Infection and immunity are related and clinical immunology and the study of infectious diseases have something to offer each other; the specialties should grow closer, not more distant. This letter will probably bring down the wrath of both parties on my head, but if they unite to condemn me it will have achieved something.

Hospital for Tropical Diseases
London NW1 0PE ANTHONY BRYCESON

IgE, PARASITES, AND ALLERGY

SIR,—I read with interest your editorial[1] and the controversial correspondence it elicited. Of particular significance to me was your suggestion that "one theoretical approach to prevention or treatment of allergic diseases would be deliberately to induce IgE responsiveness—for example, by artificial infection with parasites" and Augustin's statement[2] that "parasitic infections would be expected to exacerbate already existing allergies". I have been a life-long sufferer from hayfever and have recently carried out a series of self-infections with human hookworm *(Necator americanus)*, a well-known stimulator of IgE antibody responses.[3]

From about the age of 8 years (1949) I have had hayfever each summer, the disease being distressing enough to warrant repeated courses of antihistamines. In 1966 skin tests gave positive reactions to grass and tree pollens, *Urtica* and plantain. Courses of desensitisation were carried out in 1967 and 1968 and produced good responses until 1971. However, after 1971 courses of antihistamines were again necessary each summer.

In October, 1974, I infested myself with 250 *N. americanus* larvæ of Nigerian origin[4] to examine the hæmatological responses to the parasite and to obtain a regular supply of infective third-stage larvæ for antigen preparation.[5,6] Similar infections were established in March, July, and November, 1975, each new infection being carried out 4 weeks after the elimination of the parasites of the previous infection by the anthelmintics levamisole and mebendazole. The most recent infection is still patent, the parasites at present producing 3500-5000 eggs/g fæces.

Antibody responses have been studied, using antigens secreted by *N. americanus* in vitro, by enzyme immunoassay (ELISA)[8] and by radiolabelled anti-acetylcholinesterase technique.[9] Both methods demonstrated high levels of antibody production. During the first 13 months of the infections, specific IgE values (assayed by radio-allergosorbent test[8]) rose from a pre-infection level of 607 counts/min to 2034 counts/min, but unexpectedly, during the same period, total IgE levels (measured by double-antibody radioimmunoassay[9]) did not increase significantly when compared with pre-infection levels. However, the most pertinent finding in the context of the discussion on IgE, parasites, and allergy was that during the summers of 1975 and 1976 I remained completely free from all symptoms of hayfever.

I appreciate that the experiences of one individual shed limited light on any hypothesis relating to allergy and parasitic disease. However, in view of my own responses, I clearly cannot agree with Dr Augustin that parasitic infections would be expected to exacerbate existing allergies.

Medical Research Council, Laboratory Animals Centre,
Carshalton, Surrey SM5 4EF J. A. TURTON

1. *Lancet*, 1976, i, 894.
2. Augustin, R. *ibid.* p. 1023.
3. Ogilvie, B. M., Jones, V. E. *Progr. Allergy*, 1973, **17**, 93.
4. Ball, P. A. J., Bartlett, A. *Trans. R. Soc. trop. Med. Hyg.* 1969, **63**, 362.
5. Bartlett, A., Turton, J. A., Williamson, J. R. *Parasitology*, 1975, **71**, suppl. 32.
6. Taylor, M. M., Turton, J. A. *Tropenmed. Parasit.* 1976, **27**, 89.
7. Burt, J. S., Ogilvie, B. M. *Exp. Parasit.* 1975, **38**, 75.
8. Voller, A., Bartlett, A., Bidwell, D. E. *Trans. R. Soc. trop. Med. Hyg.* 1976, **70**, 98.
9. Yeates, R. A., Ogilvie, B. M. *J. Immun. Methods*, 1976, **12**, 57.

ZINC-THIONEIN AND HERITABLE DISORDERS ASSOCIATED WITH ABERRANT ZINC METABOLISM

SIR,—There is increasing evidence linking certain inherited disorders with atypical zinc metabolism; acrodermatitis enteropathica (A.E.) and familial hyperzincæmia (F.H.Z.) are examples. A.E., an autosomal recessive disorder characterised by severe skin lesions and abnormally low plasma-zinc,[1] responds to oral zinc.[2–5] Since zinc absorption is impaired in A.E.[6] and since zinc sulphate given by mouth raises the plasma-zinc to normal[5] and eliminates the skin lesions, this suggests that supplemental zinc can circumvent the block in zinc absorption. F.H.Z.[7] also seems to be an autosomal recessive disorder. While there were no overt clinical findings associated with the excessive plasma-zinc (averaging about six times normal) the patients were in positive zinc balance indicating that zinc absorption may have been above normal. The excess zinc in the plasma was primarily bound to albumin.

Our experiments on zinc metabolism may be relevant to the molecular basis of both A.E. and F.H.Z. Our proposal, based upon animal experiments, is that zinc-thionein (Zn-M.T.), a metallothionein, is synthesised in response to changes in plasma-zinc produced by parenteral or dietary zinc[8–10] and in turn helps to modulate short-term changes in zinc metabolism. We propose that Zn-M.T. is synthesised in intestinal mucosal cells and hepatocytes and impedes zinc absorption by sequestering newly absorbed zinc within the intestine and facilitates hepatic zinc uptake and storage. These zinc-sensitive responses can be blocked by actinomycin D or cordycepin, indicating the rate of Zn-M.T. synthesis is controlled at the genome level.[9,11] When Zn-M.T. synthesis is suppressed by these drugs zinc absorption is no longer depressed homœostatically in response to raised plasma-zinc after a meal; excess zinc cannot enter its major short-term storage organ, the liver, and it remains in the plasma.

It is plausible that A.E. and F.H.Z. result from excessive and depressed synthesis of Zn-M.T., respectively. In A.E. plasma-zinc and zinc absorption are both decreased. Excessive mucosal-cell Zn-M.T. could compete for new intracellular zinc from the diet and prevent its transfer to the plasma. An overproduction of hepatic Zn-M.T., which facilitates uptake and storage, could contribute to the depressed plasma-zinc by affecting an abnormally high rate of zinc clearance from plasma. F.H.Z. could reflect an inability to synthesise sufficient Zn-M.T. Mucosal-cell Zn-M.T. would not be available to sequester newly acquired dietary zinc, and absorption would proceed at a high rate, thus raising the plasma-zinc. This could be compounded because of the inability to make hepatic Zn-M.T., thus limiting the amount of zinc that could enter the liver from the plasma. In laboratory animals raised plasma-zinc is accompanied by suppression of mucosal cell and hepatocyte Zn-M.T. synthesis.

The symptoms of A.E. and F.H.Z. seem to be the opposite aspects of the same basic metabolic step. Moynahan has pointed out the similarities of A.E. to inherited thymic hypoplasia in cattle.[12] He proposed that gene mutation which leads to chelation of dietary zinc is the metabolic basis of both diseases. While the suggested role of Zn-M.T. in A.E. and F.H.Z. is speculative the identical physiological events that accompany the changes in Zn-M.T. synthesis experimentally are remarkably

1. Heite, H. J., Ody, R. *Hautarzt.* 1965, **16**, 529.
2. Moynahan, E. J. *Lancet*, 1974, ii, 399.
3. Michaellsson, G. *Acta derm.-vener., Stockh.* 1974, **54**, 377.
4. Thyresson, N. *ibid.* p. 383.
5. Neldner, K. H., Hambridge, K. M. *New Engl. J. Med.* 1975, **292**, 879.
6. Lombeck, I., Schnippering, H. G., Ritzl, F., Feinendegen, I. E., Bremer, H. J. *Lancet*, 1975, i, 855.
7. Smith, J. C., Jr., Zeller, J. A., Brown, E. D., Ong, S. C. *Science*, 1976, **193**, 496.
8. Richards, M. P., Cousins, R. J. *Bioinorg. Chem.* 1975, **4**, 215.
9. Richards, M. P., Cousins, R. J. *Biochem. Biophys. Res. Comm.* 1975, **64**, 1215.
10. Richards, M. P., Cousins, R. J. *Proc. Soc. exp. Biol. Med.* 1976, **153**, 52.
11. Squibb, K. S., Cousins, R. J. Unpublished.
12. Moynahan, E. J. *Lancet*, 1975, ii, 710.