Promoting Effect of Urea on the *in vitro* Passive Sensitization of Isolated Plain Muscles with Precipitating Antibody

It has been proved[1] that carbonic acid exerts an inhibitory effect on *in vitro* sensitization of isolated guinea pig plain muscles.

The following investigations provide evidence that urea has a promoting effect on passive *in vitro* sensitization of isolated tissues.

The technique used is as follows: strips of guinea pig intestine are immersed in a Tyrode solution containing a known amount of rabbit antiovalbumin antibody. When the antigen (ovalbumin) is added after a certain time allowed for contact, contraction of the muscle is observed. The intensity of the contraction is a function of the concentration of the antibody duration equal periods of contact. By comparing the amount of contraction with this produced by a standard solution of histamine, it is possible to make a rough evaluation of the intensity of the sensitization.

We have found that the addition of urea to the Tyrode solution containing the antibody enhances significantly the process of sensitization of the intestine. This effect is already evident with a concentration of 0·16 mol. of urea; but it is more striking when the urea concentration is raised to 0·8 mol.

A typical example of this enhancing effect of urea is illustrated in Fig. 1.

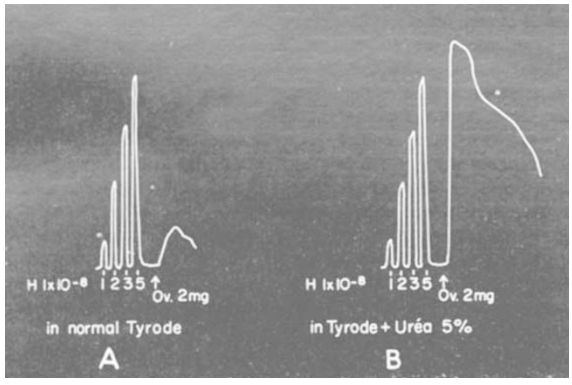

Fig. 1. Two adjacent strips of guinea pig ileum *A* and *B* sensitized passively *in vitro* with 5 μgm. N/ml. of rabbit antiovalbumin antibody. Time of incubation: 20 min. at 37° C. in Tyrode solution. *A*, control in Tyrode solution; *B*, Tyrode solution containing urea at a concentration of 0·8 mol.; *H*, addition of histamine dihydrochloride; *Ov*, addition of 2 mgm. of crystallized hen ovalbumin.

The promoting effect of urea on the sensitizing process is possible only when it is added in the presence of the antibody. Treatment of the tissue with urea, prior to or after sensitization, does not produce the same result, provided that the tissue has been sufficiently washed clear of the traces of urea. However, if the intestine has been sensitized in the presence of urea, subsequent washings do not affect the enhanced immunological response.

From these results, it can be deduced that urea affects the process of sensitization rather than the sensitivity of the intestine to histamine.

The relationship between the intensity of the anaphylactic response and the incubation time for the same antibody concentration in the standard conditions and in presence of urea is indicated in Fig. 2. Although the slopes of the sensitization curves vary with the antibody concentrations and although a wide range of variations has been observed with strips from various animals, the promoting effect of urea at

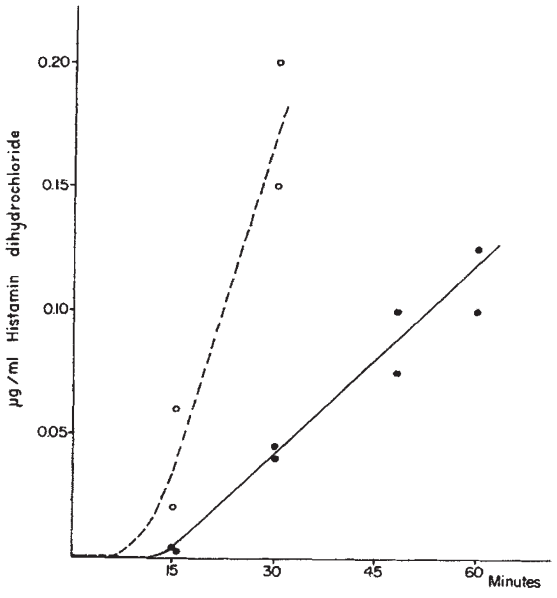

Fig. 2. Height of the anaphylactic contraction of strips of guinea pig ileum, taken from the same animal, sensitized passively *in vitro* with the same antibody concentration (16 μgm. N/ml.) and incubated during various times. ●, — Strips immersed in standard Tyrode solution; O, — strips immersed in Tyrode solution containing 0·8 mol. of urea (5 per cent). Ordinate, height of anaphylactic contraction as expressed by corresponding histamine concentrations which produce identical contraction; abscissa, time of incubation (min.)

the concentration of 0·8 mol. was always about four times.

The nature of the phenomenon described is not yet clearly understood. It is possible that urea decreases the number of the hydrogen bonds between the antibody molecules and water, and so facilitates diffusion of the antibody through the cellular structures involved in the sensitization process.

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[1] Halpern, B. N., and Binaghi, R., *Nature*, **183**, 1397 (1959).

Reversal of Effects of 2-Substituted Thiadiazoles by Nicotinamide Analogues and Precursors

The 2-substituted thiadiazoles have been found to produce a variety of biological effects—the inhibition of growth of transplanted tumours and leukæmias in mice[1,2], the production of glossitis in man[3], and an increase in *de novo* synthesis of uric acid in man[3]. These effects can be prevented by nicotinamide which has led some observers to regard the thiadiazoles as 'nicotinamide antagonists'[4,5].

Since the chick embryo produces uric acid during development, it was used for the further investigation of the effects of the thiadiazoles on synthesis of uric