more reliable information, as in an acute infection they should show an obvious rise.

There are, however, several causes of confusion in interpreting typhoid serology. Previous TAB immunisation and earlier infections with salmonellae sharing common O antigens with the enteric fever group may have stimulated antibody secretion; patients from communities where typhoid is endemic have higher H-antibody titres than do those not previously exposed to the antigen. Some patients, including some of those previously immunised, show a poor or negligible antibody response to active infection.

S typhi and *paratyphi* C possess an additional antigen, the Vi antigen (so called because of its association with virulence for mice, not man). Vi antibodies are evoked by acute *S typhi* infections; their disappearance is often taken as evidence that the organism is no longer present, though they may not be detected in known excreters of *S typhi*. A report[3] from the Public Health Laboratory Service in 1961 showed that only 70% of known carriers had Vi antibodies at a titre of 1:5 or more.

During the Aberdeen outbreak 507 cases of typhoid were notified and 403 were confirmed by culture. Widal tests were performed on patients' sera for up to two years after discharge from hospital. H antibodies could not be detected in either the acute illness or during follow-up in 15% of patients tested, 83% of whom had bacteriologically proved typhoid; and O antibodies did not develop in as many as 41%, 79% of whom had bacteriological confirmation of their disease. Failure to produce Vi antibody at any stage was seen only in 9%, and in 33 patients only Vi antibodies were present.

One hundred and eleven of the group had had TAB immunisation, but this seems to have made little difference to antibody production. For O antibodies about 60% of the non-immunised patients showed a response at some stage, compared with 54% of those who had been immunised. For H antibodies the figures were 82% and 95%, and for Vi antibodies the difference was slight—91% and 89%. Furthermore, 21% of a non-infected non-immunised group had detectable Vi antibodies, a much greater proportion than the 1% quoted by Christie.[4] One possible explanation is that other organisms possessing closely related antigens might have provoked this Vi-antibody response.

These results confirm that the Widal test is of limited value in typhoid, in which diagnosis remains essentially clinical, confirmed wherever possible by bacterial culture. Brodie looked at other serological tests and found the results equally disappointing. The sensitivity of the Coombs test for typhoid was greater, but it had the drawback of taking two days. The complement fixation test was unhelpful, as titres were low—and curiously a high percentage of anticomplementary sera was found among the immunised patients, so that the test was considered worthless in this group. Fimbrial antibodies could be detected in immunised and non-immunised patients and in healthy individuals, and the test appeared to have little diagnostic value.

The conclusions to be drawn from this mammoth study must challenge the accepted serological guidelines for the diagnosis of typhoid. Brodie suggests that H antibodies are more reliable in diagnosis than O—a reversal of the traditional view. Vi antibodies were not found consistently in chronic carriers. The study did confirm two accepted beliefs: relapse can occur despite high antibody titres, and it may not be associated with a further rise.

Possibly the Aberdeen outbreak was caused by a phage type of *S typhi* that caused a peculiar antibody response, and further information on this point would be useful. But clinicians should now be more aware of the limitations of serological tests. Laboratory confirmation of a clinical diagnosis of typhoid depends essentially on bacterial culture.

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Hyperparathyroidism in renal failure

Much of the ill health of patients with chronic renal failure is due to the secondary hyperparathyroidism that accompanies it.[1–3] At first the hyperparathyroidism does not produce symptoms, but if allowed to develop the complications may include irritable red eyes with conjunctival and corneal calcification; generalised pruritus; vascular calcification with all its dangerous sequelae, including occasionally severe ischaemic myopathic changes[4 5]; cutaneous ulceration with gangrene[4–6]; ectopic soft tissue calcification; increased bone resorption leading to pseudoclubbing, skeletal bone loss, and fractures; pseudogout; tendon ruptures[7]; and autonomous tertiary hyperparathyroidism. In children, uncontrolled azotaemic hyperparathyroidism also causes the rare complication of slipped epiphyses and metaphyseal fractures[8–10] and it is an important factor in the condition radiologists call azotaemic rickets.[10–12]

What are the pathogenesis and evolution of azotaemic secondary hyperparathyroidism, and how is it best treated? All the evidence we have suggests that the central and most important stimulus to parathyroid enlargement and hypersecretion is hypocalcaemia with a reduction in the ionised serum calcium concentration.[13–15] Recent claims that a reduced production of 1,25-dihydroxycholecalciferol may have a direct stimulating effect on parathyroid hormone secretion have not been substantiated.[16] On the Bricker-Slatopolsky hypothesis[17] the hypocalcaemia was attributed solely to retention of phosphate, but equally important may well be malabsorption of calcium, itself due to a lack of $1,25(OH)_2D_3$. This hormone deficiency results partly from loss of renal tissue and partly from hyperphosphataemia, which interferes in the normal production of $1,25(OH)_2D_3$ by the remaining intact nephrons.[15 18]

Since the serum calcium concentration is of central importance any measure intended to prevent or treat secondary hyperparathyroidism in this phase needs to promote a rise in the calcium concentration. Before they need dialysis azotaemic patients will benefit from oral calcium supplements, phosphate binders, and vitamin D metabolites such as calciferol, dihydrotachysterol, and $1a\text{-}OHD_3$.[19–21] For patients on dialysis selection of the appropriate dialysate calcium concentration is also critical.[22] A low calcium concentration (less than 1·425 mmol/l (5·7 mg/100 ml) as used in the early dialysis days) could result in a negative calcium balance and so lead to osteoporosis, progressive hyperparathyroidism, and fractures,[14 23] while a high concentration of over 2 mmol/l (8 mg/100 ml) might result in progressive metastatic calcification. A dialysate calcium concentration of between 1·55 and 1·75 mmol/l (6·2

and 7·0 mg/100 ml) appears to be the best compromise: it ensures a gain of calcium during each dialysis cycle and also adequately suppresses secondary hyperparathyroidism.[14 22 24]

In practice the response of the individual patient to these therapeutic manipulations is not always fully predictable. Any previous parathyroid hypertrophy and the degree of parathyroid autonomy play an important part. In its extreme form autonomous tertiary hyperparathyroidism is characterised clinically by osteitis fibrosa, raised total and ionised serum calcium concentrations, and greatly raised serum concentrations of parathyroid hormone and alkaline phosphatase. In these circumstances raising the serum calcium concentration further appears of no real benefit; and the parathyroid mass needs to be reduced by a subtotal parathyroidectomy,[25] after which one of the above medical therapeutic regimens should be used. In intermediate cases of parathyroid autonomy, however, the total serum calcium concentration may not be frankly raised; such patients may not respond at all well to treatment with vitamin D, calcium supplements, and phosphate binders.[25 26] Thus in assessing patients with azotaemic hyperparathyroidism a distinction needs to be made between a calcium-responsive and a calcium-unresponsive phase, the latter usually occurring in long-established and undertreated patients.

Can we prevent azotaemic hyperparathyroidism? Ideally, all patients with renal insufficiency should have any malabsorption of calcium, hypocalcaemia, or concurrent hyperphosphataemia corrected at an early stage to forestall its development. At one time phosphate restriction alone was thought sufficient to prevent the development of secondary hyperparathyroidism,[27] but a recent two-year study has shown that vitamin D may also be necessary.[28] Until quite recently treatment with vitamin D has been limited—largely because of the complications associated with its poorly supervised use. The increasing availability of 1a-OHD_3 and $1,25(OH)_2D_3$, however, with their short half life[29] seems certain to make treatment with vitamin D simpler and safer. Clinical trials of the use in early renal failure of 1a-OHD_3 and $1,25(OH)_2D_3$ (in conjunction with phosphate binders as required) should help determine the requirements for these active vitamin D metabolites at different stages of reduced renal function; only then will we know whether normal bone metabolism can be maintained and whether secondary hyperparathyroidism and the often-associated osteomalacia can be prevented.

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John Hunter's 250th anniversary

Two hundred and fifty years ago John Hunter was born in the farmhouse of Long Calderwood in the parish of East Kilbride, a few miles south of Glasgow. The family bible notes the date as 9 February, the parish register records 13 February, and John Hunter himself would celebrate his birthdays on 14 February; by tradition, if nothing else, this is the conventional date of remembrance of his birth.

At the age of 20 John came to London to join his elder brother, William, who was already establishing his reputation as an anatomist and man-midwife. He soon entered as surgeon-pupil to the new St George's Hospital, and over the next 11 years he laid the foundations of his life's study of anatomy and physiology. This was followed by three years' service as an army surgeon in the Seven Years' War. Like so many other surgeons before and since, the unfortunate wealth of gunshot wounds which he encountered added much to Hunter's surgical experience. Within a few years of his return, in 1768, he was appointed surgeon to St George's Hospital and could have devoted the rest of his active days to the life of a busy London consultant. Nevertheless, in addition to his surgical and teaching duties, John never gave up his dedication to his research and to his museum, which eventually contained well over 13 000 specimens. His appetite for work was enormous: his studies spread from transplantation of teeth to inflammation, from the ligation of blood vessels to the descent of the testis, from the hibernation of the hedgehog to the strange habits of cuckoos (to the study of which he inspired Edward Jenner, perhaps the most distinguished of his many pupils). The belief that he inoculated himself with syphilis is, however, almost certainly mistaken.[1]

A sufferer from angina pectoris, John Hunter collapsed and died at a weekly board meeting at St George's Hospital on 16 October 1793. He was buried at St Martin's Church, but his remains were moved to the north aisle of the nave of Westminster Abbey in 1859. The brass tablet there records: "His genius as a gifted interpreter of the Divine Power and wisdom at work in the laws of organic life."

These bare facts are the framework of the modern surgeon's veneration for this great man, whose labours provided the origins of the science of surgery based on observation, experiments, and the basic principles of biology.

To celebrate this important anniversary, the Royal College of Surgeons of England arranged an elaborate programme of meetings and functions for this week of 13-18 February, including a formal reception, graced by Her Majesty the Queen and Prince Philip, a Hunterian Anniversary Oration by Lord Wolfenden, and symposia on subjects close to Hunter's heart—inflammation, wound healing, and ulceration. Other meetings have been planned at provincial centres and functions