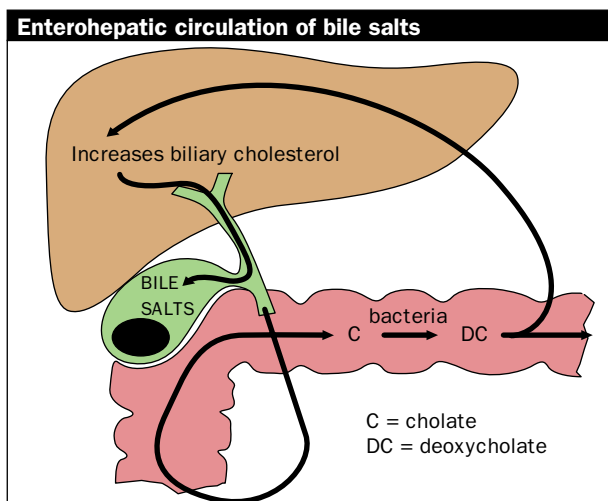




been known to reduce cholesterol supersaturation of bile and even to dissolve gallstones.¹ Interestingly, chenodeoxycholate produces this effect more by reducing bile-cholesterol secretion than by increasing bile-salt secretion.² On the other hand, administration of small doses of deoxycholate to volunteers was shown in the 1970s to raise bile-cholesterol saturation and the proportion of deoxycholate in the bile, mainly at the expense of chenodeoxycholate.^{3,4} Thus the two dihydroxylated bile salts, chenodeoxycholate and deoxycholate, have important but opposite effects on bile-cholesterol saturation. Biliary cholesterol derives mainly from cholesterol present in serum lipoproteins.² Chenodeoxycholate and deoxycholate also have opposite effects on serum cholesterol concentration, the former raising² and the latter lowering³ it.

In patients with gallstones the degree of bile cholesterol supersaturation correlates positively with the proportion of biliary deoxycholate.⁵⁻⁷ What then determines how much deoxycholate bile contains? Metronidazole reduces biliary deoxycholate, presumably by suppressing bacterial metabolism of cholate, and it decreases bile lithogenicity.⁸ Lactulose produces a similar effect, perhaps through colonic acidification, which reduces solubility of deoxycholate and possibly also colonic bacterial activity. Lactulose might also hasten intestinal transit, thus reducing time for passive absorption.⁹ In gallstone patients whose bile is supersaturated with cholesterol, wheat bran added to the diet lowers the supersaturation and the proportion of deoxycholate in the bile.¹⁰ Two studies have shown slower-than-normal intestinal transit in non-obese gallstone patients,^{6,11} and slowing transit increases lithogenicity and the deoxycholate content of bile.⁵ The right colon is probably the main site of colonic absorption of deoxycholate; no cholate remains in the faeces, all having been metabolised to deoxycholate. Questions remain about whether deoxycholate directly influences factors controlling the rate of cholesterol microcrystal formation in lithogenic bile,¹² and whether input of deoxycholate from the colon to the enterohepatic circulation depends on its rate of bacterial transformation from cholate,¹³ its solubility in colonic fluid, which declines as pH falls, or the time available for its absorption.

Preliminary reports from Hermon Dowling's unit in London of gallstone patients, including octreotide-treated acromegalic patients, who are especially prone to

gallstones, indicate that these patients have significantly more gram-positive anaerobes in their right colons than do controls without gallstones. The patients also had a greater enzymatic capacity to convert cholate to deoxycholate. In the patients slowness of colonic transit correlated with increased caecal pH and water-solubility of deoxycholate.¹⁴ Cisapride, which speeds intestinal transit, reverses many of these abnormalities.⁶

Of the factors causing gallstones, genetics and female sex are not preventable, whereas parity, obesity, hypertriglyceridaemia, fasting, and drugs leave many cases unaccounted for. With an understanding of the role of the gut should come better planning and interpretation of dietary surveys and interventions and therefore improved advice on prevention.

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- Hoffmann AF. Desaturation of bile and cholesterol gallstone dissolution with chenodeoxycholic acid. *Am J Clin Nutr* 1977; **30**: 993-1000.
- Carey MC. Homing-in on the origin of biliary steroids. *Gut* 1997; **41**: 721-22.
- Low-Beer TS, Pomare EW. Can colonic bacterial metabolites predispose to cholesterol gallstones? *BMJ* 1975; **i**: 438-40.
- Pomare EW, Low-Beer TS. Selective suppression of chenodeoxycholate synthesis by cholate metabolites in man. *Clin Sci Mol Med* 1973; **48**: 315-21.
- Marcus SN, Heaton KW. Intestinal transit, deoxycholic acid and the cholesterol saturation of bile: three interrelated factors. *Gut* 1986; **27**: 550-58.
- Dowling RH, Veysey MJ, Pereira SP, et al. Role of intestinal transit in the pathogenesis of gallbladder stones. *Can J Gastroenterol* 1997; **11**: 57-64.
- Shoda J, He BF, Tanaka N, et al. Increases of deoxycholate in supersaturated bile of patients with gallstone disease and its correlation with de novo synthesis of cholesterol and bile acids in liver, gallbladder emptying, and small intestinal transit. *Hepatology* 1995; **21**: 1291-302.
- Low-Beer TS, Nutter S. Colonic bacterial activity, biliary cholesterol saturation and pathogenesis of gallstones. *Lancet* 1978; **ii**: 1063-65.
- Thornton JR, Heaton KW. Do colonic bacteria contribute to cholesterol gall-stone formation? Effects of lactulose on bile. *BMJ* 1981; **282**: 1018-20.
- Pomare EW, Heaton KW, Low-Beer TS, Espiner HJ. The effect of wheat bran upon bile salt metabolism and upon the lipid composition of bile in gallstone patients. *Am J Dig Dis* 1976; **21**: 521-26.
- Heaton KW, Emmett PM, Symes CL, Braddon FEM. An explanation for gallstones in normal-weight women: slow intestinal transit. *Lancet* 1993; **341**: 8-10.
- Hussaini SH, Pereira SP, Murphy GM, Dowling RH. Deoxycholic acid influences cholesterol solubilisation and microcrystal nucleation time in gallbladder bile. *Hepatology* 1995; **22**: 1735-44.
- Berr F, Kullack-Ublick G-A, Paumgartner G, Munzing G, Hylemon PB. 7 α -dehydroxylating bacteria enhance deoxycholic acid input and cholesterol saturation of bile in patients with gallstone. *Gastroenterology* 1996; **111**: 1611-20.
- Abstracts of the 6th. United European Gastroenterology Week, Birmingham, UK. *Gut* 1997; **3**.

Sublingual immunotherapy for allergic respiratory disease

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Sublingual immunotherapy has been the subject of considerable scepticism over the past decade, being commonly dismissed as the extreme of a spectrum of anecdotal treatments for allergy that belonged more to the realm of homoeopathy than to scientifically based medicine. This harsh view has, until quite recently, been compounded by the dearth of hard data on the efficacy of any form of conventional immunotherapy for allergic disease, in particular within the respiratory tract. Although there is still considerable doubt about the usefulness of immunotherapy in asthma,¹ there is growing support for

its role in the treatment of rhinitis,² especially early in the disease process, when it may prevent the acquisition of a wider pattern of sensitivities³ and/or halt progression towards the development of asthma.⁴

Progress in the use of immunotherapy for the treatment of rhinitis has been matched by advances in the understanding of underlying mechanisms in clinical and experimental immunology. It is becoming clear that conventional immunotherapy with grass-pollen allergens can dampen both early-phase and late-phase responses. Lessening of late-phase responses is associated with reduced infiltration of eosinophils, and especially of CD4 T cells, into airway mucosal challenge sites.⁵

Of potentially greater significance are parallel findings that immunotherapy can reduce the amount of cytokine released by individual allergen-reactivated T cells, while at the same time shifting the balance of cytokine secretion at challenge sites away from the Th2 pattern towards the atopy-inhibitory Th1 cytokine profile, particularly interferon- γ and interleukin-12.^{5,6} Prolonged treatment could theoretically imprint this "new" Th1 response pattern into long-term Th-cell memory, thus providing potentially permanent protection against subsequent Th2-mediated allergic reactivity to the same allergen. Depending on the concentration or form of the allergen employed for immunotherapy, these low-zone tolerance (immune-deviation) mechanisms (induced by low dose of allergen) may be complemented by T-cell anergy/deletion, in which some (or in some cases all) of the cells responding to the allergen are either actively suppressed or permanently purged from the T-cell repertoire.

Recent developments in experimental mucosal immunology are also of relevance to this discussion. In particular, there is rapidly growing interest in the use of targeted mucosal antigen-delivery systems for immunotherapy of a wide range of inflammatory diseases.^{7,8} This interest is fuelled by studies that have shown selective downregulation of specific T-cell reactivity following repeated exposure of the upper respiratory and gastrointestinal mucosa to antigens delivered oronasally as aerosols or drops.⁸ Intriguingly, these manoeuvres selectively downregulate specific IgE responses and, secondarily, delayed-type hypersensitivity.⁸

In view of these recent developments, it is not unreasonable to suggest that sublingual immunotherapy, which essentially targets the oropharyngeal mucosa, is worthy of re-examination, with the refined molecular tools now available for probing the immunological sequelae of such therapy. Independent data from animals attesting to the immunomodulatory effects of such treatment, which include selective downregulation of IgE responses, have already been reported.⁹ Additionally, this issue of *The Lancet* contains a report by Giovanni Passalacqua and colleagues of a double-blind placebo-controlled trial of sublingual immunotherapy for the treatment of perennial rhinoconjunctivitis. Importantly, the treatment period was long (2 years), and outcome assessment included objective measures at sites of local (conjunctival) challenge. The results, albeit on a small sample size, seem encouraging, with the suggestion of clinical improvement associated with downmodulation of inflammatory responses at the challenge site.

Are such findings consistent with current knowledge in related areas? The study involved the use of allergen that has been chemically modified to minimise IgE binding, an approach that is being followed under several different

guises in other laboratories and within the pharmaceutical industry. There is no evidence from Passalacqua and colleagues' study that the chemical modification has altered the "tolerogenicity" of the allergen relative to its native form, although adherents to this approach would accept this proposition as perfectly reasonable. This question can be answered only by structured parallel trials similar to those being conducted for other immunotherapeutic techniques.

The most radical aspect of this mode of therapy, however, is related to the route of allergen delivery. But is it, in reality, so radical? In principle, sublingual immunotherapy involves the repeated exposure of the oropharyngeal mucosa to considerable amounts of modified allergen. As well as the sublingual study in rats referred to above,⁹ there are now numerous reports of the effect of exposures of the oronasal and upper airway mucosae for the express purpose of downregulation of immunoinflammatory responses.^{7,8} Immunoregulatory mechanisms triggered by exposure of the oronasal and upper airway mucosa are focused principally in their regional lymph nodes, and antigens delivered via the sublingual route drain to essentially the same lymph-node groups. These mechanisms are closely related to those underlying the process of oral tolerance to fed antigens, which again are operative in local gut-associated lymphoid tissues.

Consequently, there seem to be no theoretical reasons to doubt the potential of this route of allergen delivery for immunotherapy. What is needed is more and larger controlled clinical trials along the lines of that reported today, especially involving the use of alternative forms of allergen, and further experimental data on relevant cellular and molecular mechanisms. The potential advantages of the sublingual route in relation to ease of allergen administration and hence patients' compliance with therapy, especially when the course of treatment is long, provide further justification for more detailed investigation of this form of immunotherapy.

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- 1 Barnes PJ. Is there a role for immunotherapy in the treatment of asthma? No. *Am J Respir Crit Care Med* 1996; **154**: 1227–28.
- 2 Working Party, British Society for Allergy and Clinical Immunology. Position paper on allergen immunotherapy. *Clin Exper Allergy* 1993; **23** (suppl 3): 1–44.
- 3 Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997; **99**: 450–53.
- 4 Mosbech H, Osterballe O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. *Allergy* 1988; **43**: 523–29.
- 5 Durham SR, Ying S, Varney VA, et al. Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma. *J Allergy Clin Immunol* 1996; **97**: 1356–65.
- 6 Hamid QA, Schotman E, Jacobson MR, Walker SM, Durham SR. Increases in IL-12 messenger RNA+ cells accompanying inhibition of allergen-induced late skin responses after successful grass pollen immunotherapy. *J Allergy Clin Immunol* 1997; **99**: 254–60.
- 7 Weiner HL. Oral tolerance: immune mechanisms and treatment of autoimmune diseases. *Immunol Today* 1997; **18**: 335–43.
- 8 Holt PG. Immunoprophylaxis of atopy: light at the end of the tunnel? *Immunol Today* 1994; **15**: 484–89.
- 9 Holt PG, Vines J, Britten D. Sublingual allergen administration. I. Selective suppression of IgE production in rats by high allergen doses. *Clin Allergy* 1988; **18**: 229–34.