

increasing size of the older adult population, who are retaining more natural teeth and becoming a significant population for use of antiplaque/antigingivitis products.

Publications have described differences in drug responses in the elderly. Changes in pharmacokinetics have been reviewed (Ref. 49). Absorption can theoretically be altered by noted changes in gastrointestinal function, but the majority of studies have shown no difference in rate or extent of absorption of the drug examined. Distribution of a drug within the body is affected because fat content of body weight increases and intracellular water decreases. For example, albumin concentration is reduced and drugs which bind to albumin are more free to distribute to the rest of the body. Hepatic metabolism may be altered. Reduction of blood flow to the liver will decrease clearance of some drugs. Renal excretion is affected in some older adults by loss of renal mass and functional nephrons.

Russell (Ref. 50) noted that despite numerous reports in the literature of impaired GI function with aging, most functions remain relatively intact because of the large reserve capacity of the intestine, pancreas, and liver. In a review critically analyzing available information on age-related changes in the digestive and absorptive GI physiology of lipids, data suggested lipid digestion and absorption are well-preserved in the aging. However, intercurrent illness or experimental stress may produce impairment in aging animals and humans that is not seen in younger controls (Ref. 51).

Atilasoy and Holt (Ref. 52) noted that the GI tract represents an organ system characterized by rapid proliferation. Contrary to generally held prejudices, the authors write, a state of hyperproliferation, not hypoproliferation, occurs in the epithelial cells of the stomach, small intestine, and large intestine of stable-fed, aged rodents when compared to young adult rodents.

In a gavage study (Ref. 53) Yamada et al. investigated renal ammoniogenesis in isolated nephron segments from control, acidotic senescent (exhibiting deteriorating teeth due to aging), and young adult rats. No significant difference was seen in glutamine-dependent ammonia production in the segments. However, ammonia production in glomeruli from old rats was significantly greater than in young rats.

There appear to be no available consistent findings to warrant that additional gavage studies of

antigingivitis/antiplaque active ingredients in older animals will produce more meaningful findings relative to older adults than the usual gavage studies in adult animals. This is due to the great diversity which exists in the health and fitness status of the elderly population. The Subcommittee considers a comment by Ahronheim (Ref. 54) appropriate:

Although much has been written about age-related alterations in drug disposition, there is disagreement as to the extent and inevitability of these changes. Studies focusing on aged individuals suffer from several problems. Cross-sectional studies comparing young and old subjects sometimes compare young, healthy individuals with aged subjects gathered from hospitals or nursing homes. If the aged subjects are "healthy" they may nonetheless have subclinical disease, which can alter outcomes in studies that seek to determine a drug's disposition and effects. However, aged subjects that are truly healthy may represent an elite minority so that the study's results may not be applicable to the general elderly population. Longitudinal studies are almost impossible to complete and data is sparse, but recent findings indicate that the geriatric population is, indeed, heterogeneous.

In addition to these pitfalls, it is not known how generalizations about aging physiology, even if they are true, can be applied to drug disposition, since most drugs have not been subjected to exhaustive age-specific testing and few conclusions can be reached based on pharmacokinetic data. Even less is known about pharmacodynamic changes because the study of age-related tissue receptor density, activity, and sensitivity is in its infancy. We must therefore rely on clinical observations to a large extent when drawing conclusions about efficacy and potential toxicity of various agents in use. The Subcommittee concludes that the results of the usual gavage studies are adequate.

iii. *Irritation and delayed contact sensitization studies in humans.* Observations during adequate clinical studies are sufficient to demonstrate the irritation and sensitization potential of an ingredient or ingredient combination. However, if necessary, a number of methods embodying the use of patch testing have proven of value in determining skin irritation and systemic sensitization. The Subcommittee recommends one of the following three methods of patch testing to address concerns of irritancy and sensitivity:

- *Draize testing.* In the Draize human skin irritancy and sensitization tests or one of its various modifications (Ref. 55), the testing should be performed on the skin of the subject's back or arm.

- *Method of Shelanski and Shelanski.* In this method (Ref. 56), the active ingredients or the formulation under study are applied at frequent intervals of 1 or 2 days to the test site for 3 or 4 weeks. After a rest period of 2 weeks, a

single dose of the drug is applied as a challenge. The preliminary applications are made to detect primary skin irritants and provoke sensitization in susceptible individuals. The challenging dose detects whether or not the drug is a skin sensitizer.

- *Maximization procedure of Kligman.* This procedure (Ref. 57) or one of its modifications uses an irritant applied over a desquamated test site.

Desquamation is performed by using a rubbing technique that facilitates penetration, thereby hastening and accentuating the skin-sensitizing potential of the substance. Other validated human models may be used.

iv. *Microbiologic evaluation.* The Subcommittee is concerned about the potential of antigingivitis/antiplaque ingredients with antimicrobial effects to allow emergence of opportunistic pathogens, induce resistance in oral microorganisms, or allow an oral overgrowth of inherently resistant potential pathogens. Representative microbial species and their relative proportion to the total cultivable microflora in supragingival plaque and saliva should be monitored over at least a 6-month period of continuous use of the antiplaque product to determine if a shift in the oral flora has occurred that might result in the proliferation of pathogenic microorganisms, which may include *Candida* species and other yeast, *Staphylococcus aureus* and other *Staphylococcus* species, beta-hemolytic *Streptococci*, and enteric gram-negative rods. Additionally, for those antigingivitis/antiplaque ingredients where the mechanism of action is suspected to be antimicrobial, an assessment of changes in microorganisms associated with gingival disease should be carried out. One determination should be made prior to the start of use, one at the conclusion of the study, and one at an intermediate time. In vitro minimum inhibitory concentrations should be assessed for representative species to determine the development of increased resistance after prolonged antimicrobial therapy.

b. *Effectiveness.* The Subcommittee's determination of the therapeutic effectiveness of ingredients and combinations of ingredients for antigingivitis/antiplaque use is based on published and unpublished studies containing pharmacological data considered by the Subcommittee to be scientifically valid and pertinent. Clinical criteria for proof of effectiveness of a single ingredient or combination of ingredients were determined by evaluating data from valid controlled studies and by calling on the clinical expertise of the