in one almost straight line; but still the child is absolutely helpless. This symptom does not, I think, occur in other diseases than infantile paralysis in early childhood. I noticed, for instance, in a case of pneumococcal meningitis, that the child was able to raise herself in bed without any special difficulty, although her neck and back were quite stiff. This child appeared to be recovering, but died soon after.

This paralysis of the trunk is too obvious a symptom to have escaped notice before. Many writers mention it, but do not attach any special importance to it, evidently looking upon it as one of the many manifestations of the lesion of the lower motor neurone. There are two sufficient reasons for rejecting this view. (1) Any subsequent wasting of the muscles of the trunk is unusual. Complete recovery is the rule, although it may take some weeks, as in the case already quoted. This is in striking contrast to the paralysis of the legs, in which complete recovery is the exception. In the last two epidemics, which have formed the principal basis of this paper, only one case of residual paralysis of the muscles of the neck or trunk was observed. This child recovered completely from the paralysis of the trunk after about two months, but paralysis of the muscles of the neck remained with wasting. A mechanical contrivance had to be devised to hold her head up. In this case it was clear that the motor cells in the upper cervical portion of the cord had been destroyed. Permanent paralysis of the muscles of the abdominal wall is also rare. (2) Usually the muscles of the upper extremity, and occasionally those of the upper limb, escape paralysis altogether. It is impossible to suppose that such a widespread and destructive lesion could involve the thoracic and cervical portions of the spinal cord and leave out the cervical and lumbar enlargements.

There must be some connexion between this paralysis of the trunk and the rigidity previously described. They have much the same muscular distribution and are generally associated with one another. It is natural to suppose that the cerebellum is the organ involved. Usually the child can carry out all voluntary movements other than those involved in the assumption of the erect posture. The child can talk, feed itself, and otherwise use the hands as well as ever. It can move the legs in bed, lift them up, and carry out any ordinary muscular movement; but yet cannot use the legs for standing. It is clear that we have here no ordinary form of muscular paralysis, due to disease of the lower motor neurone. The incidence of the paralysis shows clearly that it must be of cerebral origin. It cannot be due to disease of the cerebral cortex, as all ordinary voluntary movements can be readily carried out, apart from those of the trunk. "Atonia" has been regarded as a result of disease of the cerebellum for many years. It is clear that in infantile paralysis the function of standing is lost for a time. This function is almost automatic. It is also exceedingly interesting that rigidity of the neck and trunk should be so often combined with paralysis of the trunk in infantile paralysis, and yet be dissociated from it in other cases; also that in some cases of meningitis rigidity should exist without any real paralysis of the trunk. The explanation would seem to be that in meningitis the cortex alone is injured, while in infantile paralysis the cerebellum is injured in addition.

The question arises, Why are these two symptoms, rigidity and paralysis, so common at this early age, whether the case be one of infantile paralysis, meningitis, pneumonia, gastro-enteritis, or other form of toxaemia? I think that one of Hughlings Jackson's axioms may be the answer to this question—namely, that the most recently acquired function is the first to be lost in disease of the nervous system. The most important functions a child acquires during the first two years of life are those of standing and walking. Few things are more striking in the newborn infant than the total want of tone in the muscles of the neck and trunk. It is continually exercising the muscles of the legs and of the arms, but it has no control whatever over the muscles of the neck. It is not till after about three months that the child is able to hold the head up; at about 12 months of age it should be able to stand and perhaps to walk. This process is very slow and gradual; even when acquired, the child is for a long time very unstable in standing, running, or walking. It seems reasonable to suppose that this function is particularly vulnerable in the second and third years of life when infantile paralysis is common. No doubt the cerebellum is the organ which controls it. The cerebellum exercises, in conjunction with the medullary and pontine nuclei, a tonic influence on the muscles of the trunk especially, and on those of the legs to a less degree, which makes the assumption of the erect posture possible. In infantile paralysis the power of assuming the erect posture is lost altogether for a time in many cases.

Landry's Paralysis and other Types.

The acute ascending type, which is often fatal and which resembles the form of paralysis described by Landry in 1859, has not formed a feature of recent epidemics in Sydney. It usually occurs in older children, and includes most of the fatal cases in some epidemics. It seems likely that further investigation along the lines here set forth might give useful results. The cerebral type is very apt to be mistaken for meningitis; there may be rigidity of the neck with convulsions, as in one of my cases. A child, aged 1 year and 11 months, was admitted in general convulsions in March, 1909; the convulsions next day were limited to the left half of the body. The left half of the body was paralysed. She was subject to fits of the Jacksonian type for some ten years, and then she passed from my observation. The cerebral cortex was no doubt the chief seat of disease in this child. Is it too much to assume that the cerebellar cortex was also affected?

I did not intend in this paper to deal with the subject of rigidity in anything like a comprehensive way, but merely to discuss one aspect of it. The work of the late Professor Hunter has directed the attention of the profession to the whole question, in a most lucid and masterly fashion. Almost all the observations given in this paper were carried out before his work was published. The issues of the BRITISH MEDICAL JOURNAL of January 31st, February 7th, 14th, 21st, and 28th, 1925, which contain references to recent researches bearing on the subject, should be consulted for a full description of Hunter's work.

THE ACTION OF PITUITARY EXTRACT ADMINISTERED BY THE ALIMENTARY CANAL.

BY

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SINCE von den Velden[1] first showed the specific action of pituitary extract in cases of diabetes insipidus this drug has been used very widely by clinicians, and has proved a helpful remedy, not only in diabetes insipidus, but also in surgical shock, and especially for its action on the uterus. This widespread use of pituitary extract has naturally led to administration by various methods. It has been recognized generally that pituitary, when given intravenously, subcutaneously, or intramuscularly, shows a distinct influence on all those organs on which it is known to act. The effect of pituitary after any method of injection is, however, limited to a comparatively short time, and repeated injections are required in order to keep the patient under the influence of the drug. In cases where repeated injections appeared to be undesirable, nasal, oral, and rectal administrations have been tried, but there has been no unanimity as to the results. Kennaway and Mottram,[2] von den Velden, Rosenbloom,[3] Rowntree,[4] Blumgart,[5] Barker and Mosenthal,[6] report that they have never observed any pituitary action after administration by the mouth. Wolpe,[7] Hamill,[8] and Donaldson,[9] on the other hand, observed a distinct action after oral administration. Abel and Gisling,[10] Rowntree, and Blumgart have produced evidence of the successful application of pituitary by the nose, and finally Rosenfeld[11] may be mentioned for having observed a slight effect after rectal administration. All these observations have been made clinically on patients suffering from diabetes insipidus or from uterine haemorrhage, except Hamill's investigation, which was carried out

on cats. As the literature up to date does not give any clear evidence of the pituitary action on blood pressure and uterine movements after administration through the different parts of the alimentary canal, an accurate study of this subject appeared to be desirable.

In the investigation here described cats were used; they were anaesthetized with chloralose and the blood pressure was registered from the carotid artery. The uterine movements were recorded in the following way. The abdomen was cut open in the mid-line just above the urinary bladder. A small incision was then made in the vaginal wall as near the vulva as possible. A glass tube was inserted and tied into the vagina and the uterus was then filled with liquid paraffin. The vaginal glass tube was connected by rubber tubing with a manometer in order to regulate the pressure, and the rise and fall of the oil caused by uterine contractions were recorded by means of a tambour. The pressure naturally varied according to the size and condition of the uterus, but on an average was about 10 cm. This method was very successful, as the abdomen could be kept closed, trifling movements of the animal did not affect the record, and an accurate investigation could be continued for a prolonged time. All experiments were completed by an intravenous injection of pituitary extract in order to test the reliability of the method. The pituitary extract used was that of Parke, Davis and Co., and my thanks are due to this firm for the free supply of the drug.

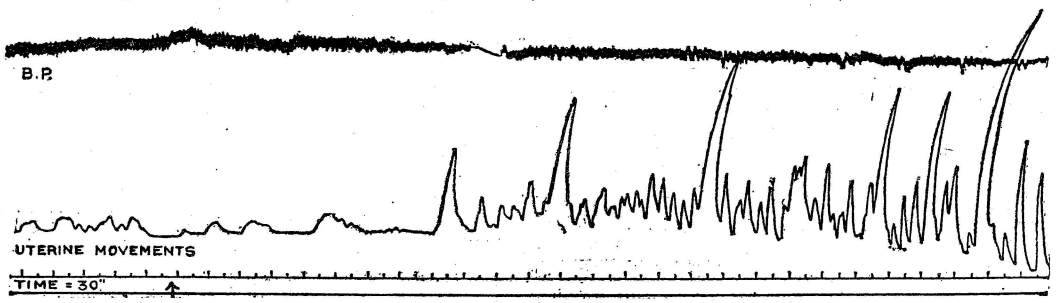

FIG. 1.—Cat, weight 3 kilos, uterus big and relaxed; at the arrow 1 c.cm. of pituitrin was administered by the mouth.

1. *Action when given by the Mouth.*

The oesophagus was tied at its entrance into the chest, and the pituitary extract was then placed under the tongue, this being considered the best place for absorption. The tracing (Fig. 1) shows quite distinctly the powerful action on the uterine muscle, and the complete lack of any simultaneous pressor effect. This experiment, which may be regarded as typical, shows quite clearly that pituitary extract is not only absorbed by the mouth, but that the absorption was remarkably rapid in the instance illustrated, a marked effect being obtained in eight minutes.

2. *Inaction when given by the Stomach.*

In these observations care was taken to avoid any absorption in the mouth. The pituitary extract (1 to 2 c.cm.) was introduced directly into the stomach by means of an elastic catheter. As a result of repeated experiments it is certain that under the conditions stated no effect is produced, either on the blood pressure or on the uterine muscle after administration by the stomach. A subsequent intravenous injection of an appropriate amount of pituitary extract given at the close of the experiment has always shown its typical effect.

3. *Inaction when given by the Small Intestine.*

In order to introduce pituitary extract directly into the small intestine a small incision was made in the mid-line of the abdominal wall and a short loop of the jejunum exposed. This exposure was always followed by a marked rise of blood pressure, and thus it was necessary to wait a certain time until the animal came back to normal conditions before giving the pituitary extract. When the blood pressure had regained its normal level 1 to 2 c.cm. of pituitary extract was injected into the jejunum by means of a very fine needle attached to a syringe, and immediately afterwards the exposed loop was replaced and the cut in the abdominal wall closed. The result of these experiments was in all cases the same as those obtained after the pituitary was introduced into the stomach—namely, that no action whatever, either on the blood pressure or on the uterus, was obtained.

4. *Action when given by the Rectum.*

These experiments were made under conditions identical with those already described: 1 to 2 c.cm. of pituitary extract was introduced into the rectum by means of an elastic catheter attached to a syringe. These experiments have shown quite clearly that pituitary extract produces a distinct but slight effect on the uterine muscle, but has no action on the blood pressure. The effect is first seen about fourteen minutes after administration.

The results obtained by using the methods described above are more or less in accordance with the bulk of observations made by clinicians. Clinical observations of this kind are by the nature of things extremely difficult to interpret, as they lack the necessary controls.

So far as Wolpe's and Donaldson's observations are concerned, the authors may probably be right in stating that pituitary extract acts when given by the mouth, but the important fact to appreciate is that the absorption of the active principle takes place in the mouth and not in the stomach. Hamill's observation that strong uterine action is produced by pituitary extract when introduced into the stomach is based on experiments which are open to many criticisms. The method of recording uterine movements was such that any small movements of the animal upset the record, and in a long experiment this is a very important point. Hamill does not appear to have employed curare to counteract this. He states himself that the records were difficult to obtain on account of peristalsis and straining. My own experience is that the method employed by Hamill is not valid for this type of experiment on account of the difficulty in interpreting the results. My own experiments point to the fact that no pituitary action whatever occurs when the drug is introduced into the stomach or small intestine in reasonable amounts.

Furthermore, it seems to me important to draw attention to the fact that pituitary extract, when absorbed from the mouth or rectum, produces only the uterine effect. I have shown elsewhere[12] that there is every evidence of the existence of two distinct principles in the pituitary body—namely, the oxytoxic and the pressor substances, the latter of which is very easily destroyed by passing through capillaries. The investigation here reported affords further proof of that assumption, for the remarkable change of the uterine movements proves the absorption of the oxytoxic principle, while the absence of effect on the blood pressure proves the non-absorption or immediate destruction of the pressor substance.

Summary.

1. When pituitary extract is administered at any part of the alimentary canal—mouth, stomach, small intestine, rectum—pressor action is never observed.

2. When pituitary extract is introduced into the stomach or small intestine it exerts no influence on uterine muscle.

3. When pituitary extract is administered by the mouth, after a latent period of about eight minutes it exerts a marked action on the uterus, increasing both the tone and automatic movements. The oxytoxic substance is therefore absorbed. The rectum absorbs the oxytoxic substance also, although the absorption is probably not so complete.

My sincere thanks are due to Dr. W. E. Dixon, F.R.S., for his kind help and criticism during the course of these experiments.

REFERENCES.

1 Von den Velden: *Berl. klin. Woch.*, 1913, 45, p. 2083.
2 Kennaway and Mottram: *Quart. Journ. Med.*, 1919, 12, p. 222.
3 Rosenbloom: *Journ. Amer. Med. Assoc.*, 1918, 70, p. 1292.
4 Rowntree: Ibid., 1924, 83, p. 399.
5 Blumgart: *Arch. Int. Med.*, 1922, 29, p. 504.
6 Barker and Mosenthal: *Journ. Urol.*, 1917, 1, p. 449.
7 Wolpe: *Berl. klin. Woch.*, 1921, 5, p. 101.
8 Hamill: *Proc. Roy. Soc. Med.* (Therap. Sec.), 17, 1921.
9 Donaldson: Ibid., 19, 1921.
10 Abel and Gisling: *Journ. Pharm. and Exper. Ther.*, 1924, 22, p. 317.
11 Rosenfeld: *Berl. klin. Woch.*, 1916, 21, p. 553.
12 Knaus: *Journ. Pharm. and Exper. Ther.*, 1925.