

influences causing thyroid involution may be transmitted by the same means; (b) that while these observations do not affect the question of the existence of specific secretory fibers, they demonstrate that such fibers are not essential in order that thyroid tissue may exhibit the characteristic morphological and physiological changes known to be associated with great variations in functional activity; (c) that these data emphasize the necessity for additional evidence on the question of specific secretory fibers for the thyroid.

123 (1055)

**On the action of sodium chloride in the prevention of proteotoxin shock.**

By **HANS ZINSSER, CHARLES C. LIEB** and **JAMES G. DWYER.**

*[From the Departments of Bacteriology and Pharmacology, College of Physicians and Surgeons, Columbia University, New York.]*

It was shown by Friedberger and Hartoch that guinea-pigs could be protected against anaphylactic shock by an intravenous injection of hypertonic salt solution immediately preceding the toxic dose of antigen. That this protection is not due, as Friedberger and Hartoch claimed, to the inhibitory action of the salt on the alexin was demonstrated by Ritz, who found that an injection of salt also exerted protective action in animals injected with proteotoxins (the anaphylatoxins of Friedberger).

Dale concluded that the protection afforded by sodium chloride against acute anaphylaxis was due to the decreased irritability of the smooth muscle. He found that if the uterus of a sensitized guinea-pig were suspended in hypertonic salt solution, the addition of the antigen no longer caused the usual anaphylactic reaction. Other stimulating substances, like pilocarpine and pituitary extract, also failed to produce their typical stimulation provided that the uterus was bathed in hypertonic salt solution.

It is the object of the present investigation to show that, when a preliminary injection of salt protects against proteotoxin shock, the absence of reaction is due to the lessened irritability of smooth muscle.

In the first place, it was necessary to confirm, if possible, the

observations of Ritz. It must be remembered that, as Friedberger and Hartoch pointed out, the protective action of salt is a limited one and if the amount of antigen given at the second injection or if the amount of proteotoxin used is much above the minimal fatal dose, the poisoning is so acute and powerful that the protective effects of the salt are entirely masked. We had considerable difficulty at first in obtaining satisfactory experiments because of our failure to appreciate this relation, but when the toxic dose did not materially exceed the minimal fatal dose there was no difficulty in determining the protective effect of salt in guinea-pigs injected with proteotoxin. Preliminary tests showed that guinea-pigs ranging in weight from 165 to 200 grams could withstand, without serious effects, the injection of 1.5 c.c. of 30 per cent. salt solution into the external jugular vein. The blood oozing from the injection wound was a bright brick red. This striking change in color can not at present be explained. The salt solution must be injected very slowly, and we allowed from 1 to 12 minutes for its introduction. An interval of 2 minutes was allowed between the injections of the salt and the proteotoxin. Though this interval may not be absolutely necessary our most successful experiments were obtained when it was observed. The following three experiments are examples of the striking protective action exerted by the sodium chloride.

#### EXPERIMENT I.

Injections were made into the jugular veins; usually the salt solution was injected at a point close to the maxilla, a ligature applied and the proteotoxin injected proximally into the same vein. The injections of salt were carried out slowly, from one to one and a half minutes taken for the introduction of one cubic centimeter.

From these experiments it is plain that the toxic action of the proteotoxin (anaphylatoxin) is prevented by the immediately preceding injection of enough sodium chloride to render the blood of the animal hypertonic.

Having confirmed the experiments of Ritz it was next necessary to determine the mechanism of this protection.

It is well known that during anaphylactic shock violent con-

| No. | Weight. | Salt, C.c. | Interval, Min. | Amount of Proteotoxin, C.c. | Result.  |
|-----|---------|------------|----------------|-----------------------------|--|
| 1.  | 185     | —          | —              | 2.5                         | Typical death in 3 minutes.  |
| 2.  | 185     | —          | —              | 2                           | Typical death in 3 minutes.  |
| 3.  | 185     | —          | —              | 1.5                         | Slight symptoms—recovers quickly.  |
| 4.  | 170     | 1.5        | 2              | 2                           | Very slight symptoms at first, gradually worse for 2½ minutes. Falls to side—then recovers.        |
| 5.  | 170     | —          | —              | 2                           | Typical death in 2½ minutes.   |
| 6.  | 165     | 1.5        | 2              | 2                           | (Very slight loss of proteotoxin during injection.) Pig shows hardly any symptoms.                 |
| 7.  | 165     | 1.5        | 2              | 2                           | Severe symptoms for one minute. Then gets better and is in good condition within five minutes.     |
| 8.  | 160     | 1.5        | 2              | 2                           | Incubation time of 45 seconds, then respiratory distress and retraction of head. Gradual recovery. |
| 9.  | 160     | —          | —              | 2                           | No interval—immediate severe symptoms. Death in 3¼ minutes.  |

Time of injection of salt was 1 minute 30 seconds in the above.

### EXPERIMENT II.

| No. | Weight. | Salt, C.c. | Interval, Min. | Proteotoxin, C.c. | Result.   |
|-----|---------|------------|----------------|-------------------|---|
| 1.  | 195     | —          | —              | 2.5               | Death in 3¼ minutes.                                      |
| 2.  | 200     | —          | —              | 2                 | Death in 3 minutes.                                       |
| 3.  | 210     | —          | —              | 2                 | Death in 4 minutes.                                       |
| 4.  | 195     | 1.5        | 2              | 2                 | Very sick. Recovers.                                      |
| 5.  | 190     | 1.5        | 2              | 2                 | Not very sick. Recovers quickly.                          |
| 6.  | 200     | 1.5        | 2              | 2                 | Very sick. Slow recovery. In good condition in 5 minutes. |
| 7.  | 190     | 1.5        | 2              | 2                 | Slightly sick. Recovers quickly.                          |
| 8.  | 180     | 1.5        | 2              | 2                 | Very sick. Gradually recovers.                            |
| 9.  | 205     | —          | —              | 2                 | Death in 4 minutes.                                       |
| 10. | 205     | —          | —              | 2                 | Death in 3½ minutes.                                      |

### EXPERIMENT III.

| No. | Weight. | Salt, C.c. | Interval, Min. | Proteotoxin, C.c. | Result.                        |
|-----|---------|------------|----------------|-------------------|--------------------------------|
| 1.  | 225     | —          | —              | 3                 | Very sick. Gradual recovery.   |
| 2.  | 210     | —          | —              | 3                 | Death in 4 minutes.            |
| 3.  | 205     | 1.5        | 2              | 3                 | Slightly sick. Rapid recovery. |
| 4.  | 200     | 1.5        | 2              | 3                 | Very sick. Gradual recovery.   |
| 5.  | 205     | 1.5        | 2              | 3                 | Slightly sick. Recovers.       |
| 6.  | 210     | —          | —              | 3                 | Death in 3¼ minutes.           |
| 7.  | 205     | —          | —              | 3                 | Death in 3 minutes.            |

tractions of certain smooth muscle groups occur. The experiments of Schultz, Dale, Weil, and others, have pointed to a definite parallelism between the irritability of smooth muscle and the condition of sensitiveness. Furthermore, Dale has shown that a hypertonic salt solution prevents the usual reaction of the uterus of a sensitized guinea-pig to antigen. It was therefore necessary for us to determine whether an increase in the tonicity of the fluid bathing the uterus would abolish the reaction of the organ to proteotoxin. In our experiments the uteri of virgin guinea-pigs were used. The animals were etherized and exsanguinated. The uterus was excised and one horn was suspended in a glass cylinder in such a manner that its contractions would be recorded on the smoked paper of a slowly moving kymograph.

On adding a little fresh guinea-pig serum to the Ringer's solution in which a uterus is suspended a powerful contraction immediately ensues. If a small amount of salt solution is now added a total inhibition of the uterine movements occurs and the organ slowly relaxes. On replacing this mixture with pure fresh Ringer's fluid the normal rhythm and tonus usually return. When serum and salt solution are added together no contraction occurs.

Similar changes take place when proteotoxin is added to the Ringer's solution bathing the uterus. The spasm which follows such an addition may be removed by the subsequent addition of enough salt to approximate the concentration likely to be found in a guinea-pig of 200 gm. after the injection of 1.5 c.c. of 30 per cent. sodium chloride. If the uterus is surrounded by such a hypertonic salt solution the addition of proteotoxin fails to produce a typical spasm.

Occasionally a powerful contraction occurs after washing a preparation which because of the presence of excess salt has not reacted to proteotoxin. The explanation of this late spasm seems to be as follows: When the proteotoxin-salt mixture is siphoned away a trace of the mixture remains in the vessel. When the pure Ringer's solution is run in the original mixture is greatly diluted. The small amount of proteotoxin still remaining is sufficient to send the uterus into spasm because the quantity of salt remaining is insufficient to lower the irritability of the muscle.

In these experiments it is apparent that in the presence of a

hypertonic solution the uterus no longer reacts to serum or to proteotoxin.

The absence of reaction is due to a lessened irritability of the smooth muscle. Since the uterus is a typical example of a smooth muscle organ, it is very likely that all smooth muscle fails to react to proteotoxin when it is bathed in hypertonic solution. Such a decrease in irritability of smooth muscle will explain the protection against proteotoxin which an intravenous injection of concentrated salt solution affords.

124 (1056)

**Clinical and experimental studies in chemotherapy with ethylhydrocuprein in measles, scarlet fever and other infections.**

By **ARTHUR D. HIRSCHFELDER** and **FREDERIC H. SCHLUTZ**.

*[From the Department of Pharmacology and the Department of Medicine, Division of Pediatrics, University of Minnesota.]*

Morgenroth and his collaborators have demonstrated the prophylactic and curative and prophylactic powers of ethylhydrocuprein, a quinin derivative, in pneumococcus septicemia in mice.

The writers have given ethylhydrocuprein hydrochloride in doses of 0.1 to 0.5 G. three times a day by mouth to 7 cases of scarlet fever whose fever then had an average duration of 8.9 days as compared with 7.4 in 7 untreated cases who came under the same conditions in the same epidemic. In eleven unselected cases of measles, however, treated with the same drug, the average duration was 4.3 days as compared with an average duration of 7.9 days in ten untreated cases. One child who received the drug at the onset of symptoms, however, had an illness of 5 days' duration in spite of the early treatment.

The above experience seems to warrant the clinical use of ethylhydrocuprein in the treatment of measles, but not in scarlet fever.

Negative results with ethylhydrocuprein were obtained in experimental rabies and experimental vaccinia, also in trachoma.