such as the gasserian and nodose. Assuming the same condition to hold in man during the early, presymptomatic period or in cases that might end without symptoms in the absence of operation, an opportunity would be open for direct introduction of virus into the peritonsillar tissues before the CNS is infected.

This possibility suggested a supplementary study of the preventive effects of local antisepsis in the throat. Six cynomolgus monkeys were subjected to the same procedure as in Series 1, excepting that 2% tincture of iodine was applied to the throat one-half minute after swabbing with virus and one minute before tonsillectomy. All these animals remained well.

Further exploration of this procedure is required before its meaning and implications can be properly evaluated. Although such pre-operative antisepsis appears to be harmless, no assurance of its preventive value against poliomyelitis in human beings can be offered.

Summary and conclusions. 1. Application of poliomyelitis virus to the pharynx of cynomolgus monkeys, followed by enucleation of the tonsils was regularly followed after 7-10 days by primary bulbar paralysis, accompanied less often by high spinal paralysis. This effect was probably due to introduction of virus into the innervations of the peritonsillar tissues, notably muscle. 2. Intrathalamic inoculation of virus followed 3 days later by tonsillectomy was regularly followed within 2 more days by bulbospinal paralysis in which all levels of the cord were involved. This effect probably indicates that trauma increases the vulnerability of nerve cells to infection already present in the central nervous system. 3. After oropharyngeal swabbing with virus and no tonsillectomy, spinal paralysis usually resulted, with bulbar manifestations in only one instance. 4. With pharyngeal application of virus followed by 2% tincture of iodine and then by tonsillectomy, all 6 animals remained well.

Received June 12, 1951. P.S.E.B.M., 1951, v77.

In vitro Action of Cortisone on Vasoconstriction Due to Histamine.* (18839)

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Two questions prompted the present study. Does cortisone alter the response of isolated smooth muscle to histamine? If it does, what mechanism is involved? The experimental evidence suggesting the participation of the hormones of the adrenal cortex in the metabolism of histamine has recently been reviewed by Rose(1) and need be mentioned only briefly. Adrenalectomized animals have been found to have a markedly diminished resistance to histamine; an increased tissue content of the compound as well as a diminished capacity of the tissues *in vivo*(2) and *in vitro* (3,4) to destroy or inactivate histamine. While these changes are partially reversible by DOCA, adrenal cortical extract (which contains cortisone as well as many other compounds) will restore the metabolism of histamine by the adrenalectomized animal to an essentially normal state(1).

Experimental procedure. An angioplethysmokymographic technic(5,6) was used to

* These studies were aided by research grants from the Masonic Foundation for Medical Research and Human Welfare and the Hochstetter Fund.

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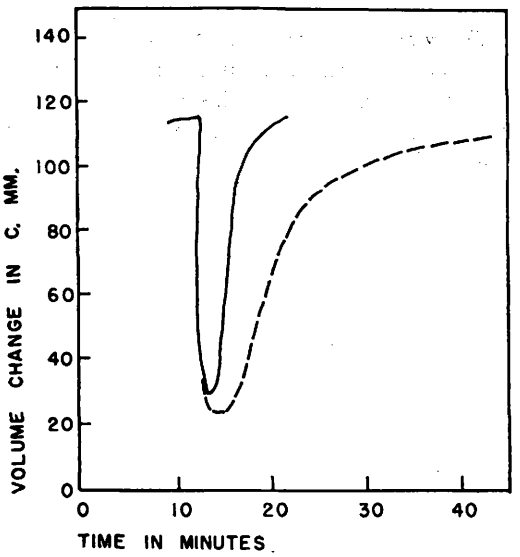

FIG. 1. Exp. #1241. Swine carotid artery. Vasoconstriction to 50 γ test doses of acetylcholine. (Control reaction, ———; Physostigmine 1:1,000,000, – – – –). Note prolongation of "curve of recovery" following inactivation of cholinesterase.

assess the modifying action of cortisone on the vasoconstriction of isolated surviving blood vessels caused by histamine. In this procedure an artery is mounted in a simple plethysmograph and perfused with Tyrode's solution for several hours. A continuous record is made of the changes of volume of the vessel during perfusion. The arteries were stimulated to constrict by injecting test doses (usually 50 γ) of histamine or acetylcholine into the perfusate in such a manner that the stimulating drug flowed through the artery in 12-15 seconds(7). Hence the constriction of the vessel and its recovery occurred in the absence of any detectable portion of the stimulus in the perfusate. The modifying action of cortisone† and control substances was determined by adding these compounds to the perfusates in the stated concentrations. The cortisone (free alcohol) was first dissolved in propylene glycol in a concentration of 2 mg per ml. Propylene glycol alone did not modify the reactivity of the arteries in the concentrations used.

Results. The angioplethysmokymographic technic produces time-volume curves (Fig. 1) indicating arterial vasoconstriction to specific stimuli. The "curve of constriction" (decrease in volume when the vessel constricts) is a function of the amount of vascular smooth muscle which is stimulated to contract. Previous studies have shown that this can be eliminated or reduced significantly by typical blocking agents(6). The "curve of recovery" (the increase in volume of the vessel as it dilates back to its original baseline) is primarily a function of the enzyme systems which destroy or inactivate the stimulating agent. The influence of cholinesterase on vasoconstriction due to acetylcholine is demonstrated in Fig. 1.

Preliminary observations of the action of cortisone indicated that it did not act as a physiological antagonist of histamine and furthermore, that it had little or no blocking action, there being no significant change in the "curve of constriction." The swine carotid artery responds to repeated test doses of histamine (50 γ) with reactions which have a similar "curve of constriction," but in which the "curve of recovery" becomes increasingly prolonged,‡ although the response to similar multiple test doses of acetylcholine over the same time period are unchanged. This rather specific prolongation of the recovery from vasoconstriction due to histamine provided the test object necessary for this study. The arteries were perfused for 2-4 hours and subjected to repeated test doses of histamine. When the recovery phase became significantly prolonged, cortisone (1:2,000,000 to 2:1,000,000 of the free alcohol) was added to the perfusate and the response to histamine was again recorded. A final control period using corti-

7. Emmel, V., Smith, D. J., To be published.

† Cortisone (free alcohol) was kindly supplied by Augustus Gibson, of Merck and Co., Rahway, N. J.

‡ During the winter months, prolongation of vasoconstriction due to histamine becomes evident after 3 test doses and marked in the fifth reaction (average of 61 arteries) while during summer months, prolongation of reaction does not become evident until after 9 test doses (average of 34 arteries) and rarely becomes as marked as in winter killed animals. These observations on the seasonal variation in this reaction extend from April 1949 to May 1951 and are being continued(8).

8. Smith, D. J., To be published.

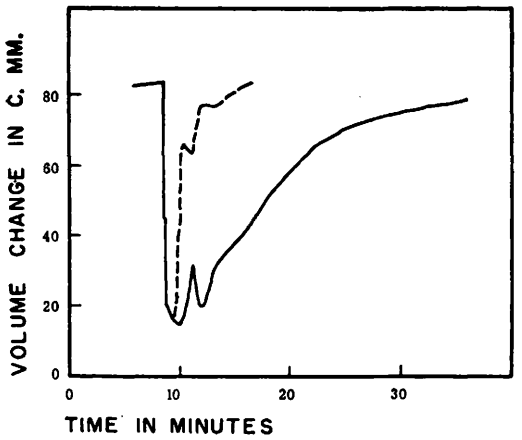

FIG. 2. Exp. #1324. Swine carotid artery. Vasoconstriction to 50 γ test doses of histamine. (Control reaction, ———; cortisone 2:1,000,000, – – –). Note marked acceleration of recovery of vessel in presence of cortisone.

sone-free perfusate was usually run.

Thirty-one experiments of this type using cortisone have been accomplished. In each instance at concentrations of 1 or 2 parts of cortisone per million, the recovery of the vessel from vasoconstriction due to histamine was accelerated (Fig. 2). In a concentration of 1 part of cortisone per 2 million, negligible effect was observed. Control observations using cholesterol in propylene glycol and propylene glycol alone were without effect on the histamine response. Three segments of a single artery were frequently examined simultaneously, each being injected at the same time. One vessel would be retained as a control while the other two were perfused with cortisone. These control vessels in no case showed the accelerated recovery from histamine shown by those vessels exposed to cortisone.

One further observation is of interest. The swine carotid artery constricts when the temperature is raised to 42°C. Cortisone causes the vessel to dilate when it is constricted by temperature.

Discussion. Our results indicate that cortisone (in concentrations of 1 part per million or greater) accelerates the recovery of the vascular smooth muscle from vasoconstriction due to histamine. The mechanism of this accelerated recovery is not completely defined by these studies. In our experience the enzyme systems inactivating the stimulating agent are a major factor in determining the form of the recovery curve. Hence it seems probable that cortisone may modify the histamine inactivating enzyme systems of smooth muscle to produce the accelerated recovery of the tissue observed in this study. This is in agreement with the results of Rose(3) and Karady, Rose and Browne(4), who demonstrated that the decreased histaminase content of the lung of the adrenalectomized rat could be restored to normal by adequate amounts of adrenal cortical extract. The question may be raised, Is this prolongation of the histamine reaction (which is reversed by cortisone) a specific change in the histamine inactivating enzymes or is this a nonspecific deterioration of the tissue *in vitro?* Two facts suggest the latter is not the case. The response to multiple doses of acetylcholine remains constant while concomitant doses of histamine produce gradually lengthening reactions. Secondly, the marked and consistent seasonal variation in the deterioration of the histamine response cannot be explained on the basis of tissue damage caused by the experimental procedure.

Summary. 1. Cortisone accelerates the recovery of vascular smooth muscle from vasoconstriction due to histamine. 2. This probably represents an action of cortisone on the histamine inactivating enzyme systems.

The valued technical assistance of Mr. Clarence P. Bray is hereby gratefully acknowledged.

Received June 15, 1951. P.S.E.B.M., 1951, v77.