from Venezuela and Malawi, such programmes might also contribute to the first objective—interrupting transmission—by promoting BCG vaccination or revaccination of contacts.[21] Achieving the third objective—preventing deformities—relies mainly on surveillance to ensure early detection of nerve damage and appropriate treatment for reactions. Until the first two objectives are achieved the paper by ffytche and colleagues will remain relevant.[1]

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Saliva as a diagnostic fluid

Second now to blood?

Interest has been increasing in non-invasive diagnostic testing. Some of this attention stems from the AIDS epidemic, which has provided a new rationale for haemophobia, while other factors include new developments in home based diagnostic tests, a demand for samples collected in the home or workplace, and the close linkage of biotechnology to diagnostic tests.

Diagnostic tests based on fluid generally use blood and urine and less frequently the esoteric fluids such as saliva, sweat, and tears. Saliva's popularity has suffered because it lacks "the drama of blood, the sincerity of sweat and the emotional appeal of tears."[1] Sweat and tears, however, are difficult to obtain in sufficient quantities for routine testing, and urine will always lack the charisma of the other fluids. Saliva, by default, therefore becomes the most favoured alternative to blood.

Over 2500 papers dealing with salivary diagnostic tests have been published since 1983, and an extensive bibliography is being prepared for a forthcoming meeting on the topic, sponsored by the New York Academy of Sciences, to be held on 22-25 October in Florida. A detailed analysis of these papers is under way, but several observations are already clear. The sources of the publications are wide and diverse in terms of both country of origin and topic. Subjects range from forensic medicine to clinical endocrinology and from dental medicine to veterinary science. Increasingly, saliva is being used to monitor antibodies (to viruses[2,3] and bacteria[4,5]), drugs of misuse,[6,7] and steroid hormones.[8,9] Saliva's main advantage is that the patient can collect samples at home when clinically relevant or in other places, including the workplace, where collecting blood or urine may be difficult.

Most molecules present in blood or urine can also be detected in salivary secretions. Their concentrations in saliva are usually one tenth to one thousandth of those in blood. Although highly sensitive methods of detection are required, technical advances have made this feasible. Studies of the correlation between concentrations in blood and saliva have found examples of excellent concordance (ethanol, cortisol, theophylline, and antibodies to HIV) and poor concordance (thyroxine, dihydroepiandrosterone, prolactin, and adrenocorticotrophic hormone).[10]

Ideally, the salivary concentration of the drug or hormone should be independent of the salivary flow rate and should correlate with blood concentrations of the substance. An important question is how drugs and hormones enter saliva. Conjugated steroids seem to enter through tight junctions in a flow related process (hormone concentration increases as salivary flow rate increases), and their concentrations in saliva are therefore unlikely to provide a useful measure of their concentrations in blood.

Finally, how saliva is collected is important. Many doctors, comfortable with collecting blood and urine, are intimidated by the idea of collecting saliva. Aesthetic and scientific considerations arise, including which fluid is being collected (whether duct saliva, whole saliva, or gingival crevicular fluid) and the method of recovering molecules from the collecting device. Gingival crevicular fluid is a serum transudate present in the mouth that often more closely resemble serum, but obtaining it in sufficient quantities is difficult. Several companies have devised oral collection devices—for example, a sac for small molecules, an immobilised support, and a device for collecting an oral transudate.

Tests based on saliva have already made substantial inroads into diagnosis. For some molecules—for example, antibodies, unconjugated steroid hormones, and certain drugs—the techniques are sufficiently sensitive to reflect blood concentrations of the substance accurately. New collecting devices should make doctors more comfortable with using saliva as an alternative to blood. Future research should define further the molecules, patients, and circumstances best suited to this form of testing.

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New developments in the fragile X syndrome

Time to consider screening?

Not only did 1991 mark an important milestone in the understanding of the fragile X syndrome but a whole new vista opened up for this most common form of familial mental retardation. The syndrome derives its name from the abnormal chromosome, which was identified in 1969.[1] Not until 1977 was a successful medium found that reliably showed the chromosome cytogenetically[2]; this procedure is both labour intensive and requires skill. Furthermore, it is not very good at detecting clinically normal carriers of both sexes, which makes reliable genetic counselling difficult.

Fragile X syndrome has a unique mode of inheritance, which is neither dominant nor recessive. Found in all racial and ethnic groups, the syndrome affects about 1:1360 males; for every five affected males there is another one who inherits the gene without being affected (described as a normal transmitting male). Mental retardation affects about 1:2000 females, although this represents only about a third of heterozygotes.[3]

Mental retardation is moderate to severe (IQ 20-70). Other features in affected males include a long face, large ears, macro-orchidism, autistic behaviour, hyperactivity, and speech disorders. The clinical features may vary, being less pronounced in females and much less so in prepubertal children. In infancy the syndrome may present as developmental or speech delay. Not uncommonly the diagnosis is made in a first child only after the birth of a second or third affected child in the family.

The milestone in the understanding of the syndrome was the identification and mapping of the fragile X mental retardation-1 gene.[4-6] Further international collaboration has solved one of the genetic paradoxes of this condition.[7] In a region of this gene there is an enlarged CGG sequence, which seems to be the fragile X mutation. Normal people have between six and 54 CGG repeats in this region. In normal transmitting males and carrier females this area expands to between 52 and 200 repeats and is thought to be a premutation. Those expressing the full mutation show a further increase in this area of up to 1000 repeats. This expansion occurs only during female meiosis. The risk of expansion from premutation to full mutation can now be accurately assessed by knowledge of the carrier CGG repeat number, which facilitates genetic counselling. Consensus is being reached about the latest DNA tests, and clinical geneticists are agreeing that screening for fragile X should be introduced once these new tests have been fully evaluated.[8]

A further problem remains. Despite being second to Down's syndrome as an identifiable cause of mental retardation fragile X syndrome is not yet diagnosed as commonly as might be expected from the original studies of prevalence. This may reflect the fact that the syndrome has attracted little publicity: few doctors and even fewer members of the public seem to know anything about it. Regionally funded screening programmes should now be considered to identify previously undiagnosed people in special schools, sheltered workshops, and accommodation for those with severe learning disabilities. Until these index cases are diagnosed neither can they receive the best attention, given what is known about the complex behavioural profile of people with fragile X syndrome,[9] nor can their families receive adequate genetic counselling. Any moves to rectify the current deficiencies will inevitably have implications for the workload of both clinical geneticists and the laboratories performing the tests.

Screening selected populations for the syndrome makes financial sense: American estimates of the costs of lifelong care of someone with the syndrome vary from $1m to $4m.[10] Five years ago Gillian Turner and colleagues, who performed large scale screening in New South Wales, concluded that "the onus is on health authorities everywhere to state why they are not screening for the fragile X syndrome."[11] We are now approaching the time when health authorities will have to start producing their replies.

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