serological test for syphilis (TPHA),
Gram stain urethral smear for microscopy,
urethral cultures for *Neisseria gonorrhoeae*,
Chlamydia trachomatis,
oral spirochaetes,5 non-sporing anaerobic organisms and *Mycoplasma*
spp. Patients with more than five polymorphs per high powered field
(× 1000) in the Gram stained smear of urethral discharge were diagnosed as
having urethritis.

Fifty one patients were recruited in total. Thirty two had no evidence of
urethritis (28 were homosexual and 43 were heterosexual). Nineteen
patients had evidence of urethritis, (17 were homosexual and two were
heterosexual). The results of microbiological investigations are listed in
table 1. Four patients in the study group had gonococcal urethritis, but
no organism emerged as an obvious candidate for the cause of NGU. We
were surprised that no patients had evidence of chlamydial infection, and also by the relatively high prevalence of *z*-haemolytic streptococci in the
urethritis and control groups.

We decided to extend the study by examining urethral specimens from a
further group of 20 asymptomatic men with particular emphasis on the
presence or absence of *z*-haemolytic streptococci. The results of this are
shown in table 2. The *z*-haemolytic streptococci from all groups were
speciated (API 20 strep) and the majority were found to be *Streptococcus mitis*.

Of the 19 patients with urethritis, 15 had NGU of whom 10 had a previous history of urethritis. The remaining five had no previous history.

From this relatively small study we conclude that orogenital contact can
be associated with the development of NGU, although two thirds of the patients with NGU had a previous history of urethritis. *Chlamydia trachomatis* does not appear to be a common pathogen in this group of patients. *Streptococcus mitis*, an oral streptococcus whose taxonomy is controversial1 appears from this study to be a common urethral commensal in men irrespective of a history of orogenital contact.

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**Table 1** Results of urethral cultures from 51 patients taking part in the study

<table>
<thead>
<tr>
<th>Organism</th>
<th>Urethritis group</th>
<th>Non-Urethritis group</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>19</td>
<td>32</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Ureaplasma urealyticum (&gt; 10^6 cfu/ml)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mycoplasma hominis (&gt; 10^6 cfu/ml)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mycoplasma spp (other)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>z</em>-haemolytic streptococci</td>
<td>7*</td>
<td>11†</td>
</tr>
<tr>
<td>Haemophilus parainfluenzae</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Oral spirochaetes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anaerobic organisms</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Isolates breakdown to 6 Streptococcus mitis, 1 Streptococcus sanguis.
†breakdown 8 Streptococcus mitis, 2 Streptococcus sanguis 1 Streptococcus milleri.

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**Table 2** Results of urethral cultures from 20 asymptomatic male patients

<table>
<thead>
<tr>
<th>Male patients</th>
<th>No isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organism</td>
<td></td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>0</td>
</tr>
<tr>
<td>Ureaplasma urealyticum (&gt; 10^6 cfu/ml)</td>
<td>0</td>
</tr>
<tr>
<td>Mycoplasma hominis</td>
<td>0</td>
</tr>
<tr>
<td>Mycoplasma (other)</td>
<td>0</td>
</tr>
<tr>
<td><em>z</em>-haemolytic streptococci</td>
<td>7</td>
</tr>
<tr>
<td>Haemophilus parainfluenzae</td>
<td>3</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>2</td>
</tr>
<tr>
<td>Oral spirochaetes</td>
<td>0</td>
</tr>
<tr>
<td>Anaerobic organisms</td>
<td>0</td>
</tr>
</tbody>
</table>

*All isolates were Streptococcus mitis

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GENERATE MATTERS ARISING

The natural history of human immunodeficiency virus infection

Kelly et al1 stated in a recent report that oral hairy leukoplakia (OHL) was
not as important a factor as the presence of oral candida in deciding the
timing for anti-retroviral therapy. Although OHL is classified along with oral candida as a manifestation of the secondary infections associated with
symptomatic HIV infection (CDC IV-C2),2 there are individuals who have OHL alone, without additional clinical or laboratory evidence of advancing
HIV disease. What is the significance of OHL when seen in isolation?

We have studied the prevalence of OHL in a similar cohort of exclusively
homosexual/bisexual men studied prospectively since 1982.24 In this
cohort, OHL in isolation was not used to classify the subjects as having IV-
C2 disease, which was based on the presence of at least two of the CDC indicator diseases.

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2 Sakell SG, Alpert S, Fiumara NJ, et al. Orogenital contact and the isolation of *Neisseria gonorrhoeae*, *Mycoplasma*


Accepted for publication 25 October 1990
We interrogated the cohort database for all HIV-infected subjects from the onset of OHL, together with details of their subsequent clinical behaviour. Having excluded those with an initial diagnosis of AIDS (CDC IV-C1, B, D, E) and on anti-retroviral treatment, there were 35 cases of OHL in the remaining categories (table). Most of these were in IV-C2, but a substantial proportion (45%) would otherwise have been classified CDC II and III.

The peripheral CD4+ count of subjects presenting with OHL displayed a wide range of values, but as a group, the CD4+ count deteriorated markedly as AIDS developed. The progression rate for these 35 subjects with OHL was 33% at 12 months and 83% at 36 months, comparable to rates determined by Kelly et al.1 and Greenspan et al.2 However, we identified four subjects with OHL (11%) who have been followed up for more than 36 months (mean 42.5, range 41–56 months), and who have not progressed to AIDS. One subject is in CDC II, the remainder in CDC III. These individuals may represent a sub-group of OHL—bearing subjects in which the severity of immunodeficiency is not as marked as in those with oral candida, for example, and in whom the rate of immunological decline seems slower. In classifying patients with OHL alone in CDC IV-C2, this heterogeneity, which may be reflected in their subsequent clinical behaviour, is lost.

In the light of current trends for earlier intervention with anti-retroviral and prophylactic agents, the clinical presence of OHL serves as an earlier (albeit "softer") marker of immunosuppression than oral can-
dida. We suggest that OHL should not necessarily be regarded as an ominous sign, but instead should prompt additional clinical and laboratory assessment of possible HIV disease progression.

Table  CDC status and peripheral blood CD4+ and CD8+ lymphocyte counts in HIV-infected homosexual/bisexual subjects presenting with oral hairy leukoplakia (OHL) and progressing to AIDS by eighteen months

<table>
<thead>
<tr>
<th>CDC status</th>
<th>Number (%)</th>
<th>Presenting with OHL</th>
<th>Mean &amp; median* T-cell counts/ul (range)</th>
<th>Progressing to AIDS</th>
<th>Mean &amp; median* T-cell counts/ul (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CD4+</td>
<td>CD8+</td>
<td>CD4+</td>
<td>CD8+</td>
</tr>
<tr>
<td>II</td>
<td>2 (6)</td>
<td>240</td>
<td>760</td>
<td>1 (8)</td>
<td>200</td>
</tr>
<tr>
<td>III</td>
<td>13 (37)</td>
<td>670</td>
<td>860</td>
<td>4 (34)</td>
<td>190</td>
</tr>
<tr>
<td>IV-A, C2</td>
<td>20 (57)</td>
<td>450</td>
<td>550</td>
<td>7 (58)</td>
<td>450</td>
</tr>
<tr>
<td>IV-B, C3</td>
<td>490</td>
<td>950</td>
<td>550</td>
<td>260</td>
<td>660</td>
</tr>
<tr>
<td>IV-C2</td>
<td>20 (57)</td>
<td>450</td>
<td>550</td>
<td>7 (58)</td>
<td>450</td>
</tr>
<tr>
<td>Totals</td>
<td>35 (100)</td>
<td>500* (150–1100)</td>
<td>650*(200–1300)</td>
<td>12 (100)</td>
<td>130* (50–620)</td>
</tr>
</tbody>
</table>

*Median values of lymphocyte counts obtained from all the subjects in each column.

Antiviral chemotherapy for retinitis in HIV-infected patients

Millar et al.1 are uncertain why zidovudine has apparently produced regression of retinitis in patients with the acquired immune deficiency syndrome (AIDS).2 They note that one possible explanation is a bidirectional interaction between cytomegalovirus (CMV) and human immunodeficiency virus (HIV) leading to down regulation of CMV replication when zidovudine inhibits HIV replication.3 Alternatively, HIV itself may play a more direct role in the development of retinitis than is currently supposed.4 Retinitis in patients with AIDS is attributed to CMV without proof that the association is causal.5 HIV-induced damage to neuroretinal cells could be the initiating event of retinitis in these patients, with CMV playing either no or only a secondary role.6 The clinical responses in AIDS-related retinitis produced in uncontrolled trials by the anti-CMV agent ganciclovir fail to establish either that the drug is effective7 or that the retinitis is caused by CMV.8 Anti-HIV chemotherapy alone or combined with anti-CMV chemotherapy could be more effective than anti-CMV chemotherapy alone in HIV-infected patients with retinitis. As assessment of combined systemic ganciclovir and zidovudine therapy is precluded by haematological toxicity,9 the role of adjunctive anti-HIV chemotherapy in retinitis will only be defined when less toxic anti-CMV agents or intravitreal ganciclovir therapy are used.

Matters arising

The natural history of human immunodeficiency virus infection.

R K Lau, P Jenkins and A J Pinching

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