REVIEW OF LITERATURE
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A major cause of neonatal mortality in India is bacterial sepsis. However, it is possible to prevent bacterial neonatal infections to a large extent. Neonatal septicemia is a common problem amongst neonatal infections. However, early diagnosis of neonatal septicemia is a vexing problem. The "gold standard" for the diagnosis of septicemia has been the isolation of micro-organisms from a blood culture. Increased C-reactive protein production is a very early and sensitive response to most forms of microbial infections.

C-reactive protein:

C-reactive protein is an acute phase reactant normally present in trace amount in the serum of healthy individuals and rises several hundred times in concentration in response to tissue injury. Clinical measurement of C-reactive protein (CRP) is valuable as a screening test for organic disease and as a sensitive objective index of disease activity as well as response to therapy in some inflammatory, infective and ischaemic conditions (Pepys, 1981).

History and discovery:

The discovery of CRP was reported in 1930 by Tillet and Francis, when they were investigating
serological reactions in acute pneumonia with various extracts of pneumococci. They observed that sera obtained from patients during acute stage of illness precipitated with an extract of pneumococcus. This non-type specific somatic polysaccharide fraction of the cell wall of pneumococci was designated by them as fraction C and later C-polysaccharide (CPS) and the substance responsible for the reactivity was termed as C-precipitin. It was seen that after the illness, the capacity of the patients sera to precipitate a polysaccharide rapidly disappeared. A rise of C-precipitin substance (which is not normally present in blood) was observed to occur in a variety of febrile and afebrile bacterial illness, as well as in non-infectious states including those following myocardial infarction and operation.

Abernethy and Avery (1941) presented evidence that the C-precipitin was a protein causing a non-specific capsular swelling reaction with some strains of pneumococci, when mixed with acute phase sera, and subsequently showed that the substance responsible was CRP (C-reactive protein). He detected CRP in non-infectious as well as infectious conditions and in the acute phase reaction.

Crystallisation of the CRP isolated from human serous fluids was first described by McCarthy in 1947. In his experiments, the crystalline protein was obtained from two pathological specimens, one a pleural fluid from
a patient with Streptococcal pneumonia and the other an abdominal fluid from a cirrhotic patient suffering from an intercurrent infection.

McCarty et al (1954) also described that crystalline CRP has its isoelectric point at pH 4.82 as determined by free electrophoresis. Its mobility in the electrophoresis cell, both alone and after addition to normal serum, coincides with that of the Beta-globulin fraction of the serum.

Source and characteristics:

According to Murlimann et al (1955) liver is the major, if not the only site of CRP synthesis. Other tissues of the reticulo-endothelial system, such as spleen and lymph nodes, and cell populations such as thoracic duct lymphocytes or peripheral blood leucocytes were all incapable of CRP production.

Kushner and Feildmann (1978) also stated that CRP is synthesised by hepatocytes. They reported that all hepatocytes are capable of producing CRP depending upon the need and time interval, though hepatocytes around portal triad, are the first one to produce CRP.

Nemir et al (1957), Nesbitt et al (1960) and Nilsson et al (1962) demonstrated CRP during the latter part of the pregnancy and at parturition, but reported that it is rarely found in umbilical cord sera.
Bellomo et al (1959) demonstrated that CRP does not pass the placental barrier and it has not been demonstrated in human milk. Possible explanation of these findings might be the presence of some kind of CRP inhibiting substance in the umbilical cord serum. They also reported, that CRP is seldom demonstrated in umbilical cord sera but is often found in sera from infants one or few days old. This indicates that infants are already capable of forming CRP when they are one day old.

The rate of CRP synthesis and secretions increases within hours of an acute injury or the onset of inflammation (Kushner and Feildmann, 1978). This increase occurs probably under the influence of humoral mediators, such as leucocytes endogenous mediator (Meriman et al, 1973) and prostaglandins PGE\(_1\) (Whicher et al, 1980).

**Structure** - Human CRP is a homogenous protein free of lipids and carbohydrates. In serum as well as in purified form, CRP has a variable molecular weight ranging from 110,000 to 144,000 daltons. Each CRP molecule consists of five identical non-glycosylated polypeptide subunits, which are non-covalently associated in a disc-like configuration with cyclic pentameric symmetry (Osmond et al, 1977). The subunit molecular weight is 21,100 daltons. Each subunit is a sequence of 187 amino acids in a single
polypeptide chain with -NH₂ terminal residue as pyrrolidone carboxylic acid and C\textsubscript{\textgreek{u}}H terminal residue as proline. The two half of cysteine residues at positions 36 and 78 are involved in disulfide bond.

Oliveira et al (1977) reported that CRP contains two residues of methionine per mole of protein which would give rise to three Cn Br fragments. CRP has been shown to bind calcium ions and in addition exhibits its various binding properties only in the presence of divalent cations.

**Role in vivo** - Role of CRP in vivo is not known. Under some circumstances it can cause inflammation, for example intradermal injections of C-polysaccharide in actually ill patients elicits a characteristic wheal and flare reaction mediated by CRP.

Siegel et al (1978) reported that CRP enables to activate the classical complement pathway which finally leads to cytolysis.

Møntensen et al (1975) reported that CRP also combines with T lymphocytes and inhibits certain of their functions. Modified CRP can also bind to the Fc receptors of macrophages to bring about phagocytosis, or to certain lymphocytes and natural killer cells to enhance the cell mediated cytotoxicity 2 to 35 folds.
Various workers have reported that CRP shares antibodies with the ability to initiate certain functions of potential significance to host defence and inflammation including precipitation, agglutination, opsonization, capsular swelling and complement activation.

Fiedel et al (1976) reported that aggregated CRP induces platelet aggregation leading to the release of thromboxane A2 causing vasoconstriction.

Tsujimoto et al (1980) reported that CRP can undergo a calcium dependent binding with phosphocholine and phosphate esters, and (hence with lipids widely distributed in mammalian and microbial cells), with multiple widely distributed polycations, including those derived from leucocyte granules.

Pepys in 1981, reported that CRP may take a part in the pathogenesis of many inflammatory condition in which its circulating concentration is elevated, it seems unlikely that, this is its major role. Pepys also reported that the main role of CRP is to recognize in plasma, the potentially toxic antigenous materials released from damaged tissues, to bind to them and thereby to detoxify them and/or facilitates their clearance.

**Interaction of CRP with complement system**

Siegel et al (1975), reported that CRP is a potent activator of the complement system when reacting
with capsular polysaccharide (CPS) and choline phosphatides. Cationic homopolymers of poly-L-lysine were found to activate complement via CRP and deplete C3 and C5 as well as early acting C components. Substances which react with CPS to result in activation of the classical C pathway includes CPS, lecithin, sphingomyelin, and protamine, this C consumption can be inhibited by phosphoryl choline. Maximum C consumption was obtained with polymers of 2000 - 8000 daltons, polymers of 1700 to 11000 and 23000 daltons were intermediate in reacting, while L-lysine, lysyl-L-lysine, tetra-L-lysine and polymers of 70,000 to 400,000 daltons lacked significant complement consuming activity. Naturally occurring polycations which consumed C in the presence of CRP included myelin basic proteins, cationic proteins of rabbit leucocytes and both lysine and arginine rich histones. The polycations which failed to induce C consumption via CRP, inhibited its consumption by both active polycation and by C-polysaccharide.

Methods of detection:

Commonly used methods of estimation of CRP in different body fluids were given by Nudelman et al in 1984. They are -
and specificity. The halo technique was considered as a simple and suitable method which allows quantitation of concentration of about 1 - 2 u gm/ml of CRP. It is thus about ten times as sensitive as the precipitin inhibition technique described by Ray and Shay in 1965. Furthermore this technique seems more suitable and accurate since titration is not required.

Kindmark (1976) recently reported a method employing radio-electro-immunodiffusion which is very sensitive, but has the disadvantage of requiring specialised equipment and long period of time to complete.

A more rapid method is nephelometry, which involves detection of aggregated CRP by light scattering.

**Normal levels:**

The normal levels of CRP in human sera according to Claus et al (1976) are given below.

<table>
<thead>
<tr>
<th>Sera</th>
<th>Number</th>
<th>Range u gm/ml</th>
<th>Median u gm/ml</th>
<th>Mean u gm/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>24</td>
<td>0.010-0.35</td>
<td>0.072</td>
<td>0.109</td>
</tr>
<tr>
<td>Normal adults</td>
<td>153</td>
<td>0.068-9.2</td>
<td>0.58</td>
<td>1.3</td>
</tr>
<tr>
<td>Hospitalised adults</td>
<td>246</td>
<td>2 - 256</td>
<td>13</td>
<td>38</td>
</tr>
</tbody>
</table>
According to Norley & Kushner (1982) most people have CRP level $\leq 2$ mg/litre but up to 10 mg/litre can be taken as normal, while Pepys (1981) and Peltola (1984) recommended 20 mg/litre as the upper limit of normal.

According to Mudgett et al (1984) following are the CRP level in normal individuals.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Upper limit of normal mg/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn (cord)</td>
<td>10</td>
</tr>
<tr>
<td>Neonate 1 week</td>
<td>30</td>
</tr>
<tr>
<td>Neonate 1 week to 1 month</td>
<td>10</td>
</tr>
<tr>
<td>Infant</td>
<td>10</td>
</tr>
<tr>
<td>School children</td>
<td>2.3</td>
</tr>
<tr>
<td>Adult</td>
<td>3 (90%)</td>
</tr>
<tr>
<td></td>
<td>10 (99%)</td>
</tr>
</tbody>
</table>

Mindochea et al (1984) studied that there was no correlation between gestational age and CRP concentration in pre-term infants.

**CRP levels in various neonatal infections:**

A. **CRP level in septisemia**

Philipson et al (1957) first described the presence of CRP in bacterial infection of neonates.
Felix et al (1966), Hanson et al (1962) and Liegel (1974) observed that CRP increased invariably in neonatal infections and more constantly in septicemia and meningitis.

Sabel et al (1974) studied 14 cases of neonatal septicemia and meningitis and compared the routine diagnostic parameters i.e. bacterial culture, total blood leucocyte count and pyrexia with the result of CRP test in these cases. They found increased CRP in 85.7% of cases with positive bacterial culture. In these series, the level of CRP closely followed the presence of positive bacterial cultures. They observed that CRP was a more reliable parameter than CSF cytoprotein profile and blood leucocyte count in cases of septic meningitis and septicemia.

Sabel and Wardsworth (1979) in another subsequent study estimated CRP in early diagnosis of neonatal septicemia. They observed usefulness of CRP in neonatal septicemia, meningitis and urinary tract infection in a neonatal unit using semi-quantitative latex agglutination as a rapid screening method, and electro-immunoassay as reference method for CRP determination. In 96% of non-infected infants CRP was $\leq 15$ mg/litre and 82% had CRP $\leq 10$ mg/litre up to 3 days of age. After 3 days of age 96% had CRP $\leq 10$ mg/litre. The initial CRP level was increased in 18 out of 18 patients, 93% with bacterial
septicemia. A rise in CRP was also seen in very pre-term infants with septicemia. The author therefore stressed the CRP is of definite value as an aid in early diagnosis of neonatal septicemia and bacterial meningitis.

Ainbender et al (1982) studied 33 infants whose birth were complicated by rupture of the amniotic membranes for 24 hours or more prior to delivery or maternal fever during labour so causing increase incidence of neonatal septicemia. Serum CRP were done for the first three or four days of life. Finally a comparison was made of serum CRP values of blood gotten at or near the time of delivery from mothers with fever during labour or premature rupture of membrane. Values between 0.5 and 1.0 mg/dl are considered to be equivocal, level \( \geq 1.0 \) mg/dl is abnormal. Infants as immature as 28 weeks gestation were able to produce serum CRP concentrations \( \geq 2.0 \) mg/dl. Among the 100 infants studied initially they found CRP values \( \leq 0.5 \) mg/dl in 65, between 0.5 and 1.0 mg/dl in 17, \( \geq 1.0 \) mg/dl but \( \leq 2.0 \) in 7, and \( \geq 2.0 \) mg/dl in 11 during the first four days of life. Among those with elevated concentrations, the peak values always occurred during the first three days of life. The seven patients with CRP concentration \( \geq 1.0 \) but \( \leq 2.0 \) mg/dl had values in the lower portion of that range and tended not to have major problems, whereas eight of the 11 infants with values \( \geq 2.0 \) mg/dl had, either singly or in combination, shock, meconium aspiration, pneumonitis, foetal distress, maternal fever.
Hindoche et al (1984) studied 27 infants (4 term and 23 pre-term). Mostly CRP concentration in 27 infants, who were not infected were less than 0.3 mg/dl, which is the lower limit of detection of CRP by electro-immunoassay. There was no correlation between gestational age and CRP concentration in pre-term infants and term infants. Eleven out of 12 infants with proved sepsis had significantly raised concentration and one infant with recurrent pseudomonas chest infection had a raised CRP concentration up to 20 mg/dl. High CRP concentration was found in infants with suspected infection. Successful treatment was followed by a decrease in the CRP concentration. Serial serum CRP determination fell rapidly in patients in whom treatment was successful.

B. CRP levels in Neurological disease:

As early as 1962, Clausen et al studied CRP levels in different types of meningitis and reported results which were quite astonishing. It was a study of 30 cases of lymphocyte meningitis, 6 each of bacterial meningitis and of acute encephalitis and 10 cases of radiculitis. In 5 out of 6 patients of bacterial meningitis, CRP was detected in CSF. The sera from these patients had raised levels of CRP.

Felix et al (1966) determined CRP in 66 cord blood specimens and on capillary blood specimens of 669 apparently normal infants and 266 infants ill with known
or suspected neurological infections during the first 6 months of life. All but one of the cord blood specimens were negative for CRP. The incidence of positive reactors increased soon after birth with 50% of normal newborns having positive reaction during first week of life. This rapidly decreased after this period or that by 1 month to 6 months of life that incidence was only 2%. The intensity of the positive reactions in the majority was only up to 1 mm. 2/3 of the patients with neurological infections had positive results. The more severe the infections, the greater the intensity of the positive reactions. They suggested that the CRP determination can be valuable diagnostic aid in infections during the first 6 months of life when the usual laboratory criteria for infections are often not helpful. However, it has its limitations. Like any other single laboratory test, it must be used in conjunction with critical clinical judgement.

Sabel and Hanson (1974) demonstrated the clinical usefulness of CRP determination in bacterial meningitis and septicemia in infancy. CRP was quantitated with the single radial immuno-diffusion technique. In 37 infants 0 - 12 months old with purulent meningitis and/or septicemia, CRP was increased in 32. The same proportion of increased CRP was found in the neonatal cases as in the older infants. Peak values of 750 ugm/ml were found in 2/3 of all cases. E. coli infections showing the most uniform pattern of high CRP values. The period of
increased CRP was closely related to risk of recurrence of the infections. After CRP has returned to normal values no recurrence occurred. In cases of neonatal E. coli infections CRP was found to be the best single parameter indicating persistence of infections, and in a group of H. influenzae infection CRP was as good as cultures of CSF, white blood cell count and protein in CSF. The findings show that CRP is a useful parameter to show the presence of meningitis and/or septicemia in infancy including the neonatal period. CRP is an easy test which can be used to direct antibiotic treatment since it rapidly detects persistence of infections or recurrences.

Veltola (1982) in later study observed the clinical usefulness of CRP for rapid monitoring of infections of CNS in 16 patients of culture proven bacterial meningitis (1 month to 8 years of age) and 14 patients of viral meningitis (2 weeks to 48 years of age). All the 16 patients of bacterial meningitis had raised serum CRP levels ranging from 80 to 400 mg/litre with a mean value of 217 mg/litre. The duration of illness, age of the patients, and the bacterial species did not seem to affect the CRP (≤ 10 mg/litre) except one who showed a minimal rise of 28 mg/litre. He noticed that serum CRP levels come back to normal, on an average within 7 days, the duration of their elevation didn't depend upon their degree of rise.
Phillips and Baker (1983) observed CSF CRP level in neonatal meningitis. They assessed CSF and serum CRP level in 7 non-infected neonates and 16 neonates with proved sepsis or meningitis. Abnormal amounts of CRP were present in the CSF of a minority (2 of 11) of neonates with meningitis, and this test could not be used to distinguish between infants with suspected infection, infants with sepsis alone or infants with meningitis. In infants with suspected infection, 7 patients showed serum CRP level up to 1.2 mg/dl, while in CSF it is up to 1.4 mg/dl. Five patients of sepsis without meningitis showed serum CRP level up to 17.7 mg/dl, while serum CRP was up to 0.6 mg/dl. In 11 patients with proved meningitis, serum CRP was up to 2.3 mg/dl, while CSF CRP was maximum up to 3.6 mg/dl, so there is no obvious relationship between serum CRP and CSF CRP level. Of the infected babies with available serum 50% had elevated CRP values, in contrast to none of the non-infected babies. The failure of CRP response was attributed to poor development of CRP production mechanism in neonates. They also observed that group B streptococci might have suppressed the CRP production in these neonates as most of the cases were due to this organism.

Clarke and Cost (1983) in a subsequent study, stressed the use of CRP in differentiating septic from aseptic meningitis in children. In a study of 35 children of meningitis, they found that all the cases of pyogenic meningitis had values more than 1.0 mg/litre while those of
Acute meningitis had values less than 1.0 mg/litre. 
The rise of serum CRP in this study in cases of meningitis was found to be higher in early stages when CSF may still not have any pleocytosis.

Seltola et al (1984) studied 22 patients (10 pyogenic and 12 aseptic) and evaluated CRP levels in them. They observed that all the 10 patients of pyogenic meningitis had serum CRP more than 20 mg/litre while none of the aseptic cases had level more than 20 mg/litre. This difference of CRP concentration in two different groups was not influenced either by the age of the patient, the causative organism, the duration of illness, the changes in CSF or by treatment prior to admission.

Sekka Valmari (1984) observed that serum CRP levels of 300 mg/litre or more proved superior to other routine laboratory tests in predicting the neurological outcome. Their study considered of 70 patients of pyogenic meningitis, all were found to have serum CRP levels of more than 20 mg/litre. They compared predictive value of CRP with that of ESR, TLC, CSF TLC, CSF protein and sugar levels. They explained that very high value of CRP, probably reflects extensive brain tissue damage, resulting in neurological sequelae, which was shown by CAT scan studies.

Beer et al (1984) stressed the value to CRP measurement in differential diagnosis of meningitis. CRP was measured with a radio-immunoassay in sera from 31
children with bacterial meningitis, 15 with tuberculous meningitis (6 with miliary tuberculosis) and 28 with rural meningitis. Concentration of CRP in patients with tubercular meningitis lay between those of patients with bacterial and viral meningitis. They stated that measurements of CRP remains a useful additional parameter in the diagnosis and management of the various types of meningitis.

C. CRP levels in pneumonia:

Mc Carthy et al (1978) studied 156 children ranging in age from one month to 16 years (mean age 40 months), 154 had WBC counts, 156 had blood cultures as well as CRP, 102 had ELR, and 196 had acute and convalescent titre performed. Five patients had bacteremia. Compared to high WBC, ELR or temperature, CRP (positive) was the single best indicator of bacteremia, lobar infiltrates, and the absence of viral or Mycoplasma titre changes. It also had the best predictive value and sensitivity for pneumonias of probable or proven bacterial etiology and the weakest correlation with pneumonias of probable viral or mycoplasma etiology. Accurate separation of viral and bacterial pneumonia on the basis of radiographic appearance is difficult. Among patients with high WBC, ELR or temperature those with CRP positive versus CRP negative had a significantly lower occurrence of titre changes ($P < 0.05$) and a significantly higher percentage of lobar infiltrates ($P < 0.01$). CRP positive was a sensitive indicator (6/7)
of those patients with either bacteremia or a positive lung tap, as high as 8 (5/6) or high temperature (5/7).

25% of patients with CRP positive had lobar infiltrates, bacteremia or a positive lung tap, only 18% with CRP positive had a titre increase or a diffuse roentgenographic picture, the sensitivity of CRP positive was 76% for lobar infiltrates and/or positive bacterial cultures. Only 7% of patients with CRP negative had either lobar pneumonia or positive bacterial cultures or both.

Srivastava et al (1984) also reported positive CRP test in respiratory infections. They studied seventy children aged 2 weeks to 12 years of age with acute pneumonia. The diagnosis was based on clinical and/or radiological evidence. Apart from routine investigations i.e. Mantoux test and X-ray chest, specimens of blood, throat swab and lung aspirate were cultured to isolate the etiological organism. Serum was tested for the presence of CRP. They reported that out of 41.4% CRP positive cases, bacterial etiology was found in 22 cases (75.8%), while 13 cases (36.2%) showed a bacterial etiology out of 41 (36.8%) CRP negative cases. They also reported that out of 70 cases, CRP was found to be positive in 29 cases, out of which bacterial etiology was found in 22 cases which is statistically highly significant ($P < 0.001$).
D. CRP level in other neonatal infections:

Salra et al (1985) studied 76 cases of neonatal infections. Serum CRP was estimated and results compared with other indicators of infections viz. TLC, DLC and bacteriological culture. Leucocytosis was observed in 68.4% cases, bacterial culture was positive in 69.7% cases. CRP was as good as index of neonatal infections as bacterial culture in cases of septicemia, Reitters disease, bronchopneumonia, pyogenic meningitis, urinary tract infection and acute osteitis. In umbilical sepsis and purulent conjunctivitis CRP test was less reliable. In umbilical sepsis out of 25 cases, only 19 cases showed a positive CRP test, while all the 25 cases showed a positive bacterial culture. In purulent conjunctivitis out of 5 cases, 4 showed a positive bacterial culture, while no case showed a positive CRP test. They considered CRP value 10 μg/ml as positive.

They also evaluated CRP test after one week of antibiotic treatment. In 9.2% cases, CRP was positive, while the bacterial culture was sterile in 100% cases. Of those cases, in which CRP test remained positive after one week of antibacterial treatment, there were 3 cases of septicemia in whom blood culture had become sterile on second investigation. Two cases out of three died eventually during second week. The third case improved clinically and CRP test also became negative after 14 days of antibacterial
therapy. Of the four cases of septic meningitis, three cases improved clinically as well as bacteriologically and CRP test also became negative.

Paul and Singh (1986) reported certain indirect early markers of neonatal infections, i.e., total leucocyte count, band count to total neutrophil ratio, morphological changes in neutrophil, mini L.R, acute phase proteins, nitroblue tetrazolium test and limulus lysate assay. They evaluated that CRP was the best indicator amongst indirect indicators. A level of more than 4 mg/ml was considered abnormal in neonates. They also reported that CRP level have sensitivity 87.5% and specificity 83.3% in neonatal infections.

Singh et al (1987) evaluate a sepsis screen in the diagnosis of neonatal sepsis by studying micro L.R., gastric aspirate for polymorphs, absolute neutrophil count, band neutrophil count ratio and CRP to show the relative efficacy of these tests. A total of 100 babies were studied, of which seventy-nine babies were of clinically suspected sepsis and 21 asymptomatic babies were taken as control. Blood was obtained by a heel lancet using an autolet. Out of 79 cases of suspected sepsis, 22 grew one or more than one pathogenic organism in the blood and 7 patients, though culture negative, had histopathologic evidence of sepsis. Out of 20 bacteriologically negative cases, 21 were strongly suspected to be septic on clinical grounds.
supported by other laboratory investigations. However in 29 babies, clinical and laboratory investigations excluded sepsis, despite suspicion of sepsis. Bacteriological profile showed the growth of klebsiella pneumoniae in majority of cases. The sensitivity and specificity of different tests taken alone and in combination was determined. They found in their study that CRP was the single most sensitive 90% and specific (91%) test. Amongst the various combinations, they found absolute neutrophil count + CRP was the most sensitive combination (77%) and band count/total neutrophil count more than 0.2 + CRP was the most specific one 92%. CRP was found to be 100% specific test when done alone but with a combination of two or more tests, there were 9% chances of over-diagnosing non-infected cases as infected. However, using a combination of three or more tests, they found 100% specificity. The tests were designated as positive if absolute neutrophil count was found suggestive of infection (Monroe et al, 1979), micro ESR > 14 mm in the first hour (Adler et al, 1975). CRP positive by latex agglutination, i.e. 0.8 mg/dl, gastric aspirate polymorphs of more than 75% (Yeung et al, 1972) and band cell/total neutrophil count > 0.2 (Philips et al, 1980).

8. CRP level in UTI:

Hallerstein et al (1982) studied 45 girls. Thirty seven were studied during one infection, seven during two,
and one during three urinary tract infections. At the
time of diagnosis, the girls ranged in age from 4 to 19 years,
39 of the patients were between 5 and 10 years of age.
The three specimens of urine obtained following bladder
sterilisation and washout from the girls who had clinical
signs of pyelonephritis but an undetermined site of
infection showed 130, 520 and 580 colonies/ml. Four of
the six girls with upper urinary tract infections by the
bladder washout test and clinical signs of acute
pyelonephritis had serum CRP concentration between 67
and 231 ugm/ml. The patient with clinical signs of acute
pyelonephritis in whom the site of infection was not
localized by the bladder washout test had a serum CRP
concentration of 75.9 ugm/ml.

Three of the girls with lower urinary tract
infections by the bladder washout test had serum CRP
concentrations greater than 30 ugm/ml, and one had a
CRP value of 30 ugm/ml. The patient with the serum CRP
concentration of 30 ugm/ml had asymptomatic bacteriuria.
One girl with clinical cystitis had a serum CRP
concentration of 35.6 ugm/ml. The girl with non-localizing
symptoms and a lower urinary tract infection by the
bladder washout test has a history of many urinary tract
infections. The temperature was 37.9° orally at the time
of the bladder washout test. She presented with a vague
history of pain in right side of abdomen and of tiredness.
The serum CRP concentration was 54.9 ug/ml. Serum CRP values greater than 30 ug/ml had renal bacteriuria, giving a predictive value of 57% for a positive test. Serum CRP concentration of 30 ug/ml or less were localized to the lower urinary tract, giving a predictive value of 83% for a negative test.

Recent Advances in CRP:

Mold et al (1981) reported that CRP is known to be protective against pneumococcal infection in normal as well as antibody suppressed mice.

Whitehead et al (1983) isolated a CRP specific human complementary DNA. It is now known that the CRP gene is located on chromosome-1.

Mantsouranis et al (1984) have very recently been able to synthesize human CRP in vitro. This discovery has immense potentials particularly in the treatment of neonatal infections.
<table>
<thead>
<tr>
<th>Methods</th>
<th>Concentration of CRP can be measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Capillary precipitation reaction (Nilsson, 1961)</td>
<td>10 micro gm/ml</td>
</tr>
<tr>
<td>2. Double diffusion latex agglutination reaction (Czocherlony, 1958)</td>
<td>0.5 micro gm/ml</td>
</tr>
<tr>
<td>3. Single radial immunodiffusion (Mancini, 1965)</td>
<td>2 micro gm/ml</td>
</tr>
<tr>
<td>4. Radio-immuno assay (Ritchie, 1975)</td>
<td>0.003 micro gm/ml</td>
</tr>
<tr>
<td>5. Radio-electro-immunodiffusion (Kindmark, 1976)</td>
<td>0.001 micro gm/ml</td>
</tr>
</tbody>
</table>

Nilsson et al (1968) studied 835 randomly selected middle-aged men for the determination of CRP, by means of double diffusion latex agglutination test and precipitation in capillary tubes. With the gel diffusion technique 84% of the sera were shown to contain CRP, whereas CRP could be demonstrated in only 25% by the capillary tube precipitation test. The results obtained with the latex technique were compared with the CRP concentration as determined by the single radial immunodiffusion (halo) technique. It was concluded that the capillary tube precipitation test is inferior to immunodiffusion methods regarding sensitivity, precipitation