cleared in six even though the reflux persisted.[20] We need better methods, and several have been explored. The detection of anti-Tamm-Horsfall antibody proved unhelpful.[21] Screening relatives of patients with vesicoureteric reflux gives a much higher yield of reflux than in the general population.[22 23] A weak association of reflux with HLA B12 has been shown.[24]

Even when an acceptable technique for the detection of reflux in the very young has been found, however, controlled trials of medical versus surgical treatment will be required to establish the optimum method of preventing kidney damage. We still have far to go before we can prevent chronic pyelonephritis in childhood. Meanwhile we may be able to arrest its progress by early detection and control of raised blood pressure, by long-term antibacterial treatment,[25] and possibly also by surgical treatment of the most severe grades of vesicoureteric reflux.[26 27]

1 Parsons, F M, in *Proceedings of the 9th Conference of the European Dialysis and Transplant Association*, eds J S Cameron, C S Ogg, and D Fries, p 3. London, Pitman Medical, 1972.
2 Fry, J, *et al*, *Lancet*, 1962, **1**, 1318.
3 Hanson, L A, *Journal of Infectious Diseases*, 1973, **127**, 726.
4 Roberts, A P, *et al*, *Journal of Medical Microbiology*, 1975, **8**, 311.
5 Lidin-Janson, G, *et al*, *Journal of Infectious Diseases*, 1977, **136**, 346.
6 Hanson, L A, in *Symposium on Pyelonephritis*, eds E H Kass and W Brumfitt. Chicago, University of Chicago Press, 1978, in press.
7 Svanborg Eden, C, *et al*, *Lancet*, 1976, **2**, 490.
8 Asscher, A W, *et al*, *British Medical Journal*, 1969, **1**, 804.
9 Williams, J D, *et al*, in *Urinary Tract Infection*, eds W Brumfitt and A W Asscher, p 160. London, Oxford University Press, 1973.
10 Freedman, L R, in *Abstracts of the 5th International Congress of Nephrology*, ed H Villareal. Basal, Karger, 1972.
11 Gower, P E, *Quarterly Journal of Medicine*, 1976, **45**, 315.
12 Asscher, A W, *et al*, in *Urinary Tract Infection*, eds W Brumfitt and A W Asscher, p 51. London, Oxford University Press, 1973.
13 Savage, D C L, *et al*, *Lancet*, 1975, **1**, 358.
14 Newcastle Asymptomatic Bacteriuria Research Group, *Archives of Disease in Childhood*, 1975, **50**, 90.
15 Lindberg, U, *et al*, *Journal of Pediatrics*, 1978, **92**, 194.
16 Cardiff-Oxford Bacteriuria Study Group, *Lancet*, 1978, **1**, 889.
17 Ransley, P G, and Risdon, R A, *Urological Research*, 1975, **3**, 111.
18 Kincaid-Smith, P, *Kidney International*, 1975, **8**, suppl 4, 81.
19 Rolleston, G L, Maling, T M H, and Hodson, C J, *Archives of Disease in Childhood*, 1974, **49**, 531.
20 Verrier-Jones, E R, *et al*, *Kidney International*, 1975, **8**, suppl 4, 85.
21 Fasth, A, Hanson, L A, and Asscher, A W, *Archives of Disease in Childhood*, 1977, **52**, 560.
22 de Vargas, A B F, *et al*, *Journal of Medical Genetics*, 1978, **15**, 85.
23 *British Medical Journal*, 1975, **4**, 726.
24 Bailey, R R, and Wallace, M, *British Medical Journal*, 1978, **1**, 48.
25 Smellie, J M, *et al*, *British Medical Journal*, 1976, **2**, 203.
26 Smellie, J M, and Normand, I C S, *Archives of Disease in Childhood*, 1975, **50**, 581.
27 Orikasa, S, *et al*, *Journal of Urology*, 1978, **119**, 25.

The laparoscope: useful tool or dangerous weapon?

Obstetricians and gynaecologists stand apart from their colleagues in the almost masochistic zeal of their self-examination and self-criticism. Hospital statistical reports, maternal mortality surveys, and perinatal mortality and morbidity reviews, often highly critical, are all part of the obstetrician's way of life. Recently the same approach has been turned to gynaecological laparoscopy in a study[1] organised jointly by the Royal College of Obstetricians and Gynaecologists, the DHSS, and the medical defence organisations.

After Steptoe's pioneering work in the early 1960s laparoscopy was taken up by British gynaecologists with remarkable enthusiasm. The ability to see the pelvic organs without formal laparotomy proved a great attraction; to many gynaecologists the ingenious instrument had something of the fascination of a new toy. Soon techniques were developed to allow minor surgery, and laparoscopy proved particularly useful for tubal sterilisation. The increasing demand for irreversible contraception has made this the predominant use of the instrument today.

Yet, despite the general enthusiasm, there have been disquieting reports of serious complications and even deaths. Uncertainty as to the true extent of these ill-effects led to setting up the joint inquiry. What can we say of the results, which reviewed 50 000 operations? On the face of it gynaecological laparoscopy appears to be outstandingly safe, with a mortality rate of only 8 per 100 000. Nevertheless, only about 80% of the estimated number of laparoscopies occurring in the year covered by the study found their way into the survey. That might not be too important if it could be established that the deficit was attributable to some institutions' not taking part in the inquiry; but, in fact, a sample taken from co-operating hospitals showed that only 79% of their patients had been entered. Possibly some of those in whom serious complications arose might have been less likely to be reported because of worry about litigation. Fixing entry into the study at the time that laparoscopy was arranged rather than when it was performed would have avoided that source of bias. Furthermore, survey forms which for various reasons could not be processed showed a 9% incidence of complications compared with 3·6% in those which were entered in the survey.

The three parts of the laparoscopic procedure that most often gave rise to complications were inducing the pneumoperitoneum, introducing the trocar, and diathermy of the tubes or other structures. One reassuring finding was that the anaesthetic risk was very low. Two of the four deaths (and perhaps three) were such that they must be regarded as specifically related to the procedure and would not have occurred with an alternative technique. In one instance a bowel injury, unrecognised at sterilisation by electrocoagulation, ultimately led to death. In another, death occurred after induction of pneumoperitoneum and was confirmed at necropsy as being due to gas embolism. Another death occurred in similar circumstances, but the report gave no details of the necropsy findings. In the fourth case cardiac arrest occurred at the end of the procedure and was not obviously related to the pneumoperitoneum. These mortality and morbidity figures are roughly comparable with those reported in similar large reviews in the United States,[2-4] with similar designs and almost certainly similar types of bias. The report compares favourably the overall mortality rate with the recurrent annual mortality rate attributable to oral contraception. A more important comparison, perhaps, is with alternative methods of sterilisation, but this information is not available.

As tends to happen with computerised data collection on a large scale, some quite unexpected and interesting figures emerge. Many of these bear on the fundamental organisation of the NHS with its large proportion of operations performed by doctors in different trainee grades, many unsupervised. The higher rate of complications in operations performed in these circumstances is a general problem not specifically related to laparoscopy. Occasionally the report gives the impression that some of the data were processed through a computer to emerge untouched by the human mind. We are told, for example, that as the complication rate was higher in operations lasting over 35 minutes the operating time should be kept below this—bizarre advice indeed.

The commendable enthusiasm generated through the Royal College of Obstetricians and Gynaecologists for this survey encouraged the voluntary co-operation of doctors

throughout the country. The project was the first of its kind, and the lessons learnt from it should allow subsequent surveys to achieve more with less effort. What procedure should be the next for a national audit of this kind? Tonsillectomy? Haemorrhoidectomy? Gastroscopy? Colectomy? There are many which deserve it as much if not more than laparoscopy.

[1] *Gynaecological Laparoscopy. The Report of the Working Party of the Confidential Enquiry into Gynaecological Laparoscopy*, eds G Chamberlain and J C Brown. London, Royal College of Obstetricians and Gynaecologists, 1978.
[2] Phillips, J, *et al*, *Journal of Reproductive Medicine*, 1976, **16**, 105.
[3] Phillips, J, *et al*, *Journal of Reproductive Medicine*, 1977, **18**, 219.
[4] Phillips, J, *et al*, *Journal of Reproductive Medicine*, 1977, **18**, 227.

A numbers game

Necessarily, the value of laboratory tests (whether used for discriminating between health and disease, to aid diagnosis, or to monitor treatment) depends on the validity of the reported result. While it is generally accepted by both clinician and laboratory specialist that what is reported can only be an approximation to the truth, and that from time to time errors may occur, the process is given an air of respectability by the tacit acceptance of a normal or reference range of values. These ranges are statistically based and designed to minimise the overlap between values in health and disease. Morgan[1] has recently reminded us that this naive approach can be misleading, for what we are doing is to compare a measurement at a single moment with a group of values. The central assumption is that the single value is truly representative of the person at that time.

The factors that influence a result are well recognised. Some affect specimen collection—venous stasis, haemolysis, and posture; among analytical factors are the method used and the standard of its performance; while age, sex, and race, and individual factors such as time of day, biological rhythms, diet, exercise, and drugs all contribute to the total variance. The larger the group, the more variables will be incorporated, the larger the reference range becomes, and the poorer will be its discrimination between health and disease. When these variables are reduced by selecting age- and sex-related ranges, attending to details of specimen collection, and using better analytical techniques, the ranges become more refined and apparently more useful. They ignore, however, the important component of intrapersonal variation.

Even if a relatively steady state is reached in an individual, then repeated samples still show a clear intrapersonal variation,[2-4] and its degree differs for different constituents of biological fluids.[4 5] Although intrapersonal and interpersonal variations are inextricably mixed, the greater the contribution of the former to total variance the smaller is the usefulness of the single-sample result. Morgan[1] illustrates the practical problem from a study in Leeds in which two blood samples for potassium estimation were drawn from a group of patients with an interval of a month. Though the number of patients with hypokalaemia (11 and 15) was similar on the two occasions, only four had a low potassium concentration both times; the patients had a greater intrapersonal variation than did controls.

There is no simple solution. Clearly, every effort must be made to reduce as many of the known variables as possible,[6] but paradoxically this increases the effect of intrapersonal variation. Replicate testing would give a better measure of an individual's "setting" for a given constituent, but that would raise laboratory and other costs. The ideal would be to test the individual against his own "normal" range—for departure from his own normal is more important than from the conventional group reference ranges. This means serial measurements over a period—one justification for the practice of some laboratories that indulge in cumulative reporting.[7] Possibly statistical techniques would provide another alternative[6]; but for the present, just as the patient is the best specimen container, equally he seems to be the best guide to biochemical markers of his own health.

[1] Morgan, D B, *Annals of Clinical Biochemistry*, 1978, **15**, 49.
[2] Williams, G Z, *et al*, *Clinical Chemistry*, 1970, **16**, 1016.
[3] Harris, E K, *et al*, *Clinical Chemistry*, 1970, **16**, 1022.
[4] Pickup, J F, *et al*, *Clinical Chemistry*, 1977, **23**, 842.
[5] Harris, E K, *Clinical Chemistry*, 1974, **20**, 1535.
[6] McPherson, K, *et al*, *Clinical Chimica Acta*, 1978, **84**, 373.
[7] Harris, E K, *Clinical Chemistry*, 1976, **22**, 1343.

Serotonin, platelets, and autism

In recent years there has been a spate of research into the role of serotonin (5-hydroxytryptamine, 5HT) in neuropsychiatric conditions in childhood.[1 2] Serotonin is concerned in synaptic transmission in the central nervous system, and abnormalities in blood serotonin concentrations have been reported in a wide range of neurological and psychiatric disorders. Close parallels exist between the properties of blood platelets and serotonergic synaptosomes in the central nervous system, and the platelet has come to serve as a model of a serotonergic neurone.[1 2] But, while there is probably a common mechanism for serotonin binding in the two locations, platelets are more directly exposed to the environment than are brain cells, and the efflux of serotonin from platelets is not necessarily comparable to transmitter release at synapses.[3] Nevertheless, such parallels have been suggested, and attention has been focused on the possibility of serotonin dysfunction in infantile autism.[4]

Schain and Freedman[5] were the first to note high blood concentrations of 5HT in a proportion of children loosely diagnosed as autistic. Similar high concentrations were also found in non-autistic children with severe mental retardation. Since then better controlled investigations have confirmed both observations.[6] Serotonin concentrations are raised in about a third of autistic children and about half of severely retarded children[7] other than those with Down's syndrome (in whom the concentrations are abnormally low[1]), and in individual children they appear to be stable over several years.[7] The mechanisms remain obscure. The increase in 5HT does not appear to be due to diet, medication, or other extraneous influences, or to differences in the number of platelets or alterations in monoamine oxidase activity.[7-9] Cohen *et al*[10] have reported lower concentrations of the serotonin metabolite 5-hydroxyindolacetic acid (5HIAA) in the cerebrospinal fluid of autistic than in that of non-autistic psychotic children. The interpretation of that finding is far from clear, however, since neither group differed significantly from controls, whose 5HIAA concentrations were intermediate between the autistic and psychotic groups.

Another approach has been to study the uptake and efflux of serotonin from the platelets of autistic children.[6] Boullin *et al*[11] reported increased serotonin efflux as a finding specific to autism, but this was not confirmed by Yuwiler *et al.*[12] Whether the conflicting results reflect differing biochemical