LETTERS TO THE EDITOR

Stavudine induced macrocytosis

Recently we noted that patients on stavudine among our cohort of HIV positive patients were tending to have an elevated mean corpuscular volume (MCV). This prompted us to perform a retrospective analysis of the case notes of all our patients on stavudine (n = 21, 19 males, two females). Four patients were excluded from analysis since one patient had bone marrow failure of unknown origin and was transfusion dependent; one patient was found to have a low folate level secondary to HIV enteropathy; and two patients known to have very high alcohol intakes. The patient found to be folate deficient had only 4 weeks’ treatment with stavudine during which time his MCV rose by 2.4 x 10^9/l. Both patients with a high alcohol intake showed increasing MCV on stavudine: one of 5.3 x 10^9/l over 8 weeks and the other 3.7 x 10^9/l over 5 months. Both female patients had normal thyroid function tests and the male patients were all clinically euthyroid. Vitamin B12 and folate levels were available for 12 patients who had been sampled when the MCV was noted to be elevated and were normal. All the patients were on prophylaxis for Pneumocystis carinii pneumonia (cotrimoxazole, dapsone, or pentamidine) for at least 6 months before starting stavudine and therapy had not been changed in any patient. Apart from these drugs none of the patients was taking any other drugs which are associated with macrocytosis. Eight patients discontinued zidovudine at the point of starting stavudine; in each case the MCV increased where it might have been expected to fall. One patient who was prescribed stavudine did not develop macrocytosis. He was challenged regarding his compliance and admitted to never having taken the drug.

The data is summarised in the table. There is a progressive increase in MCV with the duration of treatment. As this was a retrospective study, MCV values for certain periods were not available for all the patients and some patients had not yet completed 20 weeks on stavudine.

To the best of our knowledge, macrocytosis has not been reported in association with stavudine until we notified the Committee on Safety of Medicines. The mechanism of zidovudine induced macrocytosis is unknown. Since both these drugs are thymidine analogues and are known to share metabolic pathways, the mechanisms may be similar.

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Accepted for publication 15 July 1997

Progressive increase in MCV related to duration of treatment with stavudine

<table>
<thead>
<tr>
<th>Time</th>
<th>No of patients</th>
<th>Mean increase MCV (&lt;10^9/l)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15</td>
<td>93-60</td>
<td></td>
</tr>
<tr>
<td>4-12 weeks</td>
<td>14</td>
<td>97-10</td>
<td>3.95</td>
</tr>
<tr>
<td>13-24 weeks</td>
<td>12</td>
<td>100-50</td>
<td>4.71</td>
</tr>
<tr>
<td>12-18 weeks</td>
<td>9</td>
<td>106-73</td>
<td>8.41</td>
</tr>
<tr>
<td>12-20 weeks</td>
<td>7</td>
<td>105-05</td>
<td>10.47</td>
</tr>
<tr>
<td>12-20 weeks</td>
<td>7</td>
<td>112-00</td>
<td>12.44</td>
</tr>
</tbody>
</table>

Biopsy of male genital dermatoses

In 1993 a paper was published in *Genitourinary Medicine* on the experience of genitourinary physicians in the diagnosis of penile dermatoses and the usefulness of penile biopsy.1 Of 71 patients seen over a 1 year period, 60 (85%) underwent a penile biopsy as the diagnosis was not made on clinical grounds. A clinical diagnosis was made in nine patients and penile biopsy considered unnecessary. Histological findings were consistent with the initial clinical diagnosis in 33% of the 60 patients undergoing a biopsy and it was concluded that diagnosis based on clinical appearance alone is inadequate. We would like to report our experience on the use of penile biopsy within the setting of a special penile dermatoses clinic in the dermatology department in which the patients were assessed by a dermatologist with an interest in dermatoses of the male genitalia.

A specific monthly clinic was set up in the dermatology department in 1993 for the diagnosis and management of men with penile dermatoses. Patients are referred to the clinic from various sources including the genitourinary clinic, the general dermatology clinic, dermatologists from other hospitals, and general practitioners. The clinic is run by a dermatologist with an interest in diseases of the genitalia and is attended by a genitourinary physician (DH) and, more recently, a urologist (MD).

In all, 286 patients have been assessed over a 4 year period. Patients ranged in age between 18 and 50 years. The majority of patients (n = 223) ranged in age between 18 and 50 years. The commonest presenting conditions were psoriasis (n = 68), penile infections (n = 47), seborrhoic dermatitis (n = 26), lichen sclerosus (n = 36), lichen planus (n = 28), Zoon’s balanitis (n = 23), and eczema (n = 21). Less common diagnoses were vitiligo (n = 7), irritant contact dermatitis (n = 9), lichen simplex (n = 6), allergic contact dermatitis (n = 3), Bowen’s disease (n = 3), Bowenoid papulosis (n = 3), squamous cell carcinoma (n = 1) and balanoposthitis (n = 2), idiopathic penile balanitis (n = 2), and cirrinate balanitis (n = 1).

In most cases (n = 218, 77%) a clinical diagnosis was reached without the need for a penile biopsy. In total, genitourinary patients (6%) were biopsied: 19/36 (53%) patients with lichen sclerosus were biopsied of whom six (32%) had a biopsy performed to elucidate the diagnosis as a firm diagnosis could not be made on clinical grounds; 13 patients with lichen sclerosus (68%) had a biopsy performed to confirm the clinical diagnosis and assist clinical management; 17/23 (74%) of patients with Zoon’s balanitis were biopsied, in the cases to confirm the clinical diagnosis, two patients with a clinical diagnosis of Zoon’s balanitis and lichen sclerosus had dual pathology confirmed histologically; 10/28 (36%) patients with lichen planus were biopsied, of these four (40%) were biopsied to elucidate the diagnosis because of clinical uncertainty, while six were biopsied to confirm the clinical diagnosis; 5/21 (24%) patients with eczema, 4/30 (13%) patients with viral warts, 2/68 (3%) of patients with psoriasis were biopsied, in each case to confirm the clinical diagnosis. A clinical diagnosis was made if the need for biopsy was made in all cases of seborrhoic dermatitis, lichen simplex, allergic contact dermatitis, idiopathic oedema, vitiligo, and in the case of cirrinate balanitis.

There was a very high concordance between clinical diagnosis and histological diagnosis and in only two cases did the findings result in a change in the diagnosis. In both of these a clinical diagnosis of lichen sclerosus was made while in one features of lichen planus were present histologically and in the other the histological findings were non-specific.

Our experience most patients with inflammatory penile disease such as psoriasis, eczema, lichen simplex, contact dermatitis, and lichen planus have cutaneous signs at extragenital sites and a full examination of these sites is mandatory. Apart from the biopsy confirming the diagnosis, in those patients a firm diagnosis was made and attended by a genitourinary physician (DH) and, more recently, a urologist (MD).

Accepted for publication 15 July 1997

Characterisation of high level tetracycline resistant *Neisseria gonorrhoeae* isolates

Three of 1039 clinical isolates from consecutive patients with urethritis, who attended urological or STD clinics in Tokyo and Kanagawa area between 1985 and 1995, were determined as tetracycline resistant *Neisseria gonorrhoeae* (TRNG). These strains had minimum inhibitory concentrations (MICs) of >16 mg/l and gave a zone of inhibition of <30 mm from the edge of the 30 μg tetracy-

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Accepted for publication 11 November 1997 by guest.

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cine disc to the edge of confluent growth (table). In this study, we further characterised the tetM genes of these TRNG strains.

Ison et al.1 previously reported the primer pair (A: 5'-GGTCATACAGCA-CAACTCG-3' and B: 5'-TCTTCGGTACAGTTACTCG-3') for detection of tetM in N. gonorrhoeae. These sequences were derived from that of the Unasplasma sp. genome. More recently, the nucleotide sequences of the tetM genes of American and Dutch type plasmids have been determined and suggested that the tetM determinant found in the American type plasmid has a different origin from that in the Dutch type.2 Because the sequence of the tetM gene from Dutch type plasmid which corresponds to the primer B is different from that of American type plasmid,3 primer BZ (5'-GGTCATACAGCA-CAACTCG-3') was used instead of the primer B to detect Dutch type tetM. The cells grown on a Kellogg's agar medium were lysed in 100 μl of distilled water for 10 minutes at 94°C, and 1 μl of lysate was added to a polymerase chain reaction (PCR) mixture. The PCR mixture contained 0.2 mM (each) deoxynucleoside triphosphate, 50 pmol of each oligonucleotide primer, TaKaRa Taq DNA polymerase (TaKaRa Shuzo, Kyoto, Japan), and buffers provided by the manufacturer in a total volume of 50 μl. The mixture was overlaid with 50 μl of mineral oil and heated in a DNA thermal cycler PJ-2000 (TaKaRa) for 25 cycles consisting of 45 seconds at 94°C, 60 seconds at 58°C, and 60 seconds at 72°C. PCR amplification using the primer pair of A and B gave a product of the predicted size of 765 base pairs (bp) from strain 60601 but not from 5120 or 6010. On the other hand, the primer pair of A and B amplified a 765 bp fragment from strains 5120 and 6010 but not from 60601. As restriction digests usingMspI of the PCR products of 60601 gave the predicted three fragments of 370, 260, and 140 bp. MspI digests of the PCR products of 5120 and 6010 generated two bands of 540, 140, and 90 bp. The amplified products were sequenced using the ABI PRISM Dye Terminator Cycle Sequencing Ready Detection Kit (Perkin-Elmer Corp CT, USA) and the ABI 310 Genetic Analyzer (Perkin-Elmer Corp), and that from 60601, and 6010 and 5120 were identical to corresponding sequence of the tetM gene from American and Dutch type plasmids, respectively.

It is of interest that the isolation rate of TRNG was quite low and both American and Dutch type tetM genes were found in Tokyo and Kanagawa, Japan during the study period with a strain isolated in 1985 which was obtained from a patient who had been transported from another country, but has not spread in Tokyo and Kanagawa area. Ison et al.4 found two types of HpaII (MspI) digestion pattern of the PCR products from tetM in TRNG strains. In this study we clearly distinguished the American type tetM gene from the Dutch type one using the PCR with the sets of the primer pairs. Further investigations will be needed to elucidate the prevalence of each type of tetM gene in N. gonorrhoeae infections.

4. Accepted for publication 15 July 1997

MATTERS ARISING

Epidemiology of genital Chlamydia trachomatis

Simms et al.5 in their review of the epidemiology of genital Chlamydia trachomatis in England and Wales state that "as hoc prevalence and case finding studies carried out over the past 20 years were critically assessed in terms of study design and testing methodology." The authors, however, do not define what is meant by "as hoc" and do not make explicit how the cited literature was obtained, sifted, and appraised. As a consequence they fail to identify all relevant published prevalence studies.

I recently reviewed the literature relating to the prevalence of G. trachomatis infection in women attending British general practice5 which used an earlier reviewer of the literature5 (as described in my letter of April 23, 1994, JAMA 1994;272:1367-71). As I wished to ensure that all relevant studies were included I used an explicit search strategy and stated the reasons for inclusion or exclusion of the identified studies. This led to 15 relevant prevalence studies being identified and appraised. Simms et al.5, in contrast, identified only six of these studies.

As far as general practice was concerned nine studies which met defined criteria were included in the review. It was concluded that the best current estimate of the prevalence of genital chlamydia in women attending general practice is 3% to 4% but the confidence range from 2% to 12%.6 This conclusion was based on the results of two large general practice prevalence studies7 which were not quoted by Simms et al.6 Six studies were identified from a review of family planning literature with estimated prevalences of women attending family planning clinics ranging from 3% to 7%.6 The methodological quality of prevalence studies of genital chlamydia infection in women in general practice and at family planning clinics is, however, unsatisfactory. Common features of the studies reviewed were non-random sampling, small sample sizes, unclear inclusion/exclusion criteria, and use of different testing methods. This conclusion is in agreement with that of Simms et al.6.

The discrepancy between my findings and those of Simms et al.6 supports the argument made by the Evicore7 and British family planning and working group8 that all reviews of the medical literature should make explicit how the cited literature was obtained, sifted, and appraised.9 Failure to do so is likely to lead to important papers being missed.

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Reply

Dr Stokes raises a number of important issues and correctly points out that the method of assessing the literature was not fully explained.1 The paper aimed to provide a concise, comprehensive, and timely review of what is a rapidly expanding field. A literature search was carried out using Medline and by trawling the literature. However, we confined to England and Wales (one review cited by Dr Stokes was concerned with the United Kingdom as a whole).2 To ensure the reliability of the reports of studies which were assessed in terms of the population studied, the presentation of results, and the testing strategy used. Studies were only included where the raw data were presented made. Studies of diagnostic accuracy tests and diagnostic tests have undergone a rapid evolution over recent years and a wide variety of tests and testing strategies have been used. It is difficult, if not impossible, to make comparisons between studies. However, we decided to include only those studies that used a strategy based on screening and confirmatory tests.

Studies undertaken by physicians, micro-