Condylomata acuminata are caused by up to 60 different strains of the human papillomavirus (HPV). HPV 6 and 11 are typically associated with benign disease whereas HPV 16 and occasionally HPV 18 are more likely to lead to invasive squamous cell carcinoma. The disorder is usually sexually transmitted. The high proportion of male patients suggests that perianal warts are often acquired as a result of homosexual contact with an infected partner, but heterosexual acquisition is also frequent. Not all condylomata are acquired by sexual contact; the virus may persist in skin and can be transmitted by hands.

Perianal lesions are often inadequately eradicated by local topical therapy and there is a high risk of recurrence after all forms of treatment. In many cases recurrence may be due to reinfection. Diathermy ablation has been the mainstay of surgical treatment, but scissor excision is associated with a lower incidence of scarring and stenosis in extensive lesions. Combination therapy with adjuvant topical interferon and surgery may be advised for recurrent and extensive warts. Interferon should be avoided in HIV-positive patients; in this group, topical 5FU combined with surgery might be a better alternative.

HPV types 16 and 18 are associated with cervical and anal intra-epithelial neoplasia, which may progress to invasive squamous cell carcinoma, particularly in homosexual and heterosexual men, with HIV patients being particularly at risk. Such high-risk patients need careful surveillance.

**AETIOLOGY AND PREDISPPOSING FACTORS**

**HUMAN PAPILLOMAVIRUS (HPV)**

The human papillomavirus that causes perianal warts (Billingham and Lewis, 1982) is biochemically, antigenically and immunologically distinct from verruca vulgaris, the virus responsible for the common wart. HPV 1 and 4 are associated with plantar warts and HPV 2 is usually responsible for verruca vulgaris. In contrast, genital warts are caused by HPV 6 and 11 (80%), HPV 2 (18%) and HPV 16 and 18 (2%) (Cohen et al, 1990; Frasier, 1994). For years it has been known that warts can be transmitted by a cell-free filtrate (Lewis and Wheeler, 1967). Later electron microscopic studies reported by Oriel and Almeida (1970) indicated that intracellular virus particles and inclusion bodies were present in 13 of 25 patients with anogenital warts. The incubation period for HPV is 1–6 months and the virus of condylomata acuminata is difficult to eradicate.

There are more than 60 types of HPV (deVilliers, 1989). Those associated with anal condylomata are usually HPV 6, 11 and 2. HPV 6 and 11 are typically associated with benign disease (Duggan et al, 1989; Langenberg et al, 1993), whereas HPV 16 and 18 are the dominant oncologic types (Youk et al, 2001) associated with cervical cancer (Lorinez et al, 1987; Reid and Lorenz 1991), and invasive squamous cell carcinoma of the anus and perianal region. Others associated with dysplasia and invasive carcinoma are HPV 31, HPV 33, HPV 35 and HPV 45. Sequencing showed that 57% of HPV 16 were commonly found in invasive carcinoma of the cervix (Youk et al, 2001).

Accuracy of DNA typing is dependent on the method used. A single virus type is not always present; in fact, mixed infections were reported in 42% when material from condylomata, dysplasia and squamous cell carcinoma were examined (Duggan et al, 1989). Furthermore, sequential biopsies found different types on different days in 50/63 patients, so the HPV type may vary on different occasions. Thus, finding type 6 or 11 does not ensure a low risk of malignancy and emphasises the importance of completely clearing these infections, as well as ensuring adequate follow-up (Goldstone et al, 2001).

**TRANSMISSION**

The disease is spread principally by intercourse from subjects carrying the virus in the urethra, vagina, cervix or
anorectum. The task of tracing all contacts, particularly in promiscuous homosexual men, may be impossible. Another mechanism of infection is that the virus lies dormant on the mucosa of the anorectum and may only form anal warts following local trauma that allows the virus access to the tissues (Young, 1964). However, warts rarely, if ever, complicate other surgical operations or disorders like fissure or fistula, which are associated with tissue damage.

With increasing exposure of children to sexual abuse, sexually transmitted condyloma acuminata are becoming more prevalent in children—quite apart from the risk of transmission at birth from an infected birth canal or transplacental spread or by infected hands (Stumpf, 1980; Raimer, 1992; Budayr et al, 1996). There are a few patients who are not sexually active who acquire perianal warts from hand-borne transmission.

Recurrent and Reinfection

Repeated inoculation from continued sexual contact is one of the most common reasons for recurrence (Greene, 1992). HPV has a long incubation period and the virus may lie dormant in the skin for a considerable length of time, especially in thick keratinised hair-bearing areas, which may be resistant to topical therapy and which are not in close proximity to lymphatics (Hatch, 1991). HPV in pilosebaceous appendages may cause reinfection from hair shafts and sweat glands. Missed lesions may act as a reservoir of infection in the anal canal.

AIDS

Condylomata acuminata is sexually transmitted and although perianal warts may be seen in heterosexual men and women, it is common among promiscuous homosexual men (Marino, 1964; Waugh, 1972; Sohn and Robilotti, 1977). Of the 80 patients with perianal warts reported by Oriel (1971), 72 were men and 95% admitted to homosexual practices. Similarly, a high proportion of women with the disease admitted to having had anal intercourse (Abcarian and Sharon, 1982). Condylomata acuminata are a frequent feature among HIV-positive and AIDS patients, being found in 54% of men with AIDS (Palefsky et al, 1990). There is evidence in these patients of malignant transformation through AIN (intra-epithelial neoplasia) in 15%, which may progress to carcinoma-in-situ and invasive anogenital squamous cell carcinoma, often at an early age (Burns and van Goidsenhoven, 1970; Daling et al, 1982; Croxson et al, 1984; Longo et al, 1986; Bradshaw et al, 1992).

Transplant Recipients

Immunocompromised patients in general have a higher incidence of condylomata acuminata and anogenital neoplasia than the general population (Sillman and Sedlis, 1991). Genital warts are reported to affect 43% of renal transplant recipients, who are at increased risk of recurrence and dysplastic premalignant lesions (Palefsky, 1991).

Co-Existing Disease

A history of associated sexually transmitted disease is common. Abcarian and Sharon (1982) reported that 75% of their patients had attended STD (sexually transmitted diseases) clinics for treatment of other warts or sexually transmitted diseases such as gonorrhoea, Chlamydia, herpes or Cryptosporidium, and syphilis (Table 15.1). A similar pattern of co-existing disease was observed in Copenhagen (Jensen, 1985). Of the 185 men with anal condylomata in Chicago (Abcarian and Sharon, 1982), 74 had antibodies to hepatitis A or B, 20 had parasitic infections and 14 had enteropathogens associated with the gay bowel syndrome (Table 15.2).

Incidence

The incidence of anal condylomata may be increasing (Sohn and Robilotti, 1977). It is a common sexually transmitted disease (Bradshaw et al, 1992) and now represents a serious public health problem with one million new cases seen yearly (Department of Health and Social Security, 1979; Centers for Disease Control, 1986). Many more patients with anal lesions are now being referred directly to STD clinics, particularly as both general practitioners and the public are becoming more concerned with tracing contacts and identifying individuals who may be at risk of carrying the AIDS virus. AIDS patients and those receiving immunosuppression following transplantation are particularly susceptible to anogenital warts (van Driel et al, 1996).
Males are more commonly affected than women: the ratio varies from 9.2:1 to 3:1 (Powell et al, 1970; Swerdlow and Salvati, 1971; Abcarian and Sharon, 1982; Jensen, 1985).

Condylomata acuminata affect people who are most sexually active and the majority of patients are 20–30 years of age (Table 15.3). Some children are now acquiring infection at birth or from sexual abuse (Budayr et al, 1996).

### APPEARANCE AND SITES OF CONDYLOMATA

Warts may be discrete or multiple; they are usually elevated pink vegetative excrescences in the anal canal and on the surrounding perianal skin. Large lesions may coalesce to form polypoidal pedunculated or sessile masses that become hypertrophic with surface keratinisation. Lesions tend to be moist and easily traumatised, resulting in perianal bleeding.

Rectal involvement is uncommon (Corman, 1984). Jensen (1985) records involvement above the dentate line in 5 of 60 patients (9%) (Table 15.4). Warts are commonly found elsewhere, in particular on the penis, vulva, scrotum, vagina and urethra (Abcarian and Sharon, 1982). Other sites of involvement include the hands, feet and face (Table 15.5).

### CLINICAL FEATURES

Patients usually complain of pruritus ani and swellings that bleed during defecation (Table 15.6). Many patients will already have been treated for anogenital condylomata (Table 15.7). The duration of history is variable but most patients seek advice and treatment within 4–12 weeks. Occasionally warts will regress spontaneously (Pyrhonen and Johansson, 1975; Williams et al, 1976; LeBlanc et al, 1985; Kirby, 1988).

### HISTOLOGY AND MALIGNANT CHANGE

Histologically, condylomata acuminata are squamous papillomas. The principal microscopic features are papillomatosis, hyperkeratinisation, acanthosis and the presence of clear cells within the acanthotic epithelium. Normally, maturation, polarity and mild atypia is evident in the epithelium. If the lesions have been recently treated by podophyllin, enlarged cells become prominent, with a pale basophilic cytoplasm, dispersed chromatin and large perinuclear and paranuclear vacuolisation. Sometimes, eosinophilic cells with pyknotic nuclei or other nuclear alterations are seen after podophyllin treatment. These

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**TABLE 15.3 AGE DISTRIBUTION OF PATIENTS WITH CONDYLOMATA ACUMINATUM**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>20–30</td>
<td>92</td>
<td>3</td>
</tr>
<tr>
<td>30–40</td>
<td>76</td>
<td>6</td>
</tr>
<tr>
<td>40–50</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>50–60</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>185</td>
<td>15</td>
</tr>
</tbody>
</table>

**TABLE 15.4 DISTRIBUTION OF LESIONS**

<table>
<thead>
<tr>
<th></th>
<th>Podophyllin</th>
<th>Surgical excision</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perianal alone</td>
<td>4 (13)</td>
<td>6 (20)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Perianal plus:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anal canal</td>
<td>12 (40)</td>
<td>10 (33)</td>
<td>22 (37)</td>
</tr>
<tr>
<td>Anal canal, genitalia</td>
<td>5 (17)</td>
<td>6 (20)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Anal canal, genitalia, rectum</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Genitalia</td>
<td>6 (20)</td>
<td>5 (17)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Rectum</td>
<td>2 (7)</td>
<td>3 (10)</td>
<td>5 (9)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. From Jensen (1985).

**TABLE 15.5 WARTS ASSOCIATED WITH ANAL AND PERIANAL CONDYLOMATA**

<table>
<thead>
<tr>
<th>Location</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plantar</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Hands</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Facial</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Urethral</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Penile</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Scrotum</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Vulva</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

From Abcarian and Sharon (1982).
histological features are temporary and will regress completely within a few days of treatment (Prasad and Abcarian, 1980).

Giant condylomata may become locally invasive without penetrating lymphatics or blood vessels and are known as Buschke–Lowenstein tumours (Buschke and Lowenstein, 1925; Macharek and Weakley, 1960; Khoblich and Failing, 1967). They invade surrounding structures, such as the sacrum, coccyx, buttocks or even the abdominal wall (Judge, 1969; Shah and Hertz, 1972; Abcarian et al, 1976; Alexander and Kaminsky, 1979; Elliot et al, 1979). Sometimes they may undergo frank malignant change (Prasad and Abcarian, 1980; Lee et al, 1981) and, if so, treatment may fail to control the destruction of local structures, particularly the meninges, rectum and perineum, resulting in fatal sepsis (Shah and Hertz, 1972). In a review of 42 cases, the recurrence rate was 66% and malignant transformation occurred in 56% (Chu et al, 1994). This tumour is associated with HPV types 6 and 11.

Squamous metaplasia and in situ change may occur in both long-standing disease and in anal condylomata of short duration (Konketzny, 1914; Grisson and Delvaneo, 1915; Siegal, 1962; Oriel and Whimster, 1971; Fitzgerald and Hamit, 1974; Kovi et al, 1974; Croxon et al, 1984; LeBlanc et al, 1985; Longo et al, 1986). Some of these lesions become frankly malignant and result in invasive squamous cell carcinoma (Friedberg and Serlin, 1963; Sturm et al, 1975; Ejeckam et al, 1983). Carcinoma-in-situ is usually associated with HPV type 16 or 18 (Greene, 1992). Prasad and Abcarian (1980) reported six patients in their series of 330 (1.8%) with malignant change; two had giant condylomata, and frank malignant invasion had developed in four. Many more cases of invasive carcinoma have since been identified, particularly in homosexuals, immunocompromised patients and those with AIDS (Congilosi and Madoff, 1995).

Immunological factors play an important role in the malignant potential of this virus-induced cancer (Pyrhonen and Johansson, 1975). The natural history of AIDS patients with warts who develop carcinoma-in-situ differs from that of the non-AIDS group. Those with the HIV virus seem to progress rapidly from warts to in situ change. By contrast, a long history of recurrent warts over many years is recorded in patients who are not AIDS sufferers but who develop malignant change. Furthermore, the increase in malignant change in perianal warts and the prevalence of AIDS is more than coincidence.

Dysplasia should not be confused with the changes that occur following local therapy. Once malignant cells invade the stroma the diagnosis of malignant transformation should not be in doubt and these lesions should be treated as any other squamous cell carcinoma of the region (Judge, 1969; Shah and Hertz, 1972; Abcarian et al, 1976; Alexander and Kaminsky, 1979; Elliot et al, 1979). Sometimes they may undergo frank malignant change (Prasad and Abcarian, 1980: Lee et al, 1981) and, if so, treatment may fail to control the destruction of local structures, particularly the meninges, rectum and perineum, resulting in fatal sepsis (Shah and Hertz, 1972). In a review of 42 cases, the recurrence rate was 66% and malignant transformation occurred in 56% (Chu et al, 1994). This tumour is associated with HPV types 6 and 11.

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TABLE 15.6 PRESENTING SYMPTOMS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Podophyllin</th>
<th>Surgical excision</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling of lumps</td>
<td>26</td>
<td>27</td>
<td>53 (88)</td>
</tr>
<tr>
<td>Anal itching or discharge</td>
<td>21</td>
<td>23</td>
<td>44 (73)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>11</td>
<td>13</td>
<td>24 (40)</td>
</tr>
<tr>
<td>Pain or discomfort</td>
<td>6</td>
<td>8</td>
<td>14 (23)</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>2</td>
<td>1</td>
<td>3 (20)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.

From Jensen (1985).

TABLE 15.7 METHODS OF PRIOR TREATMENT IN 80 PATIENTS WITH RECURRENT ANAL CONDYLOMATA ACUMINATA

<table>
<thead>
<tr>
<th>Type of therapy</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Podophyllin</td>
<td>75</td>
</tr>
<tr>
<td>Single surgical excision</td>
<td>44</td>
</tr>
<tr>
<td>Multiple surgical excisions</td>
<td>26</td>
</tr>
<tr>
<td>Outpatient fulguration</td>
<td>17</td>
</tr>
<tr>
<td>Acid compounds</td>
<td>11</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>6</td>
</tr>
</tbody>
</table>

*Many patients were treated with multiple treatment modalities.

Malignant change has also been recorded in vulval warts (Charlewood and Shippe, 1953; Rhatigan and Saffos, 1977) and penile warts (Moraine, 1950; Rhatigan et al, 1971; Sigurgeirsson et al, 1991).

The association between anal warts, homosexual behaviour and anal cancer is now recognised, and is similar to the link between cervical cancer and its associations with the human papillomavirus. Half of patients with anal cancer have HPV type 16 and 18 DNA incorporated into the genome of their tumour cells (Schollefield et al, 1991), but
there is a great variation in the prevalence of HPV 16-associated anal cancer throughout the world (Northfield, 1991). Some patients with genital warts have evidence of intra-epithelial neoplasia (AIN), which is a recognised premalignant entity. A study of 210 homosexual and bisexual men revealed evidence of intra-epithelial neoplasia in 35%. Anal warts and HIV were independent risk factors for AIN (Carter et al, 1995). The increasing incidence of genital HPV infection has led to an increased incidence of anal cancer (Jones and James, 1992; Morgan et al 1994).

A study of 53 anal carcinomas revealed that 18 were associated with HPV: HPV 6 and 11 principally in perianal cancers and HPV 16 and 18 in anal cancer (Ramanujam et al, 1996).

**INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS**

**INVESTIGATIONS**

A search should be made for sexual contacts. The risk of reinfection must be clearly explained. Other sexually transmitted infections, particularly AIDS, hepatitis, gonorrhoea, lymphogranuloma venereum and syphilis, should be excluded. These patients should also be screened to exclude Chlamydia, herpes simplex and specific enteropathogens.

A thorough clinical assessment should include a search for oral, vaginal, urethral, vesical, and penile and scrotal warts. Patients should have a colposcopy to exclude AIN3, CIN3 or VIN3 as well as a routine speculum exam to search for vaginal warts. A proctosigmoidoscopy should be performed to exclude ano-rectal warts and cystourethroscopy is also sometimes advised. Suspicious lesions should be biopsied to exclude malignant change.

**DIFFERENTIAL DIAGNOSIS**

The only disorders likely to be confused with anal condylomata are condylomata lata of secondary syphilis and squamous cell carcinoma.

Condylomata lata are smoother and rather flatter than condylomata acuminata and there may be other signs of syphilis such as a maculopapular rash or snail track ulcers. In condylomata lata there is induration and the weeping mass emerging from the anus and can be quite difficult to see under the microscope by dark-ground illumination. The mass contains numerous spirochaetes, which can easily be seen from the roots of the May apple plant. The active agent podophyllotoxin is an antimitotic agent. It remains the most widely used topical chemical agent and has been used for at least 50 years (Kaplan, 1942; Marks, 1947). Podophyllin may be applied in liquid paraffin or in benzoin tincture, as either a 10 or 20% solution (Culp and Kaplan, 1944). Purified podophyllotoxin emulsions of 0.25 and 0.5% are available, which can be self-administered (Wang et al, 1994; Syed et al, 1994). Simmons (1981) compared treatment with 10 and 25% solutions of conventional podophyllotoxin but found that only approximately 25% of lesions completely disappeared, despite repeated applications over 3 months. Podophyllin may cause skin irritation and must be applied with great care; it cannot be used in the anal canal. Reported complications of podophyllin include severe necrosis, scarring and fistula-in-ano (Congilosi and Madoff, 1995). Purified podophyllotoxin causes less side effects and may be more effective than podophyllin (Bonnez et al, 1994).

Conventional podophyllin is applied with cotton-wool swabs on a stick. The solution is allowed a contact time of between 5 and 10 minutes, after which it is washed off. The process is repeated weekly for up to 3 months. Purified podophyllotoxin can be self-administered to perianal lesions and applied locally in the clinic to anal lesions. However, many clinicians advise surgical excision of intra-anal condylomata (Table 15.8).

**CHEMICAL AGENTS Podophyllin**

Podophyllin is a resin extract from the root of the May apple plant. The active agent podophyllotoxin is an antimitotic agent. It remains the most widely used topical chemical agent and has been used for at least 50 years (Kaplan, 1942; Marks, 1947). Podophyllin may be applied in liquid paraffin or in benzoin tincture, as either a 10 or 20% solution (Culp and Kaplan, 1944). Purified podophyllotoxin emulsions of 0.25 and 0.5% are available, which can be self-administered (Wang et al, 1994; Syed et al, 1994). Simmons (1981) compared treatment with 10 and 25% solutions of conventional podophyllotoxin but found that only approximately 25% of lesions completely disappeared, despite repeated applications over 3 months. Podophyllin may cause skin irritation and must be applied with great care; it cannot be used in the anal canal. Reported complications of podophyllin include severe necrosis, scarring and fistula-in-ano (Congilosi and Madoff, 1995). Purified podophyllotoxin causes less side effects and may be more effective than podophyllin (Bonnez et al, 1994).

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**Caustic acids**

Topical trichloroacetic or dichloracetic acid (Fowler’s solution—bismuth, sodium, triglycollamate 3%, achromycin and bichloracetic acid) has been advocated by Swerdlow and Salvati (1971). These cause tissue sloughing but are much less expensive than podophyllin. They require neutralisation by sodium bicarbonate. At least four applications are needed and the recurrence rate is approximately 25%—which is similar to that reported with podophyllin. A combination of podophyllin and trichloroacetic acid gave recurrence rates that were the same as podophyllin alone (Gabriel and Thin, 1983). Ammoniated mercury has been used (Grace et al, 1967).
CHEMOTHERAPEUTIC AGENTS

Chloroquine was applied to warts with some success (Murphy and Petty, 1965). Colchicine was found to eradicate some urethral warts (Gigax and Robinson, 1971). Attention then focused on treatment with antimitotic drugs, such as topical thiotepa (Cheng and Veenema, 1965; Halverstadt and Parry, 1969) and 5-fluorouracil (Nel and Fourie, 1973; Wallin, 1977). Bleomycin is both an antibiotic and an antitumour agent (Umezawa, 1965; Mishima and Matunaka, 1972) and, apart from pneumonitis and occasional idiosyncrasy, has remarkably few side effects, particularly when used topically. Shumack and Haddock (1979) used topical injections of bleomycin and reported no skin necrosis. Figuero and Gennaro (1980) treated 10 patients by injecting 0.1 mL of a solution containing 1 mg/mL bleomycin into the base of all lesions every 3–4 weeks over a variable period and achieved complete healing in 7.

Prolonged use of 5FU may result in erosive dermatitis. Topical 5FU has been used for vaginal or urethral warts with a 68% response rate and without recurrence at 6–12 months but in one report none of the perianal warts completely disappeared with 5FU (Pride, 1990). The greatest value of 5FU may be to prevent recurrence after successful eradication, especially in immunocompromised patients (Krebs, 1991; King, 1992). Topical 5FU has not been approved by the FDA (Food and Drug Administration) in the USA for treatment of genital warts.

IMMUNOTHERAPY

The concept of vaccinating patients against their own virus is interesting (Biberstein, 1944; Kirby, 1988), but Powell et al (1970) argued that the virus responsible for condylomata acuminata was a surface agent and unlikely to stimulate a humoral antibody response. Using autogenous vaccine, remission was reported in 28 of 35 patients (Powell et al, 1970). Immunotherapy was later advocated by Abcarian and colleagues (Abcarian et al, 1976; Abcarian and Sharon, 1977). Patients were admitted to hospital for 48 hours so that at least 5 g of tissue could be excised. After washing, the tissue was suspended in tissue culture medium containing antibiotics and homogenised. The homogenate was frozen and thawed four times prior to centrifugation. The supernatant was pasteurised by heating to 56°C, centrifuged at 4°C, cultured to ensure sterility and stored for repeated inoculation. Immunisation was achieved by six-weekly 0.5-mL injections into the deltoid muscle.

Abcarian and Sharon (1982) reported the results of treatment in 200 patients with a mean follow-up of 46 months. There were no adverse reactions. Total disappearance of the lesions around the anus was achieved in 84%; furthermore, associated genital lesions usually disappeared as well, but condylomata on the face, hands and feet were unaffected. Improvement was achieved in a further 22 patients and half of the failures achieved complete clearance after a further course of autovaccination (Table 15.9). However, the vaccine was not effective in HIV-positive patients. In recent years vaccination has fallen into disuse because of concerns about HIV status, but immunotherapy may have a role in the treatment of giant condylomata.

Wiltz et al (1995) compared recurrence rates of excision alone, bichloroacetic acid, podophyllin, interferon A or excision followed by twice-weekly autogenous condylomata acuminata vaccination for 10 weeks. The combined surgery and vaccination group had a recurrence rate of only 4.6% compared with 50% for surgery alone (Table 15.10). Goldstone and others (2001) studied 14 patients with anogenital warts and showed a 70–95% reduction of anogenital warts in 10 and complete disappearance in 3 at 6 months using $3 \times 1$ monthly subcutaneous injections of 100 µg of HsP E (fusing heat shock protein Asp 65 to E7 protein from HPV 16).

INTERFERON

Interferons are proteins with antiviral, antitumour and immunomodulatory actions that can restore natural killer cell activity (Cauda et al, 1987). Interferons alpha and gamma are available for clinical use and were found to be effective in planter warts. Interferon may be used for topical and systemic therapy (Trofatter, 1991). Intraleisional therapy is not popular with patients because of repeated skin injections, which are painful.
Side effects of interferon include viral syndrome, gastrointestinal complaints, leukopenia, thrombocytopenia and abnormal liver function. Interferon should not be used in patients with cardiac or renal failure (Browder et al, 1992). Tolerance appears to develop to viral syndrome, and non-steroidal anti-inflammatory agents often provide effective therapy.

**Topical interferon**

While topical therapy minimises side effects, two randomised controlled trials demonstrated no advantage over placebo cream. Thus at the moment topical therapy is not advised as a primary treatment (Vesterinen et al, 1984; Kraus and Stone, 1990) because of the high incidence of recurrence.

**Intra-incisional interferon**

Large doses may be given directly to an area of disease without inducing side effects. Clearance rates of 47–62% have been reported, but recurrence rates range from 20 to 40%. High costs and repeated therapy make this an unattractive mode of treatment unless the condylomata are resistant to all other forms of therapy (Welander et al, 1990; Browder et al, 1992). Current recommendations are to inject 1 x 10^6 IU under no more than five lesions, three times a week for no more than 8 weeks.

**Systemic interferon**

Systemic interferon is most useful in the treatment of large or multiple lesions which are difficult to inject. There is a high rate of side effects and variable response rates.

**Adjuvant therapy with interferon**

Adjuvant systemic interferon may reduce recurrence rates compared with surgery or laser ablation alone, but there is usually a high incidence of side effects (Eron et al, 1986; Condylomata International Collaborative Study Group, 1993).

Adjuvant topical therapy appears to have a real place in current management. A randomised study of intralesional interferon given after surgical excision or fulguration showed that the recurrence rate fell from 39 to 12% at a mean follow-up of 3.8 months (Table 15.11). Likewise a retrospective comparison of intralesional interferon and fulguration showed that adjuvant interferon reduced recurrence rates at 13 weeks from 35 to 18% (Vance and Davis, 1990). Similarly, podophyllin with intra-incisional interferon achieved a response rate of 67%, compared with 42% with podophyllin alone (Douglas et al, 1990).

**Surgical Treatment**

The mainstay of surgical therapy has been the application of physical agents such as diathermy, cryotherapy, laser and ultrasonic destruction in addition to simple surgical excision. Excision is now assuming greater importance following the recognition of early malignant transformation.

**Physical Agents**

**Cryotherapy**

Cryotherapy can be applied using nitrous oxide (Graber et al, 1967) or liquid nitrogen (Hall, 1960; Lyall, 1966; Nahra et al, 1969), but most of the earlier methods of application were crude and resulted in considerable discomfort together with destruction of adjacent tissues.

| TABLE 15.9 RESULTS OF IMMUNOTHERAPY IN 200 PATIENTS WITH ANAL CONDYLOMATA ACUMINATA |
|-----------------------------------------------|-----------------|-------------------|
| Patient group | n  | Complete clearance | Partial improvement | No response |
| Primary        | 120 | 101 (84.2) | 13 (10.8) | 6 (5) |
| Recurrent      | 80  | 66 (82.5)  | 10 (12.5) | 4 (5) |
| Total          | 200 | 167 (83.5) | 23 (11.5) | 10 (5) |

Values in parentheses are percentages. From Abcarian & Sharon (1982).

| TABLE 15.10 RECURRENCE RATES FOLLOWING TREATMENT BY VARIOUS METHODS |
|-------------------------|-----------------|
| Method                  | n  | Recurrence (%) |
| Surgery alone           | 20  | 50             |
| Bichloroacetic acid     | 10  | 50             |
| Podophyllin             | 5   | 85             |
| Interferon              | 5   | 85             |
| Surgical incision and   | 43  | 4.6            |
| vaccination             |     |                |


| TABLE 15.11 RECURRENCE IN PROSPECTIVE RANDOMISED TRIAL OF TOPICAL ADJUVANT INTERFERON |
|-----------------------------------------------|-----------------|
| Method                                      | n  | Recurrence (%) |
| Surgery, interferon and diathermy           | 25  | 12             |
| Surgery and diathermy alone                 | 18  | 39             |

From Fleshner and Freilich (1994).
and discharge. More sophisticated instruments, with inter-changeable heads that can be selected according to the volume of tissue requiring therapy, are now available (Simmons et al, 1981). There are a number of advocates of cryotherapy because treatment is painless, but satisfactory clinical data on the results are lacking and treatment requires careful control of the depth and width of therapy (Savin, 1975; Ghosh, 1977; O’Connor, 1979). One trial showed an advantage of cryotherapy over topical trichloroacetic acid in terms of both recurrence and side effects (Godley et al. 1987). Freezing is difficult to quantify, and discharge following therapy is often considerable. Most small lesions can be cleared with cryotherapy, but recurrence occurs in approximately 20% of patients over the following 6 months.

**Laser destruction**

Laser therapy may be used for the treatment of anal condylomata. Billingham and Lewis (1982) conducted a trial to compare the carbon dioxide laser with diathermy excision. One half of the perianal region was treated by laser and the other by electrocoagulation. Recurrences were more common on the side treated by laser and the patients experienced more postoperative pain on that side. Another study compared the CO₂ laser with diathermy (Duus et al. 1985). No significant differences were found in the recurrence rate, pain, healing time or scarring. At 6 months, the cure rate for refractory warts was 36% in the cautery group and 43% in the laser group. In view of the high cost of laser equipment and the risks of fumes in HIV patients, which must be removed by suction, we believe laser has only a limited role (Sawchuck et al, 1989).

**Diathermy**

Diathermy excision or contact destruction is probably used more widely than any other mode of treatment. It is remarkable, therefore, how little information is available on the immediate and long-term results of treatment (Simmons et al, 1981). Diathermy excision may be performed under local or general anaesthesia. Our policy is to use a local anaesthetic if there are numerous discrete pedunculated lesions confined to the perianal skin with no anal involvement. General anaesthesia is employed for large confluent condylomata with a wide base or when the anal canal is involved.

We use a fine-tipped diathermy probe and local anaesthesia to raise the lesion from the surrounding skin. As much skin as possible is preserved so that only the pedicle of the wart is divided. For very small lesions, the tip of the wart may be grasped with fine tissue forceps and application of the diathermy literally explodes the lesion, leaving a small white scar on the pedicle. Excessive skin loss must be avoided as this may lead to scarring and stenosis at the anal margin. We reviewed our results and found that complete initial clearance of the warts was achieved in 37 of 41 cases, but that condylomata recurred in 9 of 37 patients (24%) (Andrews et al. 1986). None of our patients developed stenosis or excessive perianal scarring. Jensen (1985) reported a similar recurrence rate of 29% at one year.

**Surgical excision**

**Scissor excision**

It has been argued that diathermy excision may be associated with excessive skin loss and potential scarring from fibrosis around the diathermised skin bridges, particularly in patients with extensive anal condylomata. Thomson and Grace (1978) therefore described the method of scissor excision. This technique may be performed under local or general anaesthesia. The base of the warts are infiltrated with a 1:300,000 solution of adrenaline (Figure 15.1a), both as a means of minimising blood loss and to lift the papilliferous lesion from the surrounding normal skin. Using a fine pair of scissors and dissecting forceps, each lesion is excised from its base (Figure 15.1b, c). This rather painstaking procedure leaves minimal epithelial defects, which tend to approximate as the adrenaline solution disperses (Figure 15.1d). It is advisable to start treatment at the most dependent site so that bleeding does not obscure visualisation of the remaining lesions. Similarly, lesions in the anal canal should be excised after infiltration with a weak adrenaline solution (Figure 15.1e, f). When excision is complete, an adrenaline-soaked pressure dressing is applied. Diathermy coagulation is not used.

Thomson and Grace (1978) reported their results in 75 patients: postoperative bleeding occurred in 4. Despite eradication of the condylomata, 42% developed recurrence during follow-up. Two randomised trials showed that scissor excision is preferable to conservative treatment with podophyllin (Jensen, 1985; Khawaja, 1989). Although diathermy may give lower recurrence rates than scissor excision, because of the risk of fumes in HIV-positive patients we believe that scissor excision is preferable in these high-risk patients.

**Wide excision**

Wide surgical excision is advised in patients with giant anal condylomata or for lesions with histological evidence of in situ malignant change (Gingrass et al, 1978; Prasad and Abcarian, 1980; Croxson et al, 1984). These patients must be followed up carefully.

If there is evidence of squamous cell carcinoma, wide excision, or preferably radiotherapy with chemotheraphy, is feasible for small lesions not invading the sphincters. In locally advanced lesions, response to radiotherapy and chemotherapy is so spectacular that traditional abdominoperineal excisions may not be needed (Buroker et al, 1976, 1977; Corman and Haggitt, 1977; Welch and Malt, 1977; Madden et al, 1981; Nigro et al, 1981) (see Chapter 16).

**Surgical or diathermy excision versus podophyllin therapy**

There is some debate as to which of the two most common forms of treatment should be offered as the initial therapy. Jensen (1985) performed a randomised trial to compare the use of 25% podophyllin in benzoin tincture given weekly for 6 weeks against scissor excision using the technique described by Thomson and Grace (1978). Surgical excision was usually performed under local anaesthesia and if very large lesions were encountered they were deliberately managed as two-stage procedures. Patients were
followed for at least a year after treatment (Figure 15.2). There was a progressive increase in recurrence rate with time, and this was significantly less at all time points after excision compared with podophyllin therapy. Initial treatment failures were also more common (see Table 15.8). The mean number of attendances for treatment was five in the podophyllin group compared with one in the surgical group, but postoperative pain was more common after surgical excision. Hence, surgical excision required fewer visits and was associated with a lower rate of recurrence.

Khawaja (1989) compared 25% podophyllin with scissor excision in a randomised trial. At 6 weeks, 79% had cleared with podophyllin compared with 89% after excision. A median of four applications were needed in the podophyllin group, whereas surgical treatment was completed in one session in 16 of the patients managed by scissor excision. In the surgical group, 11 experienced pain compared with only 5 of 19 patients treated by podophyllin. There were no complications of burns, stenosis or scarring in either group. At 42 weeks the
cumulative probability of recurrence was 60% with podophyllin but only 19% following scissor excision. Similar disappointing results have now been reported by others using podophyllin (Halverstadt and Parry, 1969; Gigax and Robinson, 1971).

Treatment in immunocompromised patients
Immunocompromised patients have a greater risk of condylomata acuminata, recurrent warts and anogenital neoplasia than the general population. Genital warts affect 43% of transplant recipients and 30% of HIV-positive patients (Sillman and Sedlis, 1991; Puy-Montbrun et al, 1992). These warts are also more aggressive, recur earlier and are more frequently dysplastic (Palefsky, 1991). Recurrence rates after surgical excision may exceed 50% (Gottesman et al, 1990).

Podophyllin may make interpretation of dysplastic lesions difficult and should probably be avoided in high-risk patients. Diathermy or laser surgery should be used with caution in HIV-positive patients because of the risk of dispersal of viral particles of HIV, HPV and hepatitis; thus some extraction facility must be used or excision should be with scissors.

Reduced recurrence when treating immunodeficient patients may be achieved with adjuvant topical 5FU (Krebs, 1991). In contrast, the role of interferon is uncertain because of the risk of an increase in transplant rejection as well as side effects such as leukopenia, virus syndrome and thrombocytopenia (Eron et al, 1986; Kovarik et al, 1988).

Follow-up must be diligent in this group because of the risk of recurrence and anal cancer.

**SUMMARY OF AUTHORS’ POLICY**

We believe that surgical excision is superior to podophyllin therapy for most patients with extensive perianal warts but accept that podophyllin is an appropriate first-line treatment for small lesions in patients presenting to STD clinics.

Scissor excision alone is probably safest in HIV-positive patients and where diathermy or laser treatment is likely to cause dispersal of the HIV virus. All potentially malignant lesions should be kept under careful scrutiny.
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