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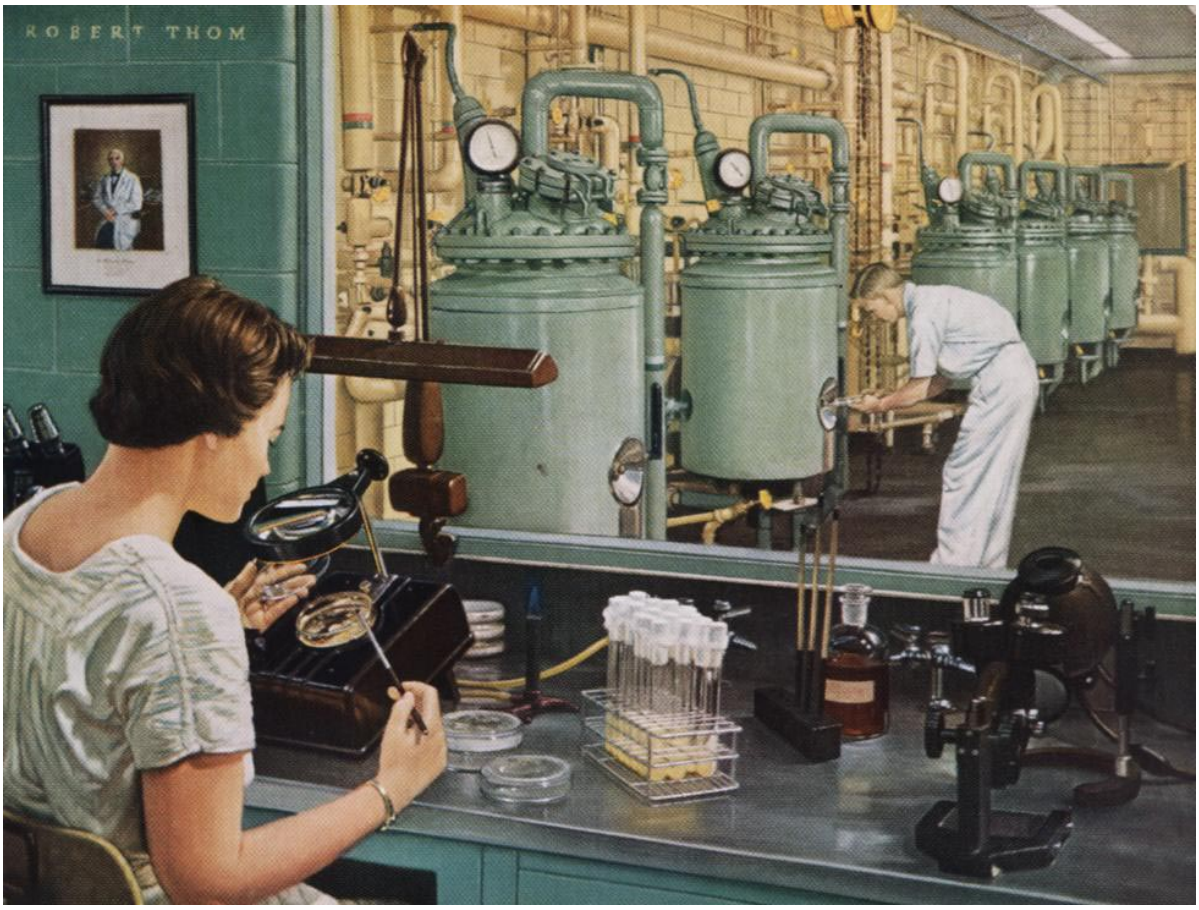

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Cover picture

The era of antibiotics

The development of penicillin in the 1940s brought new and dramatic methods of producing disease-fighting drugs, called antibiotics. Intensive research continues to find antibiotics that will conquer more of man's microbial enemies.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

George A. Bender, Director Robert A. Thom, Artist

Abnormal laboratory results

C-reactive protein

Summary

C-reactive protein elevation is part of the acute-phase response to acute and chronic inflammation. It outperforms erythrocyte sedimentation rate in terms of responsiveness and specificity for inflammation. While C-reactive protein elevation is suggestive of inflammation or infection in the appropriate clinical context, it can also occur with obesity and renal dysfunction. Conversely, a lack of C-reactive protein elevation in inflammation may be seen with hepatic failure, as well as during flares of conditions such as systemic lupus erythematosus. Using C-reactive protein in refining cardiac risk assessment is not currently recommended outside of research settings.

Key words: acute-phase reaction, erythrocyte sedimentation rate, inflammation.

Introduction

An elevated concentration of C-reactive protein in the blood is an indicator of inflammation. The bulk of C-reactive protein tests are requested for the detection of inflammatory responses associated with microbes, autoimmune diseases and drug allergies (especially to antibiotics).

The inflammatory response

Inflammation is a protective reaction of vascular connective tissue to damaging stimuli. The inflammatory response is associated with vasodilatation, increased vascular permeability, recruitment of inflammatory cells (especially neutrophils in acute inflammation), and the release of inflammatory mediators from these cells, including vasoactive amines, prostanoids, reactive oxygen intermediates and cytokines. Cytokines derived from macrophages and monocytes include tumour necrosis factor alpha (TNF-α), interleukin-1 and interleukin-6. These cytokines are primarily responsible for mediating the 'acute-phase response'[1]. They cause a change in the production of various plasma proteins by hepatocytes, including an increase in C-reactive protein. The effects of inflammation on some of the more important acute-phase proteins are shown in table 1.

C-reactive protein

C-reactive protein plays a key role in the host's defence against infection[2]. It was so named because it reacts with the C-polysaccharide of *Streptococcus pneumoniae*. In the presence of calcium, C-reactive protein specifically binds to polysaccharides such as phosphocholine moieties present on the cell surface of many pathogenic microbes. C-reactive protein binding activates the classical complement pathway and opsonises (prepares) ligands for phagocytosis. It also neutralises the pro-inflammatory platelet-activating factor and down-regulates polymorphs.

C-reactive protein is predominantly made in the liver and is secreted in increased amounts within six hours of an acute inflammatory stimulus[3]. The plasma concentration can double at least every eight hours, reaching a peak after about 50 hours. After effective treatment or removal of the inflammatory stimulus, concentrations can fall almost as rapidly as the 5-7 hour plasma half-life of labelled exogenous C-reactive protein. C-reactive protein responses may be reduced by severe hepatocellular impairment, but renal dysfunction can elevate concentrations of C-reactive protein.

Normal ranges

The median normal concentration of C-reactive protein is 0.8 mg/L, with 90% of apparently healthy individuals having a value less than 3 mg/L and 99% less than 12 mg/L. Elevated values are abnormal and suggest the presence of organic disease, although minimal C-reactive protein rises can be seen with obesity.

C-reactive protein test results can vary between laboratories. It is therefore recommended that serial C-reactive protein assessments be undertaken through a single laboratory if possible, to minimise error.

'Ultra-sensitive' or 'highly-sensitive' C-reactive protein refers to the measurement of small changes in C-reactive protein concentrations occurring below the 'normal' cut-off used to define significant infection and inflammation.

Clinical utility of C-reactive protein

While an elevated C-reactive protein value is not specific for any condition, it is a fairly sensitive marker of inflammation (greater than 90%), and so provides a valuable adjunct to a careful clinical assessment. There is often no clear correlation between C-reactive protein concentrations and disease severity. The commonest conditions associated with major elevations of C-

reactive protein concentrations are shown in table 2. Despite unequivocal evidence of active inflammatory disease and/or tissue damage, some conditions are often associated with only minor (or no) elevation of C-reactive protein concentrations (see table 2). In many of these conditions C-reactive protein remains normal in some patients despite severe disease. The mechanism of this 'selective' failure of the acute-phase C-reactive protein response is currently uncertain.

Monitoring the extent and activity of disease

In inflammatory conditions, C-reactive protein may be used to monitor the patient's response to therapy. For instance in rheumatoid arthritis, C-reactive protein concentrations correspond well to disease activity and treatment efficacy.

Screening for infection

As an adjunct to clinical assessment, a C-reactive protein test may be useful in differentiating between bacterial and viral infections. A very high C-reactive protein (greater than 100 mg/L) is more likely to occur in bacterial rather than viral infection, and a normal C-reactive protein is unlikely in the presence of significant bacterial infection. However, intermediate C-reactive protein concentrations (10-50 mg/L) may be seen in both bacterial and viral conditions. Measurement of another acute-phase reactant, procalcitonin, has been advocated as an alternative marker in these circumstances, but data are too preliminary to recommend its universal adoption.

Detection and management of intercurrent infection

The possibility of intercurrent infection must always be kept in mind, especially when immunosuppressants are being administered. Bacterial infections usefully monitored by C-reactive protein concentrations include pyelonephritis, pelvic infections, meningitis and endocarditis. Serial C-reactive protein measurements are important adjuncts to the use of temperature charts in clinical practice, as C-reactive protein concentrations are not affected by antipyretic drug therapy or thermo-regulatory factors.

In conditions such as systemic lupus erythematosus and ulcerative colitis, a major diagnostic dilemma is often posed between a disease flare and superinfection. Elevation of the C-reactive protein above usual baseline concentrations for a particular patient may provide a valuable clue to the presence of infection.

The 'metabolic syndrome'

The metabolic syndrome refers to a constellation of risk factors for cardiovascular disease and type 2 diabetes, which are generally associated with obesity and insulin resistance. The role of inflammation in the pathogenesis of metabolic syndrome is increasingly being recognised. While an association between ultra-sensitive C-reactive protein and vascular risk exists at a population level[4], data suggesting a role for ultra-sensitive C-reactive protein in assessing an individual's cardiovascular risk and offering interventions are conflicting and inconclusive.

Table 1. Acute-phase proteins

	Increased concentrations	Decreased concentrations
Protease inhibitors	alpha$_1$-antitrypsin	antichymotrypsin
Coagulation proteins	fibrinogen prothrombin factor VIII plasminogen	
Complement proteins	C1s, C2, C3, C4, C5 factor B C1 esterase inhibitor plasminogen	
Transport and storage proteins	haptoglobin haemopexin caeruloplasmin ferritin	transferrin
Miscellaneous	C-reactive protein procalcitonin serum amyloid protein fibronectin alpha$_1$-acid glycoprotein	albumin pre-albumin

Table 2. Conditions causing elevation of C-reactive protein

Major elevations	
Bacterial infections	pyelonephritis pelvic infections meningitis endocarditis
Hypersensitivity complications of infections	rheumatic fever erythema nodosum
Inflammatory disease	rheumatoid arthritis juvenile chronic arthritis ankylosing spondylitis psoriatic arthritis systemic vasculitis polymyalgia rheumatica Reiter's disease Crohn's disease familial Mediterranean fever
Transplantation	renal transplantation
Cancer	lymphoma sarcoma
Necrosis	myocardial infarction tumour embolisation acute pancreatitis
Trauma	burns fractures
Minor or no elevations	
Inflammatory disease	systemic lupus erythematosus systemic sclerosis dermatomyositis ulcerative colitis Sjogren's syndrome
Transplantation	graft versus host disease
Cancer	leukaemia

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate (ESR) also provides a measure of inflammation. It reflects concentrations of fibrinogen and alpha-globulins[5]. However, ESR is also influenced by immunoglobulins that are not acute-phase proteins. These proteins all have half-lives of days to weeks, and there is a significant lag time between changes at the clinical level and variations in the ESR. This, plus the influence of various other factors on the ESR such as diurnal variation, anaemia, food intake and red cell morphology, makes it an imprecise guide to disease activity in most cases.

C-reactive protein or ESR?

C-reactive protein is superior to ESR in terms of rapidity of response and specificity for inflammation. Measuring C-reactive protein is also more precise and reproducible and a quicker test to perform. However, ESR measurements remain helpful in certain clinical situations such as the detection of paraproteinaemias, which often do not elicit an acute phase response.

Conclusion

When used in conjunction with clinical assessment, C-reactive protein measurement is a useful tool for evaluating possible infective or inflammatory disease. However, as with any diagnostic test, false positives and false negatives can occur, and no test represents a replacement for thorough clinical review.

References

1. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999; 340: 448-54.
2. Black S, Kushner I, Samols D. C-reactive protein. J Biol Chem 2004; 279: 48487-90.
3. Marnell L, Mold C, Du Clos TW. C-reactive protein: ligands, receptors and role in inflammation. Clin Immunol 2005; 117: 104-11.
4. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336: 973-9.
5. Bedell SE, Bush BT. Erythrocyte sedimentation rate. From folklore to facts. Am J Med 1985; 78: 1001-9.

Conflict of interest: none declared.

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Maintenance treatments for bipolar disorders

Summary

Bipolar disorders are disabling and, for most patients, recurrent illnesses. Lithium is the 'gold standard' mood stabiliser in terms of efficacy, but many patients find it difficult to tolerate. The anticonvulsants sodium valproate and carbamazepine are useful despite minimal controlled evidence for their prophylactic efficacy. The approval of olanzapine and lamotrigine for maintenance treatment increases the choice of drug therapy. These new drugs, in conjunction with the development of effective psychological interventions, mean that the clinician has an increasing range of effective options to offer patients with these disabling and challenging conditions.

Key words: carbamazepine, lithium, lamotrigine, olanzapine, sodium valproate.

Introduction

Bipolar disorders (see box) are relatively common conditions with a lifetime prevalence of up to 4%[1].They lead to levels of disability which are greater than those associated with major depressive disorder (unipolar depression)[2]. Rates of disrupted relationships are high and many sufferers are unemployed and in receipt of government benefits. At least a quarter have a history of suicide attempts, with 10-20% of all patients ending their life by their own hand.

Bipolar I disorder	At least one episode of mania (current or past) Usually (but not necessarily) episodes of depression
Bipolar II disorder	Episodes of hypomania and depression No manic episodes
Mania	Pathologically elevated or euphoric mood (often also irritable) lasting at least one week. There is evidence of marked impairment of functioning. Delusions or hallucinations may occur and hospitalisation may be required.
Hypomania	Pathologically elevated (or irritable) mood lasting at least 2-4 days. While mood and behaviour are distinctly different from normal, functioning is not severely impaired. Psychotic features do not occur and hospitalisation is unnecessary.

While effective and rapid management of acute episodes of mania and bipolar depression are critical components of treatment the prevention of relapse is probably the most important aspect of management. Bipolar disorders are highly recurrent for most patients. It is the recurring nature of the condition that, unless adequately treated, gradually takes its toll in terms of the patient's capacity to maintain relationships, career and self-esteem.The average patient experiences a major relapse every 17 to 30 months, with episodes frequently lasting between three and six months. At least 25% will go through phases of rapid-cycling illness in which they experience at least four episodes in a year[3].

The challenge for the treating clinician - be that a general practitioner[4] or psychiatrist - is to ensure adequate long-term control of the illness. Effective maintenance treatment can make an enormous difference to the lives of those with bipolar disorders. The benefits observed can be some of the most dramatic seen in medical practice.

Which patients should be commenced on maintenance treatment?

There are different guidelines, but the basic principle is that most patients with recurrent, severe or disabling illness are highly likely to benefit from prophylactic treatment. Usually (but not always) the maintenance treatment will be a continuation of the drug that was effective for acute treatment (table 1). Some of these drugs are currently not subsidised for maintenance treatment (table 2).

Lithium

Although lithium was first discovered to be effective in mania in 1949, by the Melbourne psychiatrist John Cade, it is still the 'gold standard' therapy. Despite the intervening 58 years, no treatments of greater potency have yet been developed. Many patients are unable to tolerate lithium and it has limited effectiveness for the depressive phase of bipolar disorders.

There are more positive randomised double-blind controlled trials for lithium as a maintenance therapy than for any other treatment. Several meta-analyses have

Table 1. Relative efficacy of drugs in preventing manic and depressed episodes

	Preventive potency	
	Mania	**Depression**
Lithium	++	+
Carbamazepine	+	+
Valproate	+	+
Lamotrigine	+/-	++
Olanzapine	++*	+

++ strong evidence

\+ reasonable evidence

+/- equivocal evidence

* One (unreplicated) study demonstrated superiority to lithium for prophylaxis in mania

Table 2. Status of drugs currently approved in Australia for bipolar disorders

	Marketing approval		Subsidised indications	
	Acute mania	Maintenance	Acute mania	Maintenance
Lithium	✓	✓	✓	✓
Carbamazepine	✓	✓	✓	✓
Valproate	✓	✓	✓	✓
Lamotrigine	✓	✓ *	✓	✓
Olanzapine	✓	✓	✓	✓
Quetiapine	✓	✓	✓	✓
Risperidone	✓	✓	✓	✓
Ziprasidone	✓	✓	✓	✓

* Approved for prevention of episodes of bipolar depression only. This approval is not presently listed in the product information.

There is no drug or medicine specifically approved in Australia for acute treatment of bipolar depression.

confirmed the efficacy of lithium, particularly in preventing manic relapse[5]. Its capacity to prevent depressive relapse is less clear-cut. Consequently, many patients on lithium suffer from frequent and prolonged depressive episodes, despite dramatic suppression of the periods of elevated mood. Non-compliance is common (20-50% of patients) and if lithium is abruptly discontinued, the chance of sudden relapse into mania is considerable.

The main drawbacks of lithium are the need for serum concentration monitoring, the possibility of serious toxicity, and the risk of thyroid (and less commonly renal) impairment. Tremors, increased muscle tone, hyperreflexia and disorientation are signs of severe toxicity.

Anticonvulsants

In Australia sodium valproate is an anticonvulsant drug that is approved for acute treatment of mania. It is also commonly used as an alternative to lithium for maintenance treatment of bipolar disorders. Carbamazepine, another anticonvulsant, is approved for the management of mania and the maintenance treatment of bipolar disorder.

The only placebo-controlled trial of Carbamazepine in prophylaxis failed to show superiority over placebo. However, most of the five randomised double-blind comparisons with lithium reported no difference between lithium and carbamazepine. There has been only one double-blind trial of sodium valproate in the prophylaxis of bipolar disorders. This found no differences between either valproate or lithium when compared to placebo[6]. Despite this lack of evidence from controlled trials, clinical experience worldwide has seemed to confirm the benefit of these drugs in reducing relapse rates. Approved for prevention of episodes of bipolar depression only. This approval is not presently listed in the product information. There is no drug or medicine specifically approved in Australia for the acute treatment of bipolar depression.

Lamotrigine

Lamotrigine is an anticonvulsant that may also be used in Australia for the prevention of bipolar depressive episodes. This indication is not subsidised by the Pharmaceutical Benefits Scheme (PBS). There is evidence from one placebo-controlled trial for the efficacy of lamotrigine in the acute treatment of bipolar depression, but this was not replicated in several subsequent trials. Lamotrigine is neither acutely nor prophylactically effective in unipolar depression. It is not significantly superior to placebo in the acute treatment of mania.

In two trials of maintenance treatment involving 638 patients with bipolar I disorder over 18 months, lamotrigine was superior to placebo in the prevention of depressive episodes, while lithium was more effective than placebo in the prevention of mania[7]. A pooled analysis of both studies showed that lamotrigine was more effective than placebo for preventing depression, and lithium was more effective for mania. It also showed that lamotrigine was statistically more effective than

placebo in the prevention of manic episodes, but this appeared to be of limited clinical significance[8].

The main safety problem with lamotrigine is serious rash. The development of Stevens-Johnson syndrome is a major concern as it may be fatal. Major risk factors for serious rash are rapid dose escalation and failure to reduce the dose of lamotrigine on co-administration with sodium valproate.

Antipsychotics

The antipsychotic olanzapine has been approved in Australia for prevention of relapse in bipolar I disorder and this indication is included in the PBS. Olanzapine is also approved for the acute treatment of mania.

The strongest evidence for the prophylactic efficacy of olanzapine comes from a 12-month randomised double-blind comparison with lithium[9]. Olanzapine was superior to lithium in the prevention of manic and mixed episodes and equivalent to lithium for reducing bipolar depressive episodes even in the absence of psychosis. As yet, no other studies have confirmed that olanzapine has greater efficacy than lithium in preventing manic relapse.

At present there are few reports about the long-term preventive efficacy of other atypical antipsychotics, although the effect of olanzapine may turn out to be a class effect. Risperidone has been approved in Australia for continuation for six months following acute treatment of mania.

The major safety concerns with olanzapine and some other atypical antipsychotics are substantial weight gain, hyperlipidaemia and diabetes. During long-term treatment with olanzapine, lipids and glucose should be monitored, and active means instituted to encourage diet and exercise.

Combination therapy

There is minimal evidence to support the use of combinations of drugs for maintenance treatment. The main evidence comes from a study in the 1990s which found that patients unresponsive to monotherapy with lithium or anticonvulsants often responded to combined therapies. The effective combinations were lithium and carbamazepine, and lithium and valproate[10].

Is there a role for long-term antidepressants?

For many patients, the episodes of mania are relatively easilytreated, but depressive episodes are frequently less amenable to treatment. There is currently considerable controversy internationally over adding long-term antidepressants to the maintenance treatment of bipolar disorders. Antidepressants may induce manic episodes or even a rapid-cycling pattern, but the frequency of this is debated as there is some evidence that suggests induction of mania is relatively uncommon. There is some evidence that continuing antidepressants in patients who respond acutely to them has a prophylactic benefit. In one study 70% of the patients who stopped their antidepressants early relapsed into depression, compared to 36% of the patients who continued their antidepressants[11]. Some (particularly US) authorities argue that antidepressants should rarely be used in long-term treatment.

Psychological interventions

Strong evidence for the benefits of psychological interventions in reducing the likelihood of relapse (particularly depressive episodes) is accumulating from a series of randomised controlled trials. Educational techniques, empowering the patient to take responsibility for the management of their illness, have been shown to reduce relapse and improve social functioning and employment. Cognitive therapy is aimed at improving skills in managing stress and symptoms, and in identifying early warning signs of impending relapse, and teaching skills to challenge and alter unhelpful thinking styles[12]. It improves mood, coping and adherence, and reduces recurrence[13]. Interpersonal and social rhythm therapy teaches patients to regulate their social habits, sleep patterns and daily routines at times of stress[14].

Conclusion

New treatments, in conjunction with the development of effective psychological interventions for bipolar disorders, mean that the clinician has an increasing range of effective maintenance therapies to offer patients with these disabling and challenging conditions. While none of the newer drugs has been shown to be more effective than lithium, they are better tolerated by some patients.

References

1. Kessler RC, Berglund P, Demmler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62: 593-602.
2. Mitchell PB, SladeT, Andrews G. Twelve-month prevalence and disability of DSM-IV bipolar disorder in an Australian general population survey. Psychol Med 2004; 34: 777-85.
3. Angst J, Sallero R. Historical perspectives and natural history of bipolar disorder. Biol Psychiatry 2000; 48: 445-57.

4. Mitchell PB, Ball JR, Best JA, Gould BM, Malhi GS, Riley GJ, et al.The management of bipolar disorder in general practice. Med J Aust 2006; 184: 566-70.

5. Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004; 161: 217-22.

6. Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Arch Gen Psychiatry 2000; 57: 481-9.

7. Bowden CL, Calabrese JR, Sachs G, Yatham LN, Asghar SA, Hompland M, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 2003; 60: 392-400.

8. Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry 2004; 65: 432-41.

9. Tohen M, Greil W, Calabrese JR, Sachs GS,Yatham LN, Oerlingshausen BM, et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder a 12-month, randomized, double-blind, controlled clinical trial. Am J Psychiatry 2005; 162: 1281-90.

10. Denicoff KD, Smith-Jackson EE, Bryan AL, Ali SO, Post RM. Valproate prophylaxis in a prospective clinical trial of refractory bipolar disorder. Am J Psychiatry 1997; 154: 1456-8.

11. Altshuler L, SuppesT, Black D, Nolen WA, Keck PE, Frye MA, et al. Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. Am J Psychiatry 2003; 160: 1252-62.

12. Ball JR, Mitchell PB, Corry JC, Skillecorn A, Smith M, Malhi GS. A randomized controlled trial of cognitive therapy for bipolar disorder focus on long-term change. J Clin Psychiatry 2006; 67: 277-86.

13. Scott J, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. Br J Psychiatry 2006; 188: 313-20.

14. Frank E, Kupfer DJ,Thase ME, Mallinger AG, Swartz HA, Fagiolini AM, et al.Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Arch Gen Psychiatry 2005; 62: 996-1004.

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Professor Mitchell has received honoraria from GlaxoSmithKline, Eli Lilly and AstraZeneca for lectures, and has served on an advisory board for Eli Lilly in the last three years.

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Self-assessment questions

(And clinical physiology in small doses)

(Select the **best** response in each question)

1. Which statement is true regarding the acute-phase response to inflammation?
   a. Elevated ESR reflects rises in the concentrations of fibrinogen and alpha-globulins, and also of immunoglobulins in plasma.
   b. C-reactive protein is produced mainly in reticulo-endothelial cells of spleen, bone marrow and lymphatic nodes.
   c. C-reactive protein concentrations are significantly influenced by antipyretics and the body's thermoregulatory factors,
   d. In an acute inflammatory condition C-reactive protein level starts to rise 12-24 hours after the inflammatory stimulus,
   e. C-reactive protein in plasma is markedly elevated in systemic sclerosis and dermatomyositis.

2. C-reactive protein is **not** usually elevated in
   a. pyelonephritis
   b. meningitis
   c. Sjogren syndrome
   d. juvenile chronic arthritis
   e. acute myocardial infarction
   f. sarcoma

3. Clinical features of severe lithium toxicity include all of the following **except**
   a. tremor
   b. nystagmus and ataxia
   c. dysarthria
   d. hypothyroidism
   e. drowsiness and disorientation
   f. hyper-reflexia

Answers to self-assessment questions

Question 1. The correct response is (a). ESR is an acute-phase response, but unlike C-reactive protein (CRP), it reflects rises in plasma fibrinogen and alpha-globulins, and also immunoglobulins (eg. myeloma). All these proteins have half-lives of several days to weeks, in contrast to CRP which starts to rise within 6 hours of an inflammatory stimulus,and doubles in concentration about every 8 hours. CRP is not influenced by antipyretics or thermoregulatory processes. CRP is produced principally by hepatocytes (See article by Dr Reeves in this issue)

Question 2. The correct response is (c). (See table 2 in Dr Reeves' article in this issue).

Question 3. Every doctor must know the adverse effects, and toxicity symptoms and signs of lithium, and the management of these. (See article by Drs Pyle and Mitchell in this issue, and the 2007 BNF). Hypothyroidism is an adverse effect of lithium but not a feature of severe toxicity.

Professor Colvin Goonaratna, FCCP, FRCP, PhD, DSc.

Current information about drug registration

New chemical entities registered

Generic name	Brand name	Dosage form	Manufacturer	Importer	Therapeutic class / use(s)
r-DNA human erythropoietin	Epokin	Injection, 2000 iu 4000 iu Pre-filled syringe, 10,000 iu 4,000 iu 2,000 iu	C.J. Corporation, Korea	Rena Care	Anaemia associated with erythropoietin deficiency
Doxazosin	Pencor	tablet, 1 mg & 2 mg	Unison, Thailand	Lanka Medical	Vasodilator antihypertensive
Glucosamine sulfate	Flexa	tablet, 750 mg	Mega, Australia	Baurs	Degenerative arthritic diseases

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