Chapter VI

Discussion

Today, it is becoming increasingly evident that a delicate balance exists between the invading virus and the natural defenses of the host. Cell-mediated immunity responses are considered to be of primary importance in these defense mechanisms. a therapeutic agent intended to retard viral replication processes must act in concert with these defenses presumably to augment their effectiveness (Ginsberg & Glasky ; 1977). In immunodeficient patients, cell transplantation may help to restore immune function. However in subjects who have intact but hyporesponsive immune systems biological or pharmacological agents would be more of value (Hadden et al, 1977). It is apparent that antiviral agents that interfere with viral replication and concomitantly depress the development of an immune response (e.g. Ara-C) may attenuate virus-induced pathology but may not ultimately contribute to eradication of the virus and permanent host resistance. An alternative and more rational approach to the treatment of active virus infections would involve a promotion of normal resistance mechanisms.

Both cell-mediated and humoral immune responses are stimulated in wart infections. CMI responses are of major role

in the resolution of warts, however. Antibody production is associated with wart regression but it is not known whether this is the cause or the result of the regression (Matthew and Shirodaria , 1973). Antibodies are deposited in wart lesions but this occurs more often with exudation (Matthew and Shirodaria, 1973). Also, antibodies persist or are elevated in the progression of wart, indicating its non-protecting role (Viac et al., 1977).

Tagami et al., in 1974, reported a spontaneous regression of flat warts preceded by inflammatory infiltrate consisted mostly of mononuclear cells. In our study, mononuclear cell infiltrate consisting mostly of OKT-4 and OKT-8 positive cells are found to increase in numbers within lesions showing clinically evident resolution after treatment with Inosine pranobex (figures 16 through 32). In lesions exhibiting no response to treatment, no such increase in cellular infiltrate is seen (figures 33 through 44).

Of interest is the finding that patients in whom lymphocytic infiltrates were already present within the lesions prior to treatment showed rapid response while those whose warts were histologically "non-inflamed" showed no response.Berman and Winkelmann,in 1983,also demonstrated that mononuclear cell infiltration preceded regression by several weeks(Berman and Winkelmann,1983). They also found that patients whose warts failed to regress showed no inflammatory cell infiltrate in their

lesions. Surprisingly ,however, in our study no warts showed signs of inflammation or necrosis clinically despite the presence of inflammtory cell infiltrate histologically. Some authors noted that warts appeared dark upon healing due to hemorrhage and thrombosis of small blood vessels (Brodersen and Genner, 1973; Matthews and Shirodaria,1973). This finding is also not seen in our patients. Response to Inosine Pranobex was seen within 2 weeks after initiation of therapy in all who responded at all. This finding may suggest that Inosine pranobex acts as an immunostimulator by promotion of lymphocyte functions provided that immunological stimulation has taken place. This is in agreement with the findings of others that Inosine pranobex is active only when lymphocytes have been "activated" (Ginsberg & Glasky, 1977; Hadden et al., 1976; Muldoon, Mezny and Jackson, 1972; Longley, Dunning and Waldman, 1973). A skin biopsy of a lesion may then be considered somewhat predictable of therapeutic success.

As mentioned before, immunity to wart infections combines that of viral infection and tumor in many aspects.The mechanisms of immune mediated destruction of tumors (and possibly warts) involve 5 general mechanisms :

1. complement-mediated lysis following activation by immunoglobulin antibodies attached to target cells
2. antibody-dependent cell-mediated cytotoxicity(ADCC)
3. T-cell mediated cytolysis

4. specifically activated macrophage killing
5. natural killer cells

(Tagami et al.,1983)

The facts that most cells found in lesions of warts undergoing spontaneous regression are of T-lymphocytes and macrophage/monocyte series favor mechanisms mentioned in 3 and 4. By light & electron microscopy and immunohistochemical methods, the cellular infiltrates are found to be of two major patterns, that of allergic contact dermatitis and GVHR.

In lesions showing features of allergic contact dermatitis, Langerhans cells are increased in number both in the epidermis and the dermis. Moreover, they are demonstrated by electron microscopy to be apposed to the infiltrating lymphocytes, the phenomenon similar to antigenic presentation in allergic contact dermatitis.

In lesions showing GVHR characteristics, mononuclear cell infiltrate composing mainly of T-lymphocytes are confined underneath the regressing warts in a lichenoid fashion. The wart epidermis shows vacuolar degeneration of basal cells and spongiosis of the overlying Malphigian layers. The keratinocytes expressed HLA-DR antigens (Dreno et al., 1986). Also, of importance, is the feature known of as "satellite cell necrosis" characteristic of GVHR which is also found in regressing wart lesions. In late lesions the whole epidermis is effaced.

The exact mechanisms whereby lymphocytes exert their effects through stimulation by Inosine pranobex in wart regression is uncertain. Some of our findings are compatible with the abovementioned features involved in GVHR e.g.,

1. the presence of lymphocytic infiltrate in a more or less lichenoid pattern
2. exocytosis of lymphocytes into the epidermis
3. HLA-DR expression by epidermal cells
4. flattening of wart tumors.

However, in classical GVHR, cellular infiltrates are composed mainly of cytotoxic T-lymphocytes while in our study both helper/inducer and suppressor/cytotoxic cells are found in more or less equal numbers.

One may ask how long this immunity will last. By using several in vitro assays (hemagglutination inhibition, leukocyte migration inhibition test and counterimmunoelectrophoresis) it was found that the immunity did not last more than 3 months (Morison, 1975a). However, by using another assay (lymphocyte transformation) it was concluded that the immunity was very long-lasting for those who had past history of wart infection showed strongest stimulation followed by those with active infection and control group respectively (Ivanyi and Morison, 1976). The response was also specific for patients only showed response to wart antigen stimulation but not to PPD (Morrison, 1975b).

Of special interest is the question why certain patients did not respond to Inosine pranobex. Clinical types and duration of lesions may be determinant in the therapeutic response. However, our limited number of subjects does not permit us to verify their significance. Also, of importance, is the individual difference in drug response. Unlike antibiotic therapy specific for bacteria, the effectiveness of the prohost antiviral therapy depends on the host more than the virus. Genetic and environmental factors as well as the individuals' sex, age, nutrition and general medical and immunologic status may be determinant in response (Hadden et al., 1977). It is also speculated that Inosine pranobex leads to an interaction with the endogenous production of interferons which is shown through individual differences (Gross, Jogerst and Schoepf, 1986).

Another possible explanation for treatment failure in chronic wart infection is that the antigens, being within the stratum corneum, are somewhat " sequestered" from the body immune response. Thus they may escape immunologic surveillance. A local treatment modalities may have their place in this situation especially if used in conjunction with Inosine pranobex. Cryotherapy and paints (such as caustic agents) presumably cause inflammatory reactions sufficient to allow lymphocytes to become sensitized to wart antigens (Morrison, 1975a) and thus allow Inosine pranobex to exert its lymphocyte stimulating effects. Patient No. 6, after completed the study, was successfully

treated with the combined use of local treatment while he never did so before Inosine pranobex was administered.

Two weak points in this study are the limited number of subjects and the lack of control group. Therefore, we cannot really exclude spontaneous regression especially in patients whose warts had been present for less than 2 years. However by temporal association, it may be presumed that the regression is "induced" by the therapeutic agent.

In summary, Inosine pranobex may be used as an alternative treatment in patients with multiple warts, in whom local treatment is an exhaustive task, or as part of a combined treatment in those who carry recalcitrant warts. Successful treatment can be anticipated in patients who show lymphocytic infiltration within their lesions and clinical response can be expected within 2-4 weeks.

Adverse reactions are not the problem with Inosine pranobex treatment. The rise in serum uric acid levels, though statistically significant, is always transient. The only drawback is the cost of the medication. Thus further study for dosage reduction may be warranted.