

Neomycin and lactulose are thought to exert their influence on hepatic coma exclusively by interfering with the bacterial flora, but our results suggest a potential additional effect, namely interference with glutamine-dependent non-bacterial ammonia production.<sup>9</sup> This glutamine-dependent ammonia production may exceed by far the bacterial ammonia production. We suggest that the mechanism of action of lactulose and neomycin will be better understood when the potential influence of these compounds on non-bacterial ammonia generation is taken into account.

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#### ANTIBODIES TO PLASMID-ENCODED PROTEINS OF ENTEROPATHOGENIC YERSINIA IN PATIENTS WITH AUTOIMMUNE THYROID DISEASE

SIR,—Bech et al<sup>1,2</sup> have suggested an association between thyroid autoimmune disorders and humoral<sup>1,3</sup> and cellular<sup>2</sup> immunity to *Yersinia enterocolitica*. Binding sites for thyrotropin have also been described.<sup>4</sup> The role of *Yersinia* in the pathogenesis of thyroid autoimmune disorders is not, however, understood, partly because most studies were done with laboratory strains of *Y enterocolitica* of different serotypes that had lost their virulence. A pre-requisite to virulence of the most common enteropathogenic *Y enterocolitica* and *Y pseudotuberculosis* strains is the presence of a 42-46 MD plasmid which is rapidly lost after subcultivation.<sup>5</sup> Virulence in terms of serum resistance, phagocytosis resistance, and cell adherence is mediated by these plasmids.<sup>6,7</sup> These plasmids also encode for at least six proteins against which man and animals produce antibodies after *Yersinia* infection.<sup>8,9</sup> In calcium-deficient nutrient broth virulent *Yersinia* release strongly immunogenic proteins in large quantities.<sup>6,8</sup> By sodium dodecyl sulphate/polyacrylamide gel electrophoresis bands of released proteins (RPs) can be seen at 25 kD, 34 kD (*Y pseudotuberculosis*)/36 kD (*Y enterocolitica*), 38 kD, 46 kD, and 58 kD (*Y enterocolitica*)/67 kD (*Y pseudotuberculosis*).

We have investigated sera from patients with thyroid autoimmune disorders for antibodies to RPs and studied the prevalence of specific immunoglobulin classes by western blotting. The occurrence of RP antibodies in 336 healthy blood-donors and 28 patients with non-toxic goitre was compared with that in 100 patients with Graves' disease and 38 patients with Hashimoto's thyroiditis. All Graves' disease patients were hyperthyroid and had TSH-receptor antibodies. The onset of Graves' disease was estimated at admission by the patient's report of symptoms of hyperthyroidism. Patients with Hashimoto's thyroiditis had been receiving thyroxine for 1-7 years. No patient with a non-toxic goitre had thyroid antibodies. No abnormal frequencies of *Yersinia* infections were reported during the study.

Sera from patients with Graves' disease or Hashimoto's thyroiditis had increased frequencies of RP antibodies of either Ig-class compared with controls (table). The manifestation of IgA antibodies to RPs indicates a recent or persistent yersiniosis. Antibodies to 25 kD RP are of special interest, because preliminary results suggest that this antibody shares antigenic epitopes with the

#### PREVALENCE OF ANTIBODIES TO PLASMID-ENCODED PROTEINS OF ENTEROPATHOGENIC YERSINIA IN SERA OF PATIENTS WITH AUTOIMMUNE THYROID DISEASES AND IN CONTROLS

Group	IgG	IgA	Anti-25 kD RP
Healthy blood donors (n = 336)	116 (34.5%)	40 (11.9%)	10 (3.0%)
Non-toxic goitre (n = 25)	10 (40%)	3 (12%)	0
Graves disease			
Total (n = 100)	72 (72.0%)†‡	33 (33.0%)§*	14 (14.0%)§*
6 mo (n = 35)*	21 (60%)‡	11 (31%)‡	3 (9%)†
12 mo (n = 38)*	28 (74%)‡	15 (39%)‡	14 (37%)‡
Recurrent (n = 21)	17 (81%)‡	6 (29%)†	3 (14%)†
Hashimoto's thyroiditis (n = 38)	25 (66%)†*	14 (37%)†*	4 (11%)†*

\*Month after occurrence of symptoms of hyperthyroidism  
χ<sup>2</sup> test, p. † < 0.05, ‡ < 0.01, and § < 0.001 compared with blood donors; \* p < 0.05 compared with patients with non-toxic goitre.

TSH receptor.<sup>10</sup> Moreover, antibodies to 25 kD RP are transient, emerging in the first three months after infection and fading away after about one year. We observed a similar pattern when patients with Graves' disease were grouped according to the onset of hyperthyroidism. Within one year both 25 kD and IgA antibodies had reached a peak and decreased in recurrent Graves' disease. In most cases the 25 kD antibodies were detected as IgG-class immunoglobulins. IgG antibodies to RP persist for several years. Consequently IgG antibodies steadily increased to 81% in recurrent Graves' disease. An ongoing prospective study in newly diagnosed cases of Graves' disease confirms these antibody profiles—ie, no RP antibodies at the time of diagnosis and then IgA, IgG, and 25 kD RP antibodies developing within eight months.

Thus we have found a strong association between thyroid autoimmune disease and antibodies against plasmid-encoded proteins of enteropathogenic *Yersinia*. Crossreactivity of antibodies in thyroid autoimmune disease with *Y enterocolitica* or *Y pseudotuberculosis* can now be understood independently of *Yersinia* serotypes. In Graves' disease the binding of thyrotropin in *Y enterocolitica*,<sup>4</sup> the sharing of epitopes of the *Yersinia* plasmid with the thyrotropin receptor,<sup>10</sup> and the plasmid antibody profile that we have demonstrated indicate antigenic mimicry, which could well have an initiating role in the disease.

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