Mechanism of Action of Azathioprine Questioned

To the Editor:—Dr. Dretchen et al. suggest that the effect of azathioprine on neuromuscular transmission is due to the inhibition of phosphodiesterase. This may well be the case. However, from the data presented, one has to consider other actions of the drug, such as effects on the contractile process, calcium fluxes, muscle blood flow, sensitivity of the postsynaptic membrane, rate of transmitter release and, perhaps, others. These are not mentioned and disposed of, and the reader is presented with one proposed mechanism of action of azathioprine which, furthermore, is not adequately documented. The effect of the compound observed on a commercial bovine myocardial phosphodiesterase preparation, the increase in the force of contraction by azathioprine shown in an in-vivo cat soleus muscle preparation, and the observation that the effect is similar to that of theophylline can hardly be considered sufficient proof for the proposed mechanism.

The authors claim that they demonstrated that a cyclic nucleotide system may be involved in the function of the motor nerve terminal and refer the reader to two articles not yet published. In addition to this unfortunately unavailable documentation, the authors neglected, perhaps because of oversight, to cite two original papers in this field, thus depriving others of the pleasure of reading the original work of Breckenridge and the well-documented work of Goldberg on the role of cyclic AMP in neuromuscular transmission.

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To the Editor:—In considering that the action of azathioprine on the motor nerve terminal is due to an inhibition of phosphodiesterase, we had to be certain that the drug was without effects at other potential sites. In this regard we observed that azathioprine had no effect on the contraction characteristics of directly stimulated muscle, had no effect on the compound muscle action potential, had no effect on the sensitivity of the endplate to acetylcholine, and had no effect on the endplate potential amplitude. Finally, we observed that the drug had a facilitatory effect on the in-vitro rat phrenic-nerve-diaphragm preparation. This would eliminate an alteration in blood flow as a major site of action.

We have developed a theory showing how a cyclic nucleotide system might be involved in the function of the motor nerve terminal. Unfortunately these papers were published in the same month as this paper.1–3 In these papers we carefully formulate the hypothesis, as well as citing other investigations4,5 that also support the hypothesis. For this reason, we did not mention the latter articles in the paper on azathioprine. When you look at our other papers it will become apparent that the effects of azathioprine on the motor nerve terminal are identical in every respect to those of theophylline. That azathioprine does in fact inhibit bovine myocardial phosphodiesterase is only further supportive evidence; it is not the sole proof upon which we based our argument.

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