that are felt to be primary in nature. If autopsy examination is delayed, air in the venous system may be resorbed, contributing to the difficulty in diagnosis.

The symptoms of VAE are variable and non-specific. These include alteration of sensorium, chest pain, dyspnoea and dizziness. Physical examination may reveal tachycardia, tachypnoea, and signs of elevated right heart pressure. A 'mill wheel' murmur produced by movement of air bubbles in the right ventricle is the only specific sign, but it is rare, transient and a late finding.

Precordial low-frequency Doppler ultrasound is the most sensitive method for detection of venous air. Other useful indicators of VAE include helical CT, echocardiography, transoesophageal echocardiography, and aspiration of air on an indwelling central venous catheter.

Prevention and early detection are the best approaches to VAE. Because of the non-specific signs and symptoms, a high index of suspicion in the appropriate clinical setting is important, since prompt recognition and institution of treatment, including immediate placement in the left lateral decubitus position, can be life-saving. Other measures designed to restore blood flow include removal of air through a central venous catheter or direct needle aspiration and external cardiac massage. Measures designed to increase absorption of air include the use of 100% O₂ and early institution of hyperbaric oxygen.

M.K. Athar  
T. Islam  
J. Grammes  
M.N. Athar  
Department of Medicine  
Mercy Catholic Medical Center  
Drexel University College of Medicine  
Philadelphia  
USA  
e-mail: tasbirul@msn.com

References

doi:10.1093/qjmed/hci033

Isolated microscopic haematuria

Sir,

I read with interest the paper by Chow et al.1 (‘Long-term follow-up of patients with asymptomatic isolated microscopic haematuria’). The title of the paper is somewhat misleading, as in pure isolated microscopic haematuria, the urine protein excretion rate is <100 mg/day (<0.1 g/day),2 but in this study the authors also included patients with microscopic haematuria and minimal proteinuria (>0.2 g/day) and, as expected (as shown in Table 1 and Figure 2), the majority of the patients in the latter group had adverse events, because of the higher baseline protein excretion rate, possibly suggesting an underlying nephrological process. This paper re-iterates the well known fact that patients with minimal proteinuria are increased risk for disease progression.2 We shouldn’t mix apples with oranges, and then conclude that a small amount of oranges would give apples a sour taste. The title ‘Long-term follow-up of patients with microscopic haematuria, with and without minimal proteinuria,’ might have been more appropriate for this paper, which highlights the significance of ‘even minimal proteinuria’ and the need for long-term follow-up of such patients.

M.S. Parmar  
Northern Ontario School of Medicine  
Laurentian & Lakehead Universities  
Timmins  
Canada  
e-mail: atbeat@ntl.sympatico.ca

References

doi:10.1093/qjmed/hci035

Norethisterone-induced cholestasis

Sir,

Combination oral contraceptive steroids are (rarely) associated with cholestasis that resembles intrahepatic cholestasis of pregnancy. The incidence of cholestasis due to oral contraceptive steroids is approximately 1:10 000 women exposed in Western Europe, but as high as 1:4000 women exposed in
Chile and Scandinavia. The oestrogenic component of the combined oral contraceptive pill is believed to be responsible. However, we report two cases of cholestasis induced by norethisterone, a progestogen contraceptive, which resolved after withdrawal of these pills.

An 18-year-old schoolgirl developed jaundice, pruritus, fatigue and anorexia 2 weeks after starting norethisterone. She had taken 5 mg norethisterone three times daily for 10 days to delay menstruation during a skiing holiday. She was on no other medication and did not drink alcohol. Examination revealed icterus with a palpable liver edge. Blood tests showed alanine transaminase was 540 U/l, alkaline phosphatase was 102 U/l and bilirubin was 42 μmol/l. During the subsequent weeks her jaundice deepened, with bilirubin peaking at 256 μmol/l. Blood tests for viral hepatitis (hepatitis A and B, cytomegalovirus, Epstein Barr virus) and autoimmune liver disease (antinuclear antibody, smooth muscle antibody, antimitochondrial antibody) were all negative. Biochemical screening for Wilson’s disease was negative. Ultrasound scanning did not reveal any biliary obstruction. Her pruritus failed to respond to antihistamines or cholestyramine. An empirical course of oral prednisolone 25 mg daily for 1 week, with gradually tapering doses for the following 3 weeks, led to clinical and biochemical improvement. Liver biopsy was not done. Her symptoms subsided completely and her liver biochemistry was normal after 4 months.

A 34-year-old woman whose sole medication was 350 μg norethisterone (‘Micronor’, Janssen-Cilag) as a contraceptive, for 4 years, presented with pruritus and a cholestatic blood picture. She had mild icterus and scratch marks over her body, but no other abnormal findings. Bilirubin was 33 μmol/l, aspartate transaminase 179 U/l, and alkaline phosphatase 532 U/l. Hepatobiliary ultrasound and subsequently magnetic resonance scanning revealed two small incidental hepatic haemangiomata. Serological tests for hepatitis A, B and C, and Epstein-Barr virus, were all negative. Liver auto antibodies were negative. Her norethisterone pill was stopped, and there was rapid symptomatic and slower biochemical improvement.

Interestingly, this patient had also developed cholestatic jaundice 5 years earlier, while taking a combined contraceptive pill containing 500 μg norethisterone and 35 μg ethinyl oestradiol (‘Brevinor’, Pharmacia). At that time, full investigation revealed no other cause for her jaundice, and her combined oral contraceptive pill was deemed to be responsible. Her symptoms resolved and her liver biochemistry normalized on stopping the pill. She had been advised to change to a progestogen-only pill.

The oestrogen component of combination oral contraceptive steroids is usually blamed for the rare development of intrahepatic cholestasis. Oestrogen-induced cholestasis can occur in women with previous obstetric cholestasis, and has also been described in sisters. These observations indicate a genetic susceptibility. Studies in rats suggest that canalicular bile transporters, particularly multidrug resistant protein 2 (MRP-2), responsible for biliary secretion of several organic anions including bilirubin glucuronides, may be implicated in oestrogen-induced cholestasis. By lowering bile canalicular Na-K-ATPase activity, ethinyl oestradiol decreases bile acid transport independent of bile flow.

In distinction to oestrogens, progestogens are not typically implicated in cholestasis. In women with a previous history of intrahepatic cholestasis due to combined oestrogen-progestogen contraceptives and/or pregnancy, it is generally assumed that ‘progestosterone-only’ contraceptives are safe, and will avoid recurrence of this hepatic problem. However, the serum concentration of sulphated metabolites of progesterone is known to be elevated in patients with obstetric cholestasis, and progesterone metabolites may have a more important role than oestradiol metabolites in the pathogenesis of obstetric cholestasis. Patients with obstetric cholestasis have an increased ratio of 3α to 3β hydroxysteroids, and excrete large amounts of sulphated progesterone metabolites in their urine. Furthermore, there are reports of intrahepatic cholestasis when high doses of the progesterones norethisterone or megestrol acetate have been used to treat women with breast cancer. In rats, norethisterone can induce hepatic cholestasis associated with bile staining of hepatocytes.

The mechanism of cholestasis induced by progestogens is unknown. These case reports indicate that progestogens alone can also cause cholestatic jaundice and that ‘progestosterone-only’ contraceptive pills are not necessarily trouble-free in women who have experienced cholestasis with the combined (oestradiol-containing) contraceptive pill.

V. Anand
D.A. Gorard
Wycombe Hospital
High Wycombe
UK
e-mail: david.gorard@sbucks.nhs.uk
The obesity epidemic

Sir,
The recent article by Skidmore and Yarnell\(^1\) deserves some comments. Similar papers were published by other authors in the recent years.\(^2\)\(^,\)\(^3\) All claim that the increasing prevalence of obesity and overweight (in the UK and other developed countries) has become a public concern and a relevant medical (and social) problem. The data are impressive: nearly 1:3 Americans meet the definition of ‘obese’, and by including overweight individuals, we reach 60% or more of the population. This is associated with an ‘enormous burden of chronic diseases, impaired physical function and quality of life, at least 300 000 premature deaths and at least 90 billion dollars in direct health care costs annually in the USA’.\(^2\) These data are, again, impressive and alarming; the authors are right to call for action directed at physicians as well as to patients. The promotion of healthy eating and regular physical activity are important for the prevention of obesity, as well as education on good nutrition. We agree entirely with these considerations, but are they sufficient? We fear not.

In fact, we wonder how these alarming data can be coupled with the claims of many influential politicians and economists that our present standard of living is beyond any reasonable questioning, and that we should increase our expenses in order to maintain unaltered a standard of living that includes wastage of every kind.

Of course, we can continue to hope that people will learn to eat less and better, but we doubt that this policy will achieve concrete results, unless influential people such as politicians, economists, journalists and pundits can be persuaded to help the medical community in the fight against obesity and the many other diseases (such as cancer) related to our way of living.

M. Ponz de Leon

Dipartimento di Medicine e Specialità Mediche—Medicina I
P. Bosi

Dipartimento di Economia Politica
Università di Modena e Reggio Emilia
Modena
Italy

e-mail: deleon@unimo.it

References

Evaluating acid-base disorders

Sir,
In their review of acid-base disturbances in cholera, Zalunardo et al. illustrate the limitations of the conventional approach when dealing with complex clinical situations.\(^1\) The patient with cholera was thought to have both contraction metabolic alkalosis and metabolic acidosis from bicarbonate losses in diarrhoea, with the combination leading to a relatively normal arterial pH, PCO\(_2\), and plasma bicarbonate concentration. A different approach to these issues was introduced by Stewart\(^2\)\(^,\)\(^3\) and supported by Fencl\(^4\) and Kellum,\(^5\) among others. In this development, acid-base disorders can be considered to arise from alterations in three independent variables: the plasma strong ion media. We wonder how we can hope to combat and defeat the tendency to obesity and overweight, intimately related to the comfort and opulence of Western society, while there is a continuous invitation to consume more and to maintain unaltered a standard of living that includes wastage of every kind.

Of course, we can continue to hope that people will learn to eat less and better, but we doubt that this policy will achieve concrete results, unless influential people such as politicians, economists, journalists and pundits can be persuaded to help the medical community in the fight against obesity and the many other diseases (such as cancer) related to our way of living.

M. Ponz de Leon

Dipartimento di Medicine e Specialità Mediche—Medicina I
P. Bosi

Dipartimento di Economia Politica
Università di Modena e Reggio Emilia
Modena
Italy

e-mail: deleon@unimo.it

References

Evaluating acid-base disorders

Sir,
In their review of acid-base disturbances in cholera, Zalunardo et al. illustrate the limitations of the conventional approach when dealing with complex clinical situations.\(^1\) The patient with cholera was thought to have both contraction metabolic alkalosis and metabolic acidosis from bicarbonate losses in diarrhoea, with the combination leading to a relatively normal arterial pH, PCO\(_2\), and plasma bicarbonate concentration. A different approach to these issues was introduced by Stewart\(^2\)\(^,\)\(^3\) and supported by Fencl\(^4\) and Kellum,\(^5\) among others. In this development, acid-base disorders can be considered to arise from alterations in three independent variables: the plasma strong ion media. We wonder how we can hope to combat and defeat the tendency to obesity and overweight, intimately related to the comfort and opulence of Western society, while there is a continuous invitation to consume more and to maintain unaltered a standard of living that includes wastage of every kind.

Of course, we can continue to hope that people will learn to eat less and better, but we doubt that this policy will achieve concrete results, unless influential people such as politicians, economists, journalists and pundits can be persuaded to help the medical community in the fight against obesity and the many other diseases (such as cancer) related to our way of living.

M. Ponz de Leon

Dipartimento di Medicine e Specialità Mediche—Medicina I
P. Bosi

Dipartimento di Economia Politica
Università di Modena e Reggio Emilia
Modena
Italy

e-mail: deleon@unimo.it

References

Evaluating acid-base disorders

Sir,
In their review of acid-base disturbances in cholera, Zalunardo et al. illustrate the limitations of the conventional approach when dealing with complex clinical situations.\(^1\) The patient with cholera was thought to have both contraction metabolic alkalosis and metabolic acidosis from bicarbonate losses in diarrhoea, with the combination leading to a relatively normal arterial pH, PCO\(_2\), and plasma bicarbonate concentration. A different approach to these issues was introduced by Stewart\(^2\)\(^,\)\(^3\) and supported by Fencl\(^4\) and Kellum,\(^5\) among others. In this development, acid-base disorders can be considered to arise from alterations in three independent variables: the plasma strong ion media. We wonder how we can hope to combat and defeat the tendency to obesity and overweight, intimately related to the comfort and opulence of Western society, while there is a continuous invitation to consume more and to maintain unaltered a standard of living that includes wastage of every kind.

Of course, we can continue to hope that people will learn to eat less and better, but we doubt that this policy will achieve concrete results, unless influential people such as politicians, economists, journalists and pundits can be persuaded to help the medical community in the fight against obesity and the many other diseases (such as cancer) related to our way of living.

M. Ponz de Leon

Dipartimento di Medicine e Specialità Mediche—Medicina I
P. Bosi

Dipartimento di Economia Politica
Università di Modena e Reggio Emilia
Modena
Italy

e-mail: deleon@unimo.it

References