noradrenaline[1] may thus point to a 'third' excitatory mechanism for noradrenaline. This may be supported by the observation that a small, residual, pressor response to catecholamines remains even after combined α- and β-adrenoreceptor blockade[12].

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HIRST AND NIELD REPLY—We take the view that there are many similarities between the mechanisms of excitatory transmission in arterioles and vasa deferentia of guinea pigs. Both are innervated by catecholamine-containing nerves which when stimulated cause an excitatory junction potential (e.j.p.) in the underlying smooth muscle. The e.j.ps recorded from both tissues are to all intents and purposes identical[1,2]; e.j.ps from both tissues are rapidly reduced in amplitude by guanethidine and persist in high concentrations of adrenergic blocking agents. We consider that the failure of α-blockade in arterioles arises because the neuronally released transmitter activates receptors which are unlike α-receptors. In our preparation we are able to mimic the action of the neurotransmitter only when noradrenaline is applied to specific regions of the muscle; until similar experiments have been conducted on vas deferentia it seems unnecessary to reject the hypothesis that noradrenaline is the primary transmitter substance[3–6].

McGrath rightly points out that some of the authors who take the view that a second unknown transmitter is released in addition to noradrenaline, base their opinion on further experiments in which tissue noradrenaline was in some way reduced[3,6]. A common method is by prior treatment with reserpine, which dramatically reduces but does not eliminate tissue noradrenaline[7]. However, it is by no means clear that a dramatic reduction in tissue noradrenaline leads to an equally dramatic reduction in the actual amount of noradrenaline released per nerve impulse[8].

Concerning McGrath's second point, we did not mean to imply that arteriolar smooth muscle contained two distinct populations of α-receptors, although this may well be the case. We stressed that the 'junctional' receptors that we were able to activate by noradrenaline were completely different from α-receptors. To avoid the possibility of confusion it might perhaps be more appropriate to call the 'junctional' receptors γ gamma-receptors.

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Germ-line deletion of genes coding for self-determinants

JEMMERSON AND MARGOLIASH's article[1] raises provocative questions about immunological unresponsiveness to self-antigens. They found that the autoantigenic sites on rabbit cytochrome *c* correspond to those regions in the molecule where other mammalian cytochromes *c* differ, and suggested that archaic genes coding for V-region specificities of immunoglobulin recognizing shared portions of the cytochrome *c* molecule were eliminated by evolutionary pressures. This would result in immunologically silent peptide sequences, there remaining mainly V genes for the more recently evolved species-specific determinants. Thus, one mechanism of self-tolerance would be evolutionary germ-line deletion of V genes coding for specificities against self-molecule determinants.

Previous studies by one of us (N.R.R.) were directed to the antigenic properties of thyroglobulin in rabbits[2]. Two sorts of autoantibodies in rabbits were compared, those induced by immunization with rabbit thyroglobulin and those induced by immunization with foreign thyroglobulins, such as those of hog or beef. The first kind of autoantiserum resembled the rabbit antisera to rabbit cytochrome *c* described by Jemmerson and Margoliash. Tested for reaction with rabbit thyroglobulin, the rabbit thyroglobulin readily absorbed all reaction, whereas the hog (or beef) antigen removed only a small part of the antibody content. We concluded that the rabbit preferred to form antibodies to the non-shared antigenic determinants of thyroglobulin.

In contrast, rabbits immunized with hog thyroglobulin showed relatively weak reactions with rabbit thyroglobulin, and these reactions could be absorbed equally well with hog, beef and rabbit thyroglobulins. Thus, autoantibodies induced by foreign thyroglobulin are directed mainly to the shared antigenic determinants of thyroglobulin.

On the basis of absorption behaviour, then, we could distinguish two types of autoantibodies. Those elicited by thyroglobulin of the same species were directed primarily to species-specific determinants, whereas the autoantibodies evoked by foreign thyroglobulins reacted mainly with the shared antigenic determinants. Of further interest, rabbits immunized with rabbit thyroglobulin showed severe lesions of thyroiditis. Only after repeated injections were even mild lesions seen in rabbits given foreign thyroglobulin.

The basic protein of myelin (BPM), a linear-folded protein without a tertiary structure, is another well characterized autoantigen. There are some 170 amino acid residues, and the sequences for the molecule of several mammalian species reveal a number of substitution sites. Because immunization with BPM induces experimental autoimmune encephalomyelitis (EAE) in all species studied, attention has focused on the capacity of BPM, and various peptides derived from it, to induce disease. The review by Bergstrand[3] indicates that different portions of the BPM molecule have greatly differing potency in terms of induction of (1) EAE, (2) cell-mediated immunity and (3) humoral antibody.

In the induction of EAE, which requires the participation of a T-cell response, detailed studies have defined the different amino acid sequences in the homologous proteins which induce EAE in different species. Minor sequence substitutions have an enhancing effect, for example, the encephalitogenic Ser–Thr substitution at residue 79 for the rat[4], with other changes abrogating activity[5].

With heterologous BPM injected into rabbits, one of the main determinants of humoral antibody was identified in the region 90–116 (ref. 6), and this does not vary between mammalian species. Unfortunately, relatively little information is available on the amino acid sequence(s) involved in the homologous response. Studies by microcomplement fixation assays in the rabbit[7] could be interpreted as showing a pattern of cross-reactivity between homologous and heterologous BPM equivalent to that described above for thyroglobulin. In particular, when rabbits were immunized with rabbit BPM, the antibody was predominantly reactive with rabbit BPM but with extensive cross-reaction with BPM of other species. It is assumed, although not

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