Physiology. The distribution of the rates of epinephrine output is illustrated in Fig. 3.

Summary. These experiments indicate the existence of an inhibitory central mechanism, located in the region of the brain bounded by the superior colliculi and the optic chiasm, which influences epinephrine secretion from the adrenal glands. The existence of a central mechanism in the spinal cord, which exercises an opposite influence to that of this cerebral centre, was established earlier.[2] Removal of the influence of the brain centre, results in epinephrine output from the adrenals at the maximum rate of spontaneous liberation which can be sustained through the physiological activity of the spinal cord centre. This rate corresponds with the upper limit of the range of normal epinephrine secretion.[1]

Despite the fact that epinephrine was the first hormone to be isolated from its source, and to be synthesized, the functional significance of epinephrine secretion is still obscure. Physiological interpretations from pharmacological observations often have been misleading. Only quantitative experiments, yielding results within the limits of the physiological rate of liberation, can be expected to yield unequivocal information on the function of epinephrine secretion.

In the light of the experiments reported herewith, it can be seen why reflex augmentation of the rate of epinephrine secretion has not been demonstrated successfully in animals under the influence of asphyxia[8] or stimulation of sensory nerve trunks.[9] For, even if these stimuli might affect appropriate receptors, which could alter the rate of epinephrine secretion, there is no reason to assume that they might not equally influence the cerebral and the cord centres, thus defeating the possibility of eliciting reflexly either augmentation or diminution in the rate of epinephrine secretion from the adrenal glands. In preliminary tests, it was not found possible to elicit augmentation of the epinephrine output by stimulation of sensory nerves, following mechanical destruction or compression of the brain.[9a]

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Inhibition of Experimental Drug Allergy by Prior Feeding of the Sensitizing Agent.

MERRILL W. CHASE.

From the Laboratories of The Rockefeller Institute for Medical Research, New York.

In the course of studies on experimental drug allergy, it was noticed that sensitization was apt to be less successful in guinea pigs which previously had been treated briefly with the same chemical. Experiments were undertaken to establish at will such a refractory state.* For the preparatory, or blocking, treatment, the methods tried included the parenteral injection of soluble and insoluble protein conjugates of the incitant itself, repeated cutaneous application of the chemicals in very low (non-sensitizing) concentration, intravenous injections, and feeding experiments. After this preliminary treatment, a rest period of 2 weeks was allowed, and then the animals, in parallel with fresh guinea pigs as controls, were subjected to an active sensitizing course consisting of 6 or more intracutaneous injections of the incitant over a period of several weeks. Following

* In the case of neoarsphenamine, Sulzberger[4] had found that a single intravenous injection of the substance usually prevented the active sensitization sought by an intracutaneous injection made one day previously.

TABLE I.

Hypersensitivity rated as:	Prior feeding of allergen (93 animals)	Controls (77 animals)
	%	%
High	3.2	74.0
Good	0.0	16.9
Moderate	8.6	5.2
Weak	20.4	3.9
Low	46.2	0.0
Very faint, or entirely negative	21.5	0.0

another 2 weeks' rest, the outcome of the challenging sensitization was determined by a "contact test" in which the skin was painted with dilutions of the incitant in olive oil and the animals were examined for the development of cutaneous reactions.

While several substances were employed in the first experiments, the compound 2:4 dinitrochlorobenzene was chosen for chief attention because it is actively allergenic and is well known in the experimental sensitization of human beings.[1,2,3] Rather unexpectedly, and in sharp (but not absolute) contrast to all other methods employed, a blocking effect of substantial degree was found to be induced by feeding the chemical. A 1% solution of dinitrochlorobenzene in olive oil was fed from the tip of a pipette in such manner that contact of the solution with the muzzle was minimal. The feedings (0.3 cc) were made daily for 6 days, followed by an 8-day rest period; 2 or 3 such courses were given prior to the attempt at sensitization by intracutaneous injections. While the latter regularly sensitized either normal animals or animals fed the vehicle alone (olive oil), a very considerable diminution in effect was encountered in groups that had received prior feedings of the chemical. This is shown in Table I, which brings together the results from various, essentially similar experiments. It will be seen that the protection afforded was not absolute, although in some experiments well-nigh complete inhibition was attained. On the other hand, it remains possible that the protective effect may be overridden by intensive treatment with the allergen.

To examine whether the feedings had led to a blocking mechanism directed only towards the same chemical or had induced a non-specific resistance to sensitizations, the behavior of the animals to an active sensitizing course with a second, unrelated substance (*o*-chlorobenzoyl chloride) was examined. The resistant and "positive control" groups did not differ at all in their response to the new agent. This held true, also, when animals fed with one chemical then received a simultaneous series of intracutaneous injections with 2 substances, one, the specific allergen, and the other, a non-related compound. The inhibitory effect therefore was specific, and the animals were normal in their response to another compound.

That the effect is rather durable, and one apparently not dependent upon retention of the ingested substance, was demonstrated in one lot of 30 animals fed 2:4 dinitrochlorobenzene. At varying intervals, groups of approximately 10 animals were given the sensitizing course, along with an equal number of new animals as controls. Protection was still apparent even in the last group tested: here the interval between the final feeding and the beginning of the challenging course had been 27 weeks, and the final contact test was made 4 weeks later.

It is possible, then, to induce a profound and lasting protection against experimental sensitization when one starts with animals which are not already sensitive to the substance in question; this is consonant with the experiment of Sulzberger.[4] On the other hand, courses of feeding given to animals previously made sensitive to 2:4 dinitrochlorobenzene have so far shown no appreciable effect in diminishing the degree of hypersensitivity, a result in accord with attempts to decrease an established sensitivity in guinea pigs by parenteral injection of soluble protein

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[2] Landsteiner, K., Rostenberg, A., and Sulzberger, M. B., *J. Invest. Dermat.*, 1939, **2**, 25.

[3] Haxthausen, H., *Acta Dermato-Venereol.*, 1939, **20**, 257.

[4] Sulzberger, M. B., *Arch. Derm. and Syph.*, 1930, **22**, 839.

conjugates of the incitant.[5] There are, however, statements in the literature to the effect that sensitive human beings have been partially desensitized by ingestion of the specific allergen.[6,7]

Summary. Through the feeding of certain allergenic compounds to the non-sensitive subject, a state of resistance may be established against subsequent experimental sensitization of the skin by the same substance.

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Rabbit Papilloma and Vaccinia Viruses and T_2 Bacteriophage of *E. coli* in "Shadow" Electron Micrographs.*

D. G. SHARP, A. R. TAYLOR, A. E. HOOK, AND J. W. BEARD.†

From the Department of Surgery, Duke University School of Medicine, Durham, N. C.

Although electron micrography has added greatly to knowledge of the shape, size and other characters of viruses, the findings leave much to be desired. The capacity of viruses to absorb and scatter fast electrons is relatively small, and, consequently, images of the particles are likely to be of low contrast and indistinct, especially at the periphery. Contrast in influenza virus images may be enhanced slightly by treatment of the virus with osmic acid;[1] use of calcium chloride, though obscuring internal structure, aids greatly in micrography of equine encephalomyelitis[2] and influenza viruses[3] but not in the instances of the rabbit papilloma and tobacco mosaic viruses. In addition, the images are flat, and judgment of particle shape must be based solely on contour portrayed in 2 dimensions. A considerable advance in the electron micrography of viruses is the application of the shadow-casting technic recently reported by Williams and Wyckoff.[4,5,6] In this process, the molecules of metals evaporated *in vacuo* fall on the virus particles at a grazing angle and cast "shadows" which give the appearance of 3-dimensional contour to images in electron micrographs. The shape and length of the shadows cast on the background and the contour of the images afford a much better basis for judgment of the shape of the particle than the unshadowed images. Studies with this technic have been made of the vaccinia and rabbit papilloma viruses and the T_2 bacteriophage of *E. coli*. The results‡ with these 3 viruses are reported in the present paper.

Materials and Methods. The viruses were

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† Consultant to Secretary of War and Member, Commission on Acute Respiratory Diseases, Board for the Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

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[6] Williams, R. C., and Wyckoff, R. W. G.,