjorvatn *et al* 1976; Valentijn *et al* 1982; Ramanathan *et al* 1986a). Haemolytic function of this system appears to be intact and most of the investigators found near normal to moderately elevated levels. Apart from the haemolytic function, the ability of complement to solubilize IC has been studied extensively and this is discussed in the section dealing with the role of complement in IC metabolism.

In addition to the foregoing, limited studies of the genetic polymorpisms of C3 (Srivastava *et al* 1975), and C2, C4 and factorB (Grener *et al* 1980) have a been performed. There were no discernible associations between the polymorphic variants and the disease types or its manifestations in the cases of C2, C3 and factor B. There was, however, a variant of C4 (called C4 F1) found only in a group of BL and LL cases in the study. It must be stated here that more detailed analyses of the polymorphic variants need to be done using currently available molecular biology tools such as restriction fragment length polymorphism (RFLP). the findings thus obtained must then be correlated with theclinical features of leprosy.

**THE INTERACTION OF MYCOBACTERIA WITH THE COMPLEMENT SYSTEM**

*Activation by whole organism:* In 1959, Heyman and Wahlig showed that *M.tuberculosis* could activate thealternative pathway of the complement a system (AX). After a gap of nearly two decades, Kondo and his colleagues (1978) found that BCG was capable of triggering the APC. The APC activating potential of *M.leprae* was first demonstrated by Ramanathan *et al* (1980) and subsequently by others (Saha *et al* 1983; Schlesinger & Horwitz 1990a). It is known that a number of other mycobacteria apart from *M.leprae, M.tuberculosis* and BCG can also activate the APC (Parkash *et al* 1987).

*Activation by components:* In addition to the whole organism, various components of mycobacteria can also trigger the system. Rourke *et al* (1979) found that purified protein derivative (PPD) even in the absence of antibody bound C1 activated the complement system, and cord factor or trehalose dimycolate from *M.tuberculosis* could activate the APC.

Recently, it has been shown that phenolic glycolipid 1 (PGL) of *M.leprae* is capable of activating the complement system (Ramanathan *et al* 1990; Schlesinger & Horwitz, 1990b). It is interesting to note that unlike PPD or cord factor which activate only one pathway, PGL seems to act on both the pathways. Furthermore, the active moieties are found in the sugar as well as the lipid components.

*The effect of antibody on the activation by mycobacteria:* Although the activation of APC can take place under antibody free conditions, investigations done in the last decade reveal that antibodies can augment the activation through the APC (Ratnoff *et al* 1983). Thus, the addition of antibodies against rabbit erythrocytes, zymosan, bacteria such as *Escherichia coli*, neisseria, salmonella and viruses like the influenza virus potentiated their activating ability. Further, it has been found that unlike the classical pathway, the Fc portion of the immunoglobulin molecule is not critical for the APC amplifying effect.

The activation of complement by mycobacteria and their components takes place *in vitro* under antibody free conditions. However, since antibodies to mycobacteria are produced in diseased individuals, the effect of these on the activation has also been studied recently. Chakrabarty and Saha (1986), found that the addition of heat inactivated serum from active lepromatous leprosy patients but not healthy volunteers, increased the activation of complement by *M.leprae*. Subsequently, Parkash *et al* (1988) demonstrated an increase in APC activation when BCG and *M.vaccae* were precoated with antibody. Similarly, IgM class of antibodies were shown to augment the classical pathway activation of PGL while IgG class of antibodies were responsible for the increase in APC activation (Ramanathan *et al* 1990).

*Consequences of activation to the organism:* In the case of many microbes, activation of complement results in the lysis of the organisms. Since mycobacteria appear to be potent activators of the complement system, experiments were conducted to determine whether activation is followed by the destruction of the bacilli. Parkash and his colleagues (manuscript under preparation) found that BCG and *M.vaccae* did not lose their viability after reacting with human complement. Similarly, in view of the activation augmenting ability of antibody, immunoglobulins against BCG and *M.vaccae* were added before being treated with complement, However, it was found that this also did not result in the killing of the bacteria although addition of antibody increased C3 uptake by these bacteria. This was further confirmed when ultrastructural studies revealed that there were no differences between complement-reacted and the control bacilli. Although such

studies have not been made using *M.leprae,* it is reasonably safe to assume that this organism also will be similar to BCG and *M.vaccae* in its behaviour.

One major reason for the ineffectiveness of complement-mediated killing could be the tough cell wall of this group of organisms. In addition, these bacteria may employ other strategies also to evade the lyric effect of complement For example, sialic acid present in the capsule of many organisms prevents the deposition of C3b. Further mechanisms involved are microbial shedding of molecules that destroy complement, synthesis or aquisition of regulatory molecules, blockade of activation of complement before the formation of the terminal attack complex (C5b-9) and formation of a nonlytic C5b-9 complex (reviewed in Joiner 1988). It is not known whether mycobacteria, especially the pathogenic ones use any of these above mentioned mechanisms to escape complement-mediated lysis.

Currently available information indicates one mechanism employed *M.leprae* as a survival strategy. It is known that opsonisation of bacteria by complement C3b leads to phagocytosis. Although this usually aids the host to get rid of the invading organism, intracellular parasites may utilise this very property for their existence in an otherwise hostile environment Recently, Schlesinger and Horwitz (1990a) have shown that monocytes phagocytose complement-reacted *M.leprae* through CR1 and CR3. It is possible that this phenomenon of phagocytosis is likely to aid the host whose immune mechanisms are capable of killing the bacilli. On the other hand, phagocytosis probably assists theorganism to Survive in the individual who is susceptible to get the disease.

**ACTIVATION OF THE COMPLEMENT SYSTEM IN LEPROSY**

As discussed earlier, there is evidence to suggest that there is a marked degree of activation of the complement system in leprosy. A number of mechanisms seem to be operative in initiating this important phlogistic system. A major contribution towards this activation is made by *M.leprae* and PGL 1. It-is likely that cytoplasmic components of *M.leprae* are also capable of activating the system as has been found with BCG and *M.vaccae* (Parkash *et al* unpublished observations).

High levels of immune complexes (IC) have been demonstrated by several workers to occur throughout the spectrum of leprosy. It is well known that IC are potent activators of the complement system. Saha *et al* (1984) and Tyagi and her coworkers (1990) demonstrated that circulating IC from leprosy patients could activate complement.

It is known that many lysosomal enzymes such as beta glucuronidase, aryl sulfatase, acid phosphatase and cathepsin are elevated in leprosy (Palekar & Magar 1967; Venkatesan *et al* 1979). Schorlemmer and Allison (1976) found that many of the acid hydrolases and other enzymes released by macrophages on activation are capable of cleaving C3 and C5 generating a number of nascent products by a process of proteolysis. It is thereforeconceivable that lysosomal enzymes also contribute to the activation of the complement system both locally and systemically in leprosy.

**COMPLEMENT - MEDIATED INFLAMMATION IN LEPROSY**

Complement activation in the leprosy patients by any of the above mechanisms results in the generation of a number of nascent molecules. A major consequence of this activation appears to be the development of both acute and chronic inflammation.

*Acute inflammation:* Reactions that occur in leprosy represent acute episodes superimposed on the underlying chronic state. Of the two major types ofreactions that are recognized it isbelieved that Type I or the reversal reaction is due to an increase in the delayed hypersensitivity component of the T cell limb of the immune system. On the otherhand, Type II or the erythema nodosum leprosum (ENL) syndrome is considered to be mediated through the immune complexcomplement axis.

As discussed earlier, several groups of workers have demonstrated a state of hypercatabolism of the complement system during ENL reactions. A sequential study of complement levels by Ramanathan *et al* (1991) indicates that the catebolic fragment C3d is elevated at two time points in the disease process. The first is when the patient is yet to be treated and the second is during ENL reactions.

Activation of complement in the untreated state is probably due to the high levels of *M.leprae* and IC. This activation, however, is not always accompanied by overt signs of acute inflammation and may be related to the induction of a chronic granulomatous response.

The presence in the serum of complement breakdown products such as C3d and factor Ba during reactional states represents activation of the system at the sites of acute inflammation. The probable sequence of induction of acute inflammation can be partly deduced from currently available information. Since ENL occurs usually after starting treatment, it is believed that bacillary products

that are released from *M.leprae* complexed with their corresponding antibodies precipitate at various sites like the skin, joints, uveal tract and glomeruli The precipitated complexes then activate the complement system which results in the generation of molecules with anaphylatoxic and chemotactic properties. Anaphylatoxins, by virtue of their smooth muscle contracting ability, increase the local vascular permeability and produce oedema while chemotactic factors attract neutrophils into the affected site. The neutrophils then release some more tissue damaging enzymes as a result of stimulation by both IC and complement. component C3b. Thus, the presence of neutrophils, IC and complement as well as oedema and erythema at the sites of ENL reaction can be explained.

A decrease in theconcentration of complement catabolic fragments following the subsidence of ENL reaction and the control of these reactions by drugs such as corticosteroids and chloroquine which have potent complement inhibiting properties indicate the important role played by the complement system in the genesis of this type of reactions.

Although it is widely believed that reversal reactions are due to increased delayed hypersens itivity, evidence suggestive of involvement of complement in this phenomenon also, is now available. Ramanathan *et al* (1984, 1986) reported an increase in the levels of C3d and a decrease in the amount of complement mediated IC solubilization in patients undergoing reversal reactions. A number of investigators are of the view that an increase in delayed hypersensitivity is responsible for the production of these reactions. It is likely that theconcomitant activation of macrophages locally leads to the release of proteases which then generate nascent complement products. Therefore, this system probably supplements thedelayed hypersensitivity induced inflammatory processes in reversal reactions.

*Chronic granulomatous inflammation:* A central role for the production of chronic granulomatous inflammation by the complement system was proposed by Schorlemmer and his coworkers (1977). This model was formed on the basis of two major findings: (i) The ability of agents which induce granulomatous inflamation to activate the complement system on the one hand and to stimulate the macrophages to release lysosomal hydrolases and complement components locally, and (ii) the property of lysosomal enzymes to cleave C3 and C5 generating active products.

The capacity of *M.leprae* to activate the complement system and to stimulate the macrophages is well recognized now. Thus, once *M.leprae* gains entry into the tissues of the host, it activates the complement system locally. This results in

thegeneration of inflammation and the production of C5a which acts as a chemoattractant drawing initially neutrophils and later monocytes (which mature into macrophages) into the site. Before the onset of specific immune processes which kill the bacilli or in the individual who is not capable of producing a bactericidal response, the bacteria persist interacellularly in the macrophages stimulating them to release both lysosomal enzymes and complement components such as C3 and C5. The enzymes activate C5 to form C5a and C5b. Since C5a is a potent chemotactic factor for monocytes, recruitment of fresh macrophages takes place, gradually building up a collection of macrophages resulting in a granuloma. This is the initial attempt of the host in an immune individual and the main mechanism in a susceptible person to physically limit the spread of organisms further.

In subjects who mount an adequate immune response to *M.leprae*, ***the*** granuloma resolves when the bacilli are eliminated. On the other hand, when the immunity is only partially adequate, such as in those who develop the paucibacillary forms of the disease, the granuloma is maintained by other mechanisms, especially those involving T cell responses.

A further means of perpetuating thechronic granulomatous inflammation initiated through complement activation is provided by antigen-antibody complexes which occur in patients through the spectrum of leprosy. This is based on the finding that IC are potent activators of both complement and macrophages. Further, it has been shown experimentally, that IC are capable of inducing a granulomatous response involving antigen antibody systems of non-mycobacterial and mycobacterial antigens (Spector & Heesom 1969; Ridley *et al* 1982).

**THE ROLE OF COMPLEMENT IN IC METABOLISM IN LEPROSY**

It is now recognised that the complement system plays a pivotal role in containing and eliminating IC from the body. This appears to be mediated through three major mechanisms which are: (i) prevention of immune precipitation, (ii) solubilization of precipitated IC and (iii) elimination of IC mediated through complement receptors.

*Prevention of immune precipitation:* First described by Schifferli and his co-workers (1980), this function of the complement system is mediated by components belonging to the classical pathway which prevent the aggregation and precipitation of IC that have reacted with the first component C1. Although this appears to be an important mechanism, there are no published reports of the status of this function of the complement system in leprosy.

*Solubilization of precipitated IC:* A new function of the complement system was described by Miller and Nussenzweig in 1975. They found that when precipitates of antigen-antibody complexes reacted with a large excess of complement, they were broken down into smaller aggregates and lost their ability to activate complement further and to bind to cellular receptors. This function is mediated essentially by components of the alternative pathway, though C2 and C4 of the classical pathway also contribute substantially. A depression of complement - mediated solubilization (CMS) has been reported in many diseases where IC appears to play a pathogenic role (Schifferli *et al* 1981; Baatrup *et al* 1983).

Ramanathan *et al* (1986a) reported that CMS was reduced in patients undergoing reactions of both types but not in patients who did not suffer from reactions. Subsequently, Chakrabarty and his coworkers (1988) also noted a similar decrease in the levels of CMS in leprosy patients. However, they did not find any difference between the reactional and non-reactional patients. A prospective study of untreated multibacillary leprosy patients in whom sequential estimations of CMS were performed revealed that there was a reduction in CMS levels well before the onset of reactions which persisted long after their subsidence also. This did not correlate with either C3d or immunoglobulins (both free and complexed) titres (Ramanathan *et al* 1991).

The possible involvement of the complement system in the production of reversal reaction was discussed in an earlier section. Ramanathan *et a1* (1986a) and Chakrabarty *et al* (1988) found that BT patients with reaction had much lower CMS levels than non-reactional BT patients. A sequential study of CMS, similar to the one reported in LL patients (Ramanathan *et al* 1991) was undertaken by us in BT patients. Here again, we found that reactional patients exhibited markedly lower CMS levels than those who did not develop reactions at all during a four year clinical followup (manuscript under preparation). In these cases also, the depressed CMS persisted even after the clearance of the disease and it did not correlate with circulating IC or C3d levels.

In brief, studies on complement-mediated IC solubilization reveal that (i) the reduction in the levels of CMS is essentially confined to patients prone to getting lepra reactions of both Type I and Type II, (ii) the reduction persists for long periods even after the susbsidence of reaction and in BT patients even after the disease itself becomes inactive, (ii) the lower levels of CMS contrast with the near normal or slightly elevated haemolytic complement levels and (iv). the levels do nor correlate with circulating IC or C3d concentrations.

In view of the selective depression of CMS in reactional patients and since solubilized or partially solubilized IC are known to be potent immunomodulators, a hypothesis can be proposed with the defective CMS as a predisposing factor for reactions (Ramanathan *et al* 1986b).

The inability to inactivate and dispose of the IC that are formed during the course of the disease effectively, results in the modulation of the immune system. Thus, in BT patients, this may lead to stimulation of T cells mediating delayed hypersensitivity; and in LL patients, this results in the activation of B cells leading to an increase in the immunoglobulin levels along with the formation of antigen-reactive T cells. The latter effect may be responsible for shedding of more antigens from *M.leprae* eventually producing more IC, thereby setting up a self-perpetuating cycle. Further, unsolubilized IC by themselves will activate macrophages, complement and other phlogistic systems resulting in an inflammatory process. Thus, IC could initiate inflammation in both types of lepra reaction. While, it is likely that this inflammation is mediated through delayed hypersensitivity associated mechanisms in Type I reaction, IC may play an additional role of mediating the inflammatory process in the ENL syndrome. This hypothesis is shown schematically in Fig 2.

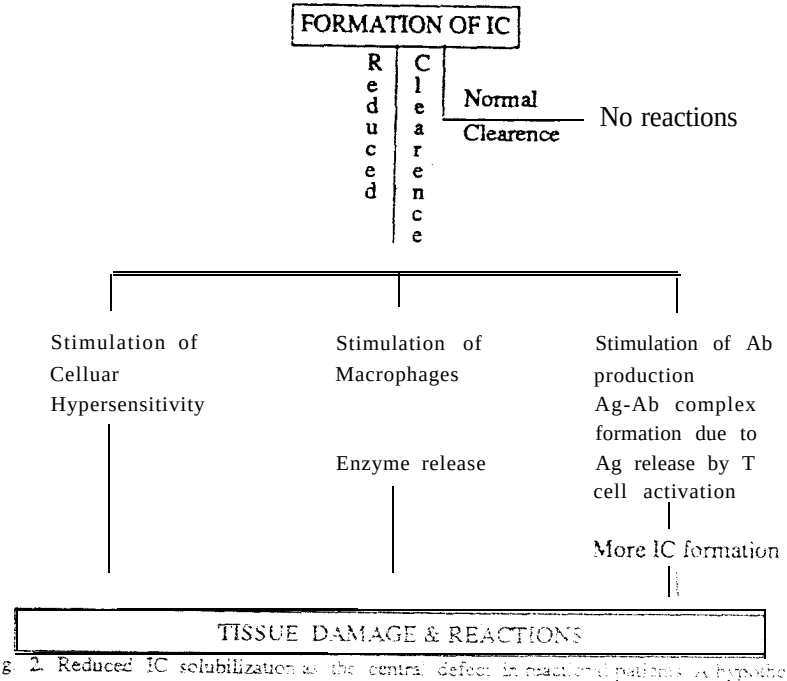


Fig. 2. Reduced IC solubilization as the central defect in reactional patients - a hypothesis

*Elimination of IC through complement receptors:* A third mechanism which is recognised to eliminate IC using the complement system is through complement receptors(CR). Of the various CRs, CR1 has been extensively studied in individuals suffering from IC mediated phenomena and it has been suggested that there is a reduction in the number of CR1 in such patients.

To date, there has been only one reported study of complement receptors in leprosy (Tausk *et al* 1985). These authors noted a significant decrease in the number of CR1 present on the red blood cells of patients with lepromatous leprosy but not in those with paucibacillary disease. It is argued by these workers that the reduction in CR1 could be due to receptor occupancy by circulating IC. Clearly, further studies of these receptors are needed to evaluate their status and their role in various forms of leprosy and their relationship to such complications as reaction.

## CONCLUSIONS

From the foregoing, the following are apparent: (i) There is a hypercatabolism of the complement system in leprosy along with a reduction in the solubilization of IC through complement; (ii) *M.leprae* and its constituents can activate the complement system; and (iii) The complement system gets activated in leprosy by more than one stimulus. This can result in the generation of both acute and chronic inflammatory processes. Phagocytosis of complement -reacted *M.leprae* early in the course of the disease is of advantage to the host who is capable of initiating bactericidal mechanisms. On the other hand, this helps the organism to gain entry into an immunologically privileged site in a susceptible host.

Although a considerable amount of information regarding the pathophysiology of the complement system in leprosy is available now, there are still several areas of theoretical and practical importance to be covered in this field. The present review concludes with some of the lines of enquiry which need to be pursued in the next decade: (i) Apart from its thick cell wall, does *M.leprae* get protected from the effects of complement in influencing the course of events in the early stages of host-parasite interaction? (ii) What is the role of complement in influencing site course of events in the early stages of host- parasite interaction? (iii) What is the reason for the dichotomy between the haemalytic function and the ability to solubilize IC? Are different polymorphic forms, especially those belonging to the class III products of the major histocompatibility region responsible for the schism between two of the functions

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