12.12.1 The acute phase response and C- reactive p

12.12.1 The acute phase response and C- reactive protein 2199

12.12 The acute phase response, hereditary periodic fever syndromes, and amyloidosis CONTENTS 12.12.1 The acute phase response and C-reactive protein 2199 Mark B. Pepys 12.12.2 Hereditary periodic fever syndromes 2207 Helen J. Lachmann, Stefan Berg, and Philip N. Hawkins 12.12.3 Amyloidosis 2218 Mark B. Pepys and Philip N. Hawkins 12.12.1 The acute phase response and C-reactive protein Mark B. Pepys ESSENTIALS The acute phase response—trauma, tissue necrosis, infection, inflam- mation, and malignant neoplasia induce a complex series of non-specific systemic, physiological, and metabolic responses including fever, leucocytosis, catabolism of muscle proteins, greatly increased de novo synthesis and secretion of a number of 'acute phase' plasma proteins, and decreased synthesis of albumin, transthyretin, and high- and low-density lipoproteins. The altered plasma protein concentration profile is called the acute phase response. All endo- thermic animals mount a similar response, suggesting that it may have survival value, and increased availability of proteinase inhibi- tors, complement, clotting, and transport proteins presumably enhances host resistance, minimizes tissue injury, and promotes re- generation and repair. Acute phase proteins—these are mostly synthesized by hepato- cytes, in which transcription is controlled by cytokines including interleukin 1, interleukin 6, and tumour necrosis factor. The circu- lating concentrations of complement proteins and clotting factors increase by up to 50 to 100%; some of the proteinase inhibitors and α1-acid glycoprotein can increase three- to fivefold; but C-reactive protein (CRP) and serum amyloid A protein (an apolipoprotein of high-density lipoprotein particles) are unique in that their concen- trations can change by more than 1000-fold. C-reactive protein—this consists of five identical, nonglycosylated, noncovalently associated polypeptide subunits. It binds to au- tologous and extrinsic materials which contain phosphocholine, including bacteria and their products. Ligand-bound CRP activates the classical complement pathway and triggers the inflammatory and opsonizing activities of the complement system, thereby con- tributing to innate host resistance to pneumococci and probably to

recognition and safe ‘scavenging’ of cellular debris. Clinical features—(1) determination of CRP in serum or plasma is the most useful marker of the acute phase response in most inflam- matory and tissue damaging conditions. It is a stable analyte, easy to measure, and has proven value in monitoring therapeutic responses. (2) Acute phase proteins may be harmful in some circumstances. Sustained increased production of serum amyloid A protein can lead to the deposition of AA-type, reactive systemic amyloid, a serious and if untreated, usually fatal condition that can complicate chronic infective and inflammatory diseases. CRP, through its capacity to acti- vate complement, can exacerbate ischaemic (and possibly also other forms) of tissue damage. Introduction The principal plasma proteins that change in concentration in the acute phase response are listed in Table 12.12.1.1. C-reactive protein (CRP) has particular clinical utility as a robust and easily measured systemic marker for monitoring the extent, activity, and response to therapy in many inflammatory, infective, and tissue-damaging conditions. C-reactive protein CRP was the first protein to be discovered that behaves as an acute phase reactant, and was named for its calcium-dependent inter- action with the somatic C-polysaccharide of pneumococci, in which CRP recognizes phosphocholine residues. CRP also binds to other

 substances that contain phosphocholine, including phospho- lipids, some plasma lipoproteins, and the plasma membranes of damaged cells. In addition, CRP binds specifically to small nu- clear ribonucleoprotein particles when these are exposed in dead or damaged cells. The CRP molecule consists of five identical, nonglycosylated, noncovalently associated polypeptide subunits, each of mass 23027 Da and containing 206 amino acid residues. The subunits have a flattened β-sheet jellyroll fold with a single intrachain disulphide bond, and are arranged in an annular config- uration with cyclic pentameric symmetry. There is a single calcium-dependent ligand-binding site on the medial aspect of each subunit, all located on the same planar face of the molecule. A distinct but closely related plasma protein, serum amyloid P component, which is not an acute phase protein in humans, has a very similar molecular structure with the same fold, characteristic of the lectin-fold super- family. CRP and serum amyloid P component belong to the phylo- genetically conserved pentraxin family. Although many properties of human CRP have been reported in experimental systems, no structural polymorphism of human CRP has been observed nor has any human CRP deficiency been described, so the actual functions of human CRP in humans are not yet known. Ligand-bound CRP activates the classical complement pathway via C1, and can trigger the inflammatory and opsonizing activ- ities of the complement system. A significant biological function of CRP may thus be to recognize and scavenge cellular debris, promoting its safe clearance and helping to maintain tolerance to potential autoantigens. CRP may also contribute to innate resist- ance against infection with bacteria that express phosphocholine, and experiments in CRP knockout mice show that CRP is essential for innate host defence against pneumococci. On the other hand, complement activation by CRP binding to damaged tissue exacer- bates ischaemic and possibly other forms of tissue injury. However, in healthy subjects, infusion of pure CRP has no proinflammatory, proatherogenic, or any other adverse effects. Serum concentration of CRP Circulating CRP is synthesized by the hepatocytes under tran- scriptional regulation by the proinflammatory cytokines, especially IL-6. CRP is a trace protein in apparently normal healthy individ- uals, the median value in adults being 0.8 mg/litre, with an inter- quartile range of 0.3 to 1.7 mg/litre. Among apparently healthy subjects, 90% of CRP values are less than 3 mg/litre and 99% less than 10 mg/litre. Serum CRP concentrations are lower in healthy newborns, but reach adult values within a few days. Normal values in the indigenous Japanese population are substantially lower than in white Caucasians. Serial studies of normal

subjects and of monozygotic and dizygotic twins show that each individual's base- line CRP value is rather constant and is substantially genetically determined. Baseline CRP is strongly correlated with body mass index, especially abdominal obesity, and is also higher in smokers, hypertensive subjects, diabetics, those who take little or no exercise, and individuals from the lower socioeconomic classes. Occasional higher values of CRP seen in ostensibly healthy people almost cer- tainly reflect intercurrent subclinical pathology. In large surveys of the unscreened general population, there is a trend towards higher values with increasing age, with the median value rising to about 2 mg/litre, and this likely reflects the higher incidence of many dif- ferent pathological processes with age. Serum CRP concentration rises rapidly in the acute phase re- sponse and can exceed 300 mg/litre by 48 h after a severe stimulus such as acute systemic bacterial infection, major trauma or surgery, or acute myocardial infarction. With uncomplicated resolution of injury or effective treatment of infection, the circulating CRP con- centration generally falls equally rapidly. The speed of change and incremental range of CRP concentra- tions are exceptional among all the acute phase proteins, apart from serum amyloid A protein, which behaves in a similar fashion. The half-life of CRP in the circulation is 19 h and is constant in all conditions, regardless of the presence of an acute phase re- sponse or its cause. In contrast to other acute phase proteins, such as clotting factors, complement proteins, transport proteins, and proteinase inhibitors, CRP does not undergo major local seques- tration or consumption, fragmentation, or complex formation. This means that, unlike most of the other acute phase reactants, the single major determinant of the circulating concentration of CRP is its rate of synthesis. Since this in turn is dependent on the intensity of the acute phase stimulus, the serum CRP level usually closely reflects the extent and activity of disease. These properties underlie the value in clinical practice of precise measurement of the serum CRP concentration. Drug or other treatments do not affect CRP production unless they also affect the disease process that is responsible for the induction of CRP synthesis. The only ex- ception is combined ciclosporin and steroid treatment given after renal transplantation. This suppresses the CRP response to renal allograft rejection, though not that provoked by infection. The only physical condition that seriously interferes with the capacity to in- terpret CRP levels is severe hepatocellular impairment, since CRP is made exclusively in the liver. Table 12.12.1.1 Plasma protein concentrations in the acute phase response Protein Increased Decreased Proteinase inhibitors α1-antitrypsin Inter α-antitrypsin α1-antichymotrypsin Coagulation proteins Fibrinogen Prothrombin Factor VIII Plasminogen Complement proteins Cls Properdin C2, B C3, C4, C5 C56 C1INH Transport proteins Haptoglobin Haemopexin Caeruloplasmin Miscellaneous C-reactive protein Albumin Serum amyloid A protein Transthyretin (prealbumin) Fibronectin High-density lipoprotein α1-acid glycoprotein Low-density lipoprotein Gc globulin

12.12.1 The acute phase response and C-reactive protein 2201 Conditions associated with marked increases in serum CRP concentration Most tissue-damaging processes, infections, inflammatory diseases of unknown aetiology, and malignant neoplasms are associated with a major acute phase response of CRP. CRP production is exquisitely sensitive to all these pathologies and is thus a nonspecific response to disease. It can never, on its own, be used as a diagnostic test. However, if the CRP result is interpreted in the light of full clinical information about the patient, it can provide exceptionally useful in- formation for clinical management. Thus in nearly all the conditions listed in Box 12.12.1.1 the CRP concentration reflects quite precisely the extent and activity of disease. With deterioration, the CRP value rises, whereas with spontaneous or therapeutically induced remis- sion, the CRP value falls, and it thereby supplies an objective index of progress that is rarely available in any other way. Infection Most forms of systemic microbial infection are associated with

high serum CRP concentrations and, although the peak values attained in different patients cover a wide range, serial assays in individual subjects usually show an excellent correlation between the CRP value and the severity of disease and its response to treatment. Acute sys- temic Gram-positive and Gram-negative bacterial infections are among the most potent stimuli for CRP production. Systemic fungal infections occurring in immunodeficient hosts are also associated with high CRP values, whereas the concentrations in chronic bac- terial infections such as tuberculosis and leprosy are usually rather lower, though nevertheless still markedly raised. Uncomplicated viral infections, particularly meningitis, may induce only a very modest response or none at all. Clinical rhinovirus infection (common cold) and influenza are associated with minor increases in CRP concentration in a proportion of individuals, though this may reflect secondary bacterial infection. However, severe influenza virus, sys- temic cytomegalovirus or herpes simplex infections of immunosup- pressed patients cause a major CRP response. Little is known about the CRP response to metazoan parasitic infestation in otherwise healthy subjects but malaria, especially Plasmodium falciparum in- fection, is associated with high CRP values, as are Pneumocystis spp. and Toxoplasma spp. infections in immunodeficient patients. Minor or localized low-grade infection may not stimulate CRP production greatly, but the major CRP response in acute, serious bacterial infection is almost invariable and is present at all ages from premature neonates to older people. It also occurs in patients who are immunosuppressed or immunocompromised, whether by a pri- mary disease such as leukaemia, lymphoma, or other malignancy, by AIDS, or by treatment with cytotoxic drugs, corticosteroids, or ir- radiation. This is of particular importance in the very young, in older people, in compromised hosts, and in any other patient in whom the usual clinical signs and symptoms of infection, including fever and neutrophil leucocytosis, may be masked or lacking (Figs. 12.12.1.1 and 12.12.1.2). Furthermore, at the onset of bacterial infection, es- pecially in patients who are otherwise well following elective surgery or myocardial infarction, the CRP response frequently precedes clinical symptoms, including fever, by up to 24 to 48 h. Once infection is diagnosed or suspected and antimicrobial treatment has been commenced, frequent monitoring of the serum CRP concentration provides an objective means of assessing the Box 12.12.1.1 Conditions associated with major increases in serum CRP concentration • Infection and immunological complications of infection • Inflammatory disease:

— Rheumatoid arthritis

— Juvenile chronic (rheumatoid) arthritis

— Ankylosing spondylitis

— Psoriatic arthritis

— Systemic vasculitis

— Polymyalgia rheumatica

— Reiter’s disease

— Crohn’s disease

— Familial Mediterranean fever, CAPS • Necrosis:

— Myocardial infarction

— Tumour embolization

— Acute pancreatitis • Trauma:

— Surgery

— Burns

— Fractures • Malignant neoplasia:

— Lymphoma

— Hodgkin’s disease

— Carcinoma, sarcoma Fig. 12.12.1.1 A 69-year-old diabetic man was admitted with a 3-day history of confusion, cough, and incontinence of urine. There was clinical and radiological evidence of a left-sided pneumonia and although both the temperature and white cell count remained normal, the CRP value was high (119 mg/litre), confirming the suspicion of infection. Following treatment with amoxicillin, 250 mg three times daily, the CRP concentration fell rapidly, in a characteristic exponential manner, and he made a speedy recovery with return of continence and improved mental state.

section 12 Metabolic disorders 2202 response, which is often not otherwise available. Effective therapy is associated with a rapid, exponential fall in CRP value, with a half- life of about 24 h, and occurrence of this pattern is an encouraging prognostic sign (Fig. 12.12.1.2). Normalization of the CRP usually corresponds to clinical cure of the infection and may thus be used to determine the necessary duration of antimicrobial therapy. On the other hand, especially in neutropenic or immunodeficient pa- tients, persistent elevation of CRP at the end of a course of anti- biotics often presages relapse or recurrence of infection. When bacterial infection is complicated by abscess formation or for any other reason is less readily eradicated by antimicrobial drugs, the serum CRP concentration may remain elevated or may fall lin- early rather than exponentially during treatment. Such a pattern should raise questions regarding the dosage of the drugs, the sen- sitivity of the organism, and/or stimulate a diagnostic search both for localized pus and for other underlying, noninfective pathologies such as malignancy. Indeed, in the absence of one of the chronic idio- pathic inflammatory conditions which are known to be associated with high CRP concentrations (see later subsections), the persist- ence of a raised serum CRP concentration is usually a grave prog- nostic sign indicating the presence of either uncontrolled infection and/or other serious pathology likely to cause death. However, with alteration in the antimicrobial drug regimen or the evacuation of pus or elimination of other pathology, the rapid fall in CRP that may then be observed is an encouraging objective sign of clinical improvement. These considerations apply at all ages and regardless of intercur- rent pathology, with the exception of severe hepatocellular impair- ment. In view of the very small amount of serum required for the assay and the speed and precision of automated CRP immunoassays, it is apparent that routine monitoring of serum CRP makes a valu- able contribution to the recognition and management of infectious diseases. Situations in which these applications have been well docu- mented are listed in Box

12.12.1.2. Meningitis is of particular interest in view of its potential severity and the importance of rapid diagnosis and appropriate treatment. Bacterial meningitis is associated with much higher serum CRP levels at presentation than cases of aseptic or proven viral meningitis. The latter frequently have CRP concentrations within the normal range or which are only very slightly raised, unless they develop sec- ondary bacterial infective complications; patients with tuberculous meningitis have intermediate values. Appropriate therapy for either bacterial or tuberculous meningitis causes the CRP concentration to fall, and this can be used to monitor objectively the response to treatment. Baseline CRP values are much lower at birth and for the first few days than in older children or adults. Also, neonatal infections pro- gress much more rapidly and can have a fatal outcome before the CRP response has produced concentrations detectable in routine assays. It is therefore essential to use highly sensitive methods cap- able of detecting and precisely measuring CRP in the range 0.05 to 5.0 mg/litre, otherwise the critical initial acute phase response to in- fection will be missed. Inflammatory disease Most of the chronic inflammatory diseases of unknown aetiology (Box 12.12.1.1), with some notable exceptions described later in this chapter, are associated with high CRP values when they are ac- tive. Serial measurements of CRP in individuals with any of these Fig. 12.12.1.2 An 86-year-old woman had been refusing food and drink for 6 weeks. She was dehydrated, but rehydration in hospital failed to improve her mental state. She was paranoid and refused nursing and medical care. Paraphrenia was diagnosed and deterioration continued. A CRP concentration of 130 mg/litre and a white cell count of 13.5 × 109/litre were then found. Chest radiography, normal on admission, now showed a cavitating lesion from which 150 ml of pus were aspirated. Intravenous ampicillin reduced neither the CRP nor the white cell count, prompting a change of therapy to gentamicin and metronidazole. Streptococcus equinus was finally identified in the pus and treatment was changed to benzyl penicillin alone. The CRP value then fell exponentially but rather slowly. The patient’s clinical and mental state gradually improved and she was eventually discharged. Box 12.12.1.2 Applications of serum CRP measurement in infectious disease • Pyogenic bacterial infections, including:

— bacteraemia and septicaemia in children and adults

— bacteraemia and septicaemia in neonates

— bacterial and other infections in immunosuppressed patients

— bacterial infections after major elective surgery or other invasive procedures

— infective relapse after abdominal surgery for sepsis

— peritonitis in patients on chronic ambulatory peritoneal dialysis

— acute appendicitis (differential diagnosis)

— evaluation of antibiotic therapy for female pelvic infection

— laryngotracheitis/pharyngitis/epiglottitis in children

— chorioamnionitis after premature rupture of membranes

— disseminated versus localized gonococcal infection

— infection precipitating sickle cell crisis • Meningitis (viral < tuberculosis < bacterial) • Deep fungal infection

12.12.1 The acute phase response and C-reactive protein 2203 diseases generally reflect the extent and activity of their condition as determined by clinical examination and by other laboratory tests. Rheumatoid arthritis is the most common and important disease in this group and the correlation between CRP values in individual patients and the extent and activity of arthritis is very well estab- lished. Importantly, there are appreciable differences between the CRP concentrations attained in different subjects with apparently similar severity of arthritis, but in each case the CRP value always reflects current disease activity. Furthermore, CRP values precisely predict future progression of bone erosion and joint damage. Left unchecked, high CRP values are inevitably followed by progressive erosive disease, whereas treatments that reduce the CRP concentra- tion retard or arrest this process. In some of the inflammatory disorders, for example, systemic vas- culitis or Crohn's disease (Fig. 12.12.1.3), unlike rheumatoid arth- ritis, the pathology is relatively inaccessible to direct examination, and serum CRP measurement provides the best available, objective index of disease activity. Furthermore, the presence or absence of a CRP response can distinguish between symptoms or organ dysfunc- tion that are due to currently active inflammation and those that are the consequence of fibrosis and scarring from previous episodes. This can be very important when treatments include steroids and other powerful and potentially hazardous immunosuppressive, anti- inflammatory, and cytotoxic drugs. It permits precise titration of dosages and may help to avoid excessive or unnecessary use. Induction of clinical remission and control of the underlying dis- ease process is associated with prompt normalization of the CRP. However, CRP also becomes abnormal with intercurrent infection, a common complication of some of these disorders and their treat- ments, and this serves to focus diagnostic attention often before the infection has become too severe or even before it is clinically evident. Monitoring the CRP response to antimicrobial therapy can then help to confirm the diagnosis and the efficacy of therapy. Persistent elevation of the CRP after eradication of infection may indicate relapse of the underlying inflammatory disease, requiring additional anti-inflammatory treatment. Necrosis Untreated acute myocardial infarction is invariably associated with a major CRP response, as is elective embolization leading to necrosis of tumours in the liver and elsewhere. The peak concentration of CRP occurs about 50 h after the onset of pain in acute myocardial infarc- tion patients who do not undergo revascularization, and is earlier and smaller following effective early revascularization. CRP produc- tion usually correlates in magnitude, though not in timing, with the peak serum concentration of the specific myocardial markers, cre- atine kinase MB and troponin. In patients who recover uneventfully, the CRP value falls rapidly towards normal in the usual exponential fashion. However, complications such as persistent cardiac dysfunc- tion, further infarction, aneurysm formation, intercurrent infection, thromboembolism, or postinfarction syndrome are associated with either persistently raised CRP values or a secondary increase after the initial decrease. Myocardial rupture is seen only in patients with high peak CRP values (>200 mg/litre) and the peak CRP concentration after acute myocardial infarction strongly predicts overall outcome, including survival, in the short, medium, and long term. Stable angina and coronary arteriography investigations do not stimulate CRP production, whereas other relevant causes of chest pain, including pulmonary embolism, pleurisy, or pericarditis, pro- duce raised CRP values. Routine assays of CRP after infarction or in patients with chest pain may thus assist in diagnosis

and in the recognition and management of complications, including iatrogenic infection associated with invasive cardiovascular monitoring. Serum CRP concentrations closely reflect the severity and progress of acute pancreatitis, providing a better guide to intra-abdominal events than other markers such as leucocyte counts, erythrocyte sedimentation rate (ESR), temperature, and the plasma concentra- tions of antiproteinases. A CRP concentration greater than 100 mg/ litre at the end of the first week of illness is associated with a more prolonged subsequent course and a higher risk of the development of a pancreatic collection. Serial CRP measurements can therefore guide the use of appropriate imaging techniques and help to confirm resolution before discharge from hospital. Trauma and surgery The CRP concentration always rises after significant trauma, sur- gery, or burns, peaking after about 2 days and then falling towards normal with recovery and healing. Infections or other tissue- damaging complications alter this normal pattern of CRP response Severe Moderate Mild Improving 40 0 (mg/ day) (183) Prednisolone C-reactive protein (mg/l) ESR (mm in 1h) 100 0 Stool frequency 16 12 8 4 0 July 1979 (days) Hospital admission 1979 (months) 1980 59 60 61 62 63 64 65 66 67 Body weight (kg) Improving 16 14 2 1 2 1 0 1 0 1 2 8 8 6 Fig. 12.12.1.3 A 26-year-old man with pancolonic Crohn’s disease.
He was admitted with severe exacerbation; temperature 38°C; pulse
110 beats/min; 16 stools per day; haematocrit 41.5%, leucocytes
13.8 × 109/litre. Rectal mucosa severely inflamed with histiocytic granulomas on biopsy. Rapid improvement occurred with oral and rectal prednisolone, ampicillin, and metronidazole, with complete clinical and histological remission on day 11. A relapse 5 months later responded promptly to a short course of oral and rectal prednisolone. CRP and ESR values were both high during the initial exacerbation. The rapid response to treatment was paralleled by a prompt fall in CRP concentration, whereas the ESR responded more slowly. Despite clinical remission and a normal ESR, the CRP remained slightly elevated, suggesting persistent low-grade inflammatory activity, and it rose further during a subsequent relapse when the ESR did not change. Reproduced from Fagan A, et al. (1982). Serum levels of C-reactive protein in Crohn’s disease and ulcerative colitis. Eur J Clin Invest, 12, 351–9, with permission.

section 12 Metabolic disorders 2204 and the failure of the CRP to continue falling, or the appearance of a second peak, may precede clinical evidence of intercurrent infection by 1 to 2 days. Serial prospective CRP measurement is therefore ad- visable in such patients. Malignancy Most malignant tumours, especially when they are extensive and metastatic, induce an acute phase response. This is particularly so with those neoplasms that cause systemic symptoms such as fever and weight loss, for example, Hodgkin’s disease (stage B) and renal carcinoma, but raised CRP values are seen with many others. In some studies, notably of prostatic carcinoma and bladder car- cinoma, the CRP concentration at presentation has been found to correlate with the overall tumour load and also with the prognosis, being higher for a given mass of tumour in those patients who sub- sequently fare worse. The CRP value may also correlate better with progress and regression of tumour than other, more specific tumour markers. However, given the nonspecific nature of the acute phase response and the limited number of adequate studies performed a definite role for CRP measurement in the management of cancer patients, other than in cases of intercurrent infection, has not been established. Allograft rejection In the era before routine immunosuppression with combined ciclosporin and steroid treatment, rejection episodes following renal allografting were generally associated with increased production of CRP. However, this treatment almost completely suppresses the CRP response to allograft rejection. In contrast, the acute phase response of serum amyloid A protein is unaffected and, importantly, intercur- rent

infection still stimulates greatly increased production of both CRP and serum amyloid A protein. Conditions associated with minor increase in serum CRP concentration Despite unequivocal evidence of active inflammation and/or tissue damage, the conditions listed in Box 12.12.1.3 are usually associ- ated with only minor increases in the serum CRP concentration, and in many cases it may even remain normal in the face of severe disease. The contrasts of systemic lupus erythematosus (SLE) with rheumatoid and other arthritic conditions shown in Box 12.12.1.1, and between ulcerative colitis and Crohn's disease, are very striking. However, intercurrent microbial infection provokes a major CRP response in all the conditions shown in Box 12.12.1.3, and this is of great value in diagnosis and management, especially in SLE and leukaemia. The basis of the apparently selective failure of the acute phase response of CRP (which is also shown by serum amyloid A protein) is not known, but presumably involves defect(s) in the pathways that mediate the acute phase response to autologous in- flammation and tissue damage. Pyrexia is common in SLE and may be caused by microbial in- fection or by activity of the lupus itself. Both SLE and its treatment predispose to infection, and steroids and immunosuppressive drugs can mask the usual symptoms and signs of infection. Furthermore, infection can trigger exacerbations of SLE. This is a serious clinical situation and infection remains one of the most common causes of death in patients with SLE. CRP values of 60 mg/litre or more are very rare in SLE in the absence of infection, whereas values below 60 mg/litre are seen in patients with documented infection only when it is rather mild and often localized (e.g. to the skin or lower urinary tract). Differential diagnosis and management of fever in SLE are thus considerably improved by the measurement of serum CRP concentration (Fig. 12.12.1.4). Box 12.12.1.3 Conditions associated with minor increases in serum CRP concentration • Systemic lupus erythematosus • Scleroderma • Dermatomyositis • Ulcerative colitis • Leukaemia • Graft-versus-host disease 41 37 °C 150 100 50 0 November ESR C-reactive protein ESR (mm in first hour) (mg/l) Fever Rash Arthritis Cefuroxime Gentamicin Abdominal pain Diarrhoea E. coli septicaemia Pulse doses methylprednisolone Prednisolone 30 mg/day Jan Dec 28 22 16 4 Sept Jun 0 1 ra M Fig. 12.12.1.4 A 12-year-old girl with a 3-year history of SLE; recurrent febrile episodes, polyarthritis, cutaneous vasculitis, and episodes of asymptomatic bacteriuria. Intermittent treatment was with prednisolone, azathioprine, and plasma exchange. Serum CRP concentration was only marginally increased throughout but erythrocyte sedimentation rate was persistently high. Fever recurred with diarrhoea and abdominal pain. All microbial cultures were negative except for growth of Escherichia coli from the urine. Despite oral cefalexin and prednisolone her condition deteriorated, with severe neutropenia, probably due to azathioprine. The CRP value rose from 36 to 101 mg/litre and then 137 mg/litre, and at this stage her blood culture grew Escherichia coli. Intravenous antibiotics were given and the serum CRP concentration fell rapidly, but there was little clinical improvement. Active SLE appeared then to be the sole cause of the fever and this was confirmed by the development of a diffuse vasculitic rash and polyarthritis. Three pulse doses of methylprednisolone were given intravenously on successive days and produced a dramatic improvement in her clinical state with resolution of the fever. This case illustrates (1) the differential response of CRP to fever resulting from activity of SLE alone and fever due to bacterial infection; (2) the rapid response of CRP both to the onset and to the effective treatment of serious bacterial infection; and (3) the failure of ESR measurements to provide any useful information in this complex and rapidly evolving clinical situation. Reproduced from Pepys MB, Langham JG, de Beer FC (1982). C-reactive protein in systemic lupus erythematosus. Clin Rheum Dis, 8, 91–103, with permission.

 The reason why leukaemia patients fail to mount more than a modest CRP response, even during induction therapy when there is massive death of leukaemia cells, is not known. However, the CRP response to infection is normal. Since all febrile episodes in leu- kaemia must initially be treated as infective, the main value of CRP monitoring is to determine the response to therapy and assist in de- cisions about its duration. Acute or chronic graft-vs-host disease after bone marrow transplantation is usually associated with only a modest CRP response, if any. However, the immunosuppressive treatments used to prevent bone marrow rejection and to control graft-vs-host disease render the patients susceptible to intercurrent infections, often with unusual microorganisms, and these are always associated with high CRP values. CRP monitoring is therefore very useful in post-transplant management. Interpretation of clinical serum CRP measurements The CRP response is not specific and CRP measurements on their own can therefore never be diagnostic of any particular condition, nor should they be used in isolation for any other clinical purpose. The CRP value can only be interpreted in the light of all other avail- able clinical and laboratory information. Provided this is done, it can make a most useful contribution to overall assessment of the patient and determination of the best management. The applications fall into three main categories: • Screening for organic disease • Monitoring of extent and activity of disease—infection, inflam- mation, malignancy, and necrosis • Detection and management of intercurrent infection Screening for organic disease CRP production is a very sensitive response to organic disease. A normal CRP value therefore eliminates many possible types of path- ology and is a reassuring finding. Those serious conditions that stimu- late CRP production only weakly, if at all, for example, SLE, ulcerative colitis, and leukaemia, are all readily recognized by clinical examin- ation and simple routine investigations. The presence of a raised CRP value is unequivocal evidence of active pathology, though this may not necessarily be the cause of the complaint for which the patient pre- sented. Such a finding, in the absence of other obvious abnormality, warrants a repeat CRP assay after a few days when a trivial cause such as an upper respiratory tract infection will have resolved. Further in- vestigation of a persistently raised CRP concentration will then de- pend on the severity of the complaint and other clinical findings. Monitoring extent and activity of disease Once the diagnosis is established, in those diseases which cause major CRP production, serial measurements reflect activity and re- sponse to treatment and can be used for monitoring. However, they can only be interpreted provided other possible intercurrent causes of an acute phase response, particularly infections, are excluded. Detection and management of intercurrent infection Production of CRP is a very sensitive response to most forms of infection and a raised concentration is thus a useful guide to the possible presence of infection in otherwise normal subjects or in- dividuals with a primary condition that predisposes to infection. In disorders that themselves increase the CRP concentration, the decision as to whether infection is present or not must depend on clinical examination and other laboratory tests; the role of CRP testing is then to demonstrate rapidly and objectively whether there is a response to whatever treatment is used. Effective antimicrobial therapy of infection is always associated with a prompt fall in the CRP, whereas persistent CRP production indicates continuing infec- tion and/or activity of the underlying disease. There is no other ob- jective test that yields this sort of information so accurately. Changes in the results of clinical examinations and tests of organ function usually lag hours or days behind the CRP response. Other considerations CRP and body temperature The acute phase response, which is best measured clinically by quan- tification of the serum CRP concentration, is part of the systemic re- sponse to disease. Monitoring of this same response by measurement of body temperature is an integral part of routine clinical manage- ment. CRP production is triggered by the same

cytokines that cause fever, and the serum CRP concentration is therefore in part a bio- chemical surrogate for the body temperature. However, the CRP re- sponse is not susceptible to the many vagaries of thermoregulation and of routine clinical measurement of body temperature. The precise numerical value of the CRP concentration and its changes over time reflect much more accurately than the temperature the intensity of the underlying stimulus. Furthermore, there is often a CRP response in the absence of fever, especially in neonates and older people, and also in many chronic inflammatory conditions at any age. There is thus a good case for charting serial serum CRP concentrations along- side the standard temperature chart in appropriate patients. CRP or ESR? The only other comparable nonspecific index of disease that is rou- tinely measured is the ESR. The ESR reflects, in part, the intensity of the acute phase response, especially that of fibrinogen and the α-globulins, but is also largely determined by the concentration of immunoglobulins, which are not acute phase reactants. These pro- teins all have half-lives of days to weeks. ESR thus changes very much more slowly than the CRP concentration, and it rarely reflects precisely the clinical status of the patient at the time of testing. ESR is also dependent on the number and morphology of the red cells, which bear no relationship to the acute phase response. In addition, there is a significant diurnal variation in ESR, depending on food intake, which is not seen in the CRP concentration. Finally, the dy- namic range of the ESR is much less than that of CRP concentration and the precision and reproducibility of ESR measurement is poor compared to the robust clinical chemistry immunoassays available for CRP. The ESR is therefore of limited use as an objective index of disease activity on which management decisions can be based. In all clinical situations that have been carefully evaluated, ran- ging from acute bacterial infections to the chronic remittent in- flammatory diseases, such as Crohn’s disease, rheumatoid arthritis, and other inflammatory arthropathies, and systemic vasculitis in its various forms, frequent prospective measurements of CRP reflect disease activity very much more closely than measurements of the ESR. However, the ESR remains a useful screening test for the detec- tion of paraproteinaemias, especially multiple myeloma, in which an acute phase response is often absent.

section 12 Metabolic disorders 2206 CRP and cardiovascular disease The 1994 report of a prognostic association between increased CRP and serum amyloid A protein values and outcome in severe un- stable angina, and the discovery of a significant predictive associ- ation between baseline CRP values in the general population and future coronary events, triggered an avalanche of work in this field. These observations became increasingly controversial, but the re- cent publications of very large-scale observational and genetic epidemiological studies have eventually resolved the major issues. The key questions are whether the measurement of baseline CRP concentration provides information useful for the assessment and management of cardiovascular disease risk, and whether CRP itself contributes to the pathogenesis of atherosclerosis, atherothrombosis, and/or ischaemic tissue injury. The possible involvement of CRP in atherogenesis was first sug- gested by the binding of CRP to low-density lipoprotein and the pres- ence of CRP in atherosclerotic lesions. In recent years, a wide range of proinflammatory and cell-activating effects have been claimed for CRP, based on in vitro studies with various cell types. Unfortunately, nearly all this work was done with commercial CRP preparations produced in recombinant bacteria, and none of the positive obser- vations have been reproducible with authentic pure human CRP isolated from human source material. The amazing range of potent proinflammatory and cell-activating properties ascribed to CRP is not consistent with the fact that neither the administration of large amounts of pure human CRP in normal healthy animals nor the 1000-fold natural acute phase response of CRP in patients are as- sociated with any such effects. Furthermore, intravenous

infusion of authentic, pure, pharmaceutical grade human CRP into healthy adult human volunteers had no proinflammatory, proatherogenic, or any other adverse effects. In experimental animal models of ath- erosclerosis, CRP either has no effect on atherogenesis in vivo or is atheroprotective. Human epidemiological studies of atherosclerosis burden have had varying results, but overall provide no compelling evidence for an association with CRP values. Baseline CRP values are significantly associated with all the known risk factors and pathogenetic mechanisms for coronary heart disease events, and about 70% of the variance in baseline CRP is ascribable to these factors. Although CRP concentration is thus not independently associated with cardiovascular disease risk, a statistically significant association remains even after maximal ad- justment. However, the level of association is markedly less than was originally reported and is comparable with the association with cardiovascular disease risk of other nonspecific systemic markers of inflammation, such as low plasma albumin, raised white cell count, ESR, and serum amyloid A protein. The Emerging Risk Factors Collaboration meta-analysis of 52 major epidemiological studies of baseline CRP values and cardiovascular disease prediction, showed that CRP measurement adds almost no useful information to risk assessment, potentially helping to prevent only one additional event over a period of 10 years for every 400–500 people screened. Also, since statins lower risk when administered at any level of low-density cholesterol and in all subgroups of the population, re- gardless of intercurrent disease or additional risk factors, there is no justification for the use of CRP measurement to select patients for statin treatment. Indeed, measuring the exquisitely nonspecific CRP in this context, without comprehensive review of a patient with a raised value, risks missing other important pathologies. The unfortunate conflation of association with causality triggered much speculation about whether CRP is a pathogenetic factor for cardiovascular disease events. However, Mendelian randomization genetic epidemiological studies looking at hereditary polymorphisms associated with higher or lower baseline CRP values all show no association with cardiovascular disease risk. This negative outcome is entirely consistent with the negative in vivo animal studies of CRP and atherogenesis. In contrast, experimental animal studies robustly show that human CRP can exacerbate pre-existing ischaemic injury via a complement dependent mechanism and that this can be blocked by experimental drugs that inhibit CRP function. Preliminary clinical studies of extra-corporeal absorption of CRP, to lower the circulating CRP concentration, are in progress in patients with acute myocardial infarction. Future testing of more effective novel CRP blocking drugs should demonstrate whether this mechanism is clinically relevant. Serum amyloid A protein Serum amyloid A protein, an apolipoprotein of high-density lipo- protein particles, is a marked acute phase reactant, its concentration rising from normal levels of about 2 mg/litre by as much as 1000- fold. It is essential to monitor and control serum amyloid A protein levels in patients with reactive systemic, AA type amyloidosis (see Chapter 12.12.3). It is a critical marker of disease control in patients with hereditary periodic fever syndromes, to ensure that they do not develop systemic AA amyloidosis. Serum amyloid A protein concen- tration is also the most sensitive marker of rejection episodes in renal allograft recipients and is useful in routine monitoring of these patients. FURTHER READING Boralessa H, et al. (1986). C-reactive protein in patients undergoing cardiac surgery. Anaesthesia, 41, 11–15. Casas JP, et al. (2008). C-reactive protein and coronary heart disease: a critical review. J Intern Med, 264, 295–314. C-reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC) (2011). Association between C reactive protein and cor- onary heart disease: mendelian randomisation analysis based on in- dividual participant data. BMJ, 342, d548. Elliott P (2009). Genetic loci associated with C-reactive protein levels and risk of coronary heart disease. JAMA, 302, 37–48. Emerging Risk Factors Collaboration (2009). C-reactive protein concentration and risk of coronary heart disease, stroke and mor- tality: an individual participant meta analysis. Lancet,

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