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ANIMALS

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From the Pharmacotherapeutical Institute of the University of Leiden

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Since Eykman found in 1893 that fowls fed on a diet of polished rice only would after some weeks show signs of "polyneuritis gallinarum" and that this disease could be cured by feeding the animals with the bran of the rice, a large amount of work in deficiency diseases has been performed. As a result of this work, which during the last years was taken up with great zeal by American investigators, our knowledge of the factors determining the outbreak of deficiency diseases and our knowledge of the several accessory foodstuffs, fat soluble A, water soluble B and so forth has been very much increased. On a certain point however—and a very important point too—we are still groping in the dark. We know that by giving to animals a diet lacking in certain substances, these animals will show after a certain time definite symptoms of illness, but the question as to what is finally the cause of the illness in these animals is not yet solved. There is a theory that withdrawal of certain foodstuffs from the diet merely increases the sensitiveness of the animal for bacterial infection but this theory, if being supported at all by experimental data, can certainly not give an adequate explanation for all cases of deficiency diseases. There are theories that ascribe the symptoms of deficiency diseases to the formation of a "poison" in the body of the avitaminous animals, but of the nature of this hypothetical poison nothing is known.

McCarrison (1) in a very extensive study on deficiency diseases and accessory foodstuffs supports the view that the lack of vitamins induces above all a defect in "matière nucléaire" in



the body, which defect the body tries to meet by reducing the amount of that material in several organs.

Recently Uhlmann (2) found that a vitamine preparation "orypan" (and also other vitamines) contain substances which have an action on smooth muscles very closely resembling that of pilocarpine and previous to this work it had already been shown by Bickel (3) that extracts of spinaches exert a pilocarpine-like action. On the bases of these findings it would be possible to ascribe many of the deficiency symptoms to a lack of "pilocarpine-like" substances which stimulate smooth musculature. Such a view would be in accordance with the opinion expressed by Hopkins, Abderhalden, Bang and others, who also seem to incline to consider the vitamines as being stimulants for cell activity.

One of us (V.) had in collaboration with Bögel (4) and independently of Uhlmann's work studied the influence of extracts from foodstuffs containing either fat soluble A or water soluble B, on isolated muscle and isolated gut, on the isolated rabbit's ear and on the Laewen Trendelenburg preparation of the frog, on blood pressure in dogs and on the sugar excretion in pancreas diabetic dogs. They could in certain instances find a slight action of their extracts, but they did not feel justified to ascribe this pharmacological action to the vitamin fraction of their extracts.

As however Verzár and Bögel were through external circumstances during the performance of the experiments related above, not in a position to carry out metabolism experiments they were unable to verify the "vitamine" action of their extracts and moreover the extracts used by them were derived from another source than those of Uhlmann. The present writers are of the opinion that Uhlmann's results are not disproved by the experiments of Verzár and Bögel.

Although, as stated above, a theory ascribing the curative effect of vitamines in deficiency diseases could to a certain degree be supported by the results of some experiments, we are of the opinion that this question cannot at all be considered as being settled. Since work that had been done by one of us (S. v. L.) seemed to open the possibility of coming a little nearer to the

solution of the question under discussion we felt justified in undertaking a series of experiments which will be reported here.

The starting point of our work was determined by the following considerations.

Among the symptoms exhibited by animals suffering from deficiency diseases, disturbances in the action and in the innervation of striped and smooth muscles play a large part. It is known that these disturbances in the function of muscles can be to some extent explained by the fact that signs of extensive degeneration in nerves and muscles are to be found. The degeneration in the spinal nerves in cases of avitaminose has long been known. That also in these cases degenerative signs can be demonstrated to a large extent in the neuromuscular system of the gut and the other visceral organs was recently emphasized by McCarrison (1).

These organic lesions in nerves, muscles and secretory organs can however never explain the entire complex of symptoms in avitaminoses, since it is possible to cure an animal suffering from polyneuritis in an extraordinary short time. Hence it must be assumed that the symptoms of deficiency diseases are at least partly of functional nature, i.e., the organs of the animal do not react to the stimuli being present in the body at that time, but these organs can be brought into action quasi at once by the injection of the adequate vitamine.

If now it is asked why those muscles (and in the present paper we will only consider the smooth muscles), did not react properly before the vitamine was injected it seems to us that from a theoretical standpoint three solutions of the question might be deemed possible.

a. The smooth muscles of the organs do not react because substances which under physiological conditions are the normal stimulants for these organs are during the deficiency diseases not present in adequate amounts.

b. The smooth musculature does not react because its sensitiveness to stimulating substances, present in normal amount, has been lowered.

c. The sensitiveness of smooth musculature is normal, also the

amount of stimulating principles is normal, but there is a lack of (colloidal) substances in the body of the animal which under normal conditions tend to facilitate the action of drugs on smooth musculature. That colloidal substances really occur under normal conditions in the animal body had been shown by one of the present writers in corroboration with his co-workers (5, 6, 7) and we were especially interested to find out whether some symptoms of deficiency diseases would be caused by a lack of these substances. Although this last mentioned assumption could be proved not to be true, we deemed it advisable to publish our results as it appears to us that the question of the ultimate cause of the symptoms in avitaminosis cannot be solved, and the importance which Uhlmann's researches may have in this matter cannot be rightly valued before it is known which of the three possibilities mentioned above is the right one.

The immediate aim of our experiments was to make out whether in deficiency diseases a diminished or anyhow a changed sensitiveness of the smooth musculature to drugs could be demonstrated. If a change in sensitiveness had been found it would of course have been necessary to differentiate between the sub b and c, mentioned possibilities.

We performed our experiments on fowls and cats. Deficiency diseases were induced in the fowls by feeding them with polished rice for some weeks whereas the cats were fed exclusively on meat which after having been made alkaline had been heated in the autoclave for three hours at 120°. This last method which has been described by Voegtlin and Lake (8) gave us good results.

We are of course aware of the fact that the food we gave our animals in these experiments was not only lacking in one certain vitamine but was deficient in many respects but on account of what is known in the literature it could be assumed that the symptoms which our animals showed would be mainly dependent on a lack of water soluble B. This question however was immaterial to us since we first had to investigate whether there could be demonstrated any differences at all in the reaction of normal and avitaminous animals. Only if this had been proved to be the case it would have been necessary to differentiate between the effect of the omission of different vitamins.

The avitaminous animals were only experimented upon when they showed very markedly the characteristic symptoms of polyneuritis; as a matter of fact some of the animals were nearly moribund during the experiments so that it was hardly possible to narcotize them. In most cases we used very light ether narcosis and some times urethane narcosis. A cannula was tied in the carotids for measurement of the blood pressure (with Hg manometer) and another cannula in the vena femoralis in cats and in one of the veins of the wing in fowls to make the injections with the various drugs. The vagi were prepared free near the larynx, tied and cut. We then determined the minimum dose of adrenaline, choline and histamine which by intravenous injection just gave a distinct but slight action on the blood pressure; in many cases also the influence of larger doses was tried. All drugs were given in such a dilution that 0.5 to 1 cc. had to be injected. The injection always lasted exactly twenty seconds. After the sensitiveness for the drugs mentioned had been tested we determined the minimal strength of electric current which on stimulation of the vagus nerve gave a distinct fall of blood pressure, and after that we tried to find the minimal amount of atropine which could inhibit this vagus action. When the blood pressure experiment was finished, the animal was killed and the gut removed. Isolated strips of gut were then suspended in Tyrode solution and the sensitiveness to pilocarpine, histamine, choline and atropine was tested. Sometimes we also used strips of the esophagus in these experiments.

As the sensitiveness of normal fowls to drugs was not known to us, we had to make preliminary determinations on them. The results of these experiments are included in the present paper. It was hardly necessary to make control experiments on cats since the normal reactions to the drugs to be tested were known to us.

EXPERIMENTS ON FOWLS

Normal fowls. The reaction of 5 normal fowls was studied. The exact data obtained in these experiments will be given in the tables below. The blood pressure at the beginning of these experi-

ments varied from 110 to 152 mm. Hg. Very small doses of adrenaline viz., 0.0005 mgm. adrenaline (Parke, Davis and Company) dissolved in 1 cc. of NaCl solution and injected at a constant rate in twenty seconds gave generally a drop in blood pressure; slightly larger doses gave a rise, preceded or followed by a drop, whereas doses of 0.001 to 0.005 mgm. generally gave a rise in blood pressure. The sensitiveness of the various animals to adrenaline differed widely. Fowl II reacted to 0.01 mgm. of adrenaline with a drop of 12 mm. Hg followed by a rise of 16 mm. Hg whereas fowl I gave a drop in blood pressure of 24 mm. Hg after injection of 0.0005 mgm. adrenaline. It was often difficult to determine exactly the minimum active dose of adrenaline, so the figures given in table 1 are approximate ones and indicate the doses after which a *distinct* rise of blood pressure following the adrenaline injection was seen independently of whether this rise was preceded or followed by a fall in blood pressure. It was thought at first that it would be of advantage to differentiate exactly between doses that would give a fall and doses that would give a rise, as we deemed it possible that avitaminous animals would behave differently in this respect. This however proved not to be the case. Also in the fowls suffering from deficient diet we noted sometimes a rise and sometimes a drop of blood pressure after small doses of adrenaline. As moreover even in the same animal the reaction to adrenaline was not a constant one, since the same dose of adrenaline, which gave a rise of blood pressure before might cause a drop of pressure half an hour later, we left these differences out of consideration and give in table 1 those doses which caused a distinct rise in blood pressure.

Choline. A study of the action of choline on the blood pressure seemed very promising to us as choline belongs to the normal constituents of the blood. The result however was disappointing. The doses that may give a distinct drop in blood pressure vary widely in different animals. We often found a reaction after small doses, but fowl VI for instance failed to react on 2 mgm. of choline. So we gave choline injections only in a few cases. As far as we could make out there are no differences in this respect

between the behaviour of normal fowls and of animals suffering from avitaminosis.

Histamine. In the beginning of our experiments we used a sample of ergamine obtained by the kindness of Dr. Dale. Later we used the same preparation obtained from Burroughs and Welcome. These ergamine experiments gave very clear results. 0.01 mgm. of ergamine always gives a distinct drop in blood pressure (15 to 20 mm. Hg) sometimes smaller doses were also active. In table 3 we give only one instance of histamine action in normal fowls. In another series of experiments however on normal fowls in this laboratory it was found that 0.01 mgm. of ergamine is always active.

Action of atropine on effect of vagus stimulation

It is of course not possible to determine in every single experiment the exact minimal dose of atropine which will inhibit the effect of vagus stimulation. One has to try a very small dosis first and if this one is not sufficient a higher dose is given, till a dose is found which inhibits the vagus effect. But with this mode of procedure it is not known whether in determining the effective dosis all the single doses have to be added or not. Presumably part of the atropine injected with the first doses will be destroyed or will be bound somewhere in the body at the moment the last dosis is given. On the other hand it is known that the action of atropine, once being established lasts for a considerable time so that certainly part of the atropine of the first injections will add its effect to that of the later injections. We considered as an active dose of atropine the sum of the small doses given till the vagus stimulation had no influence on the blood pressure. In this way we found as effective doses of atropine 0.01 to 0.02 mgm.

Action on isolated gut

It was known from former experiments that the sensitiveness of pieces of catgut suspended in Tyrode solutions to pilocarpine, histamine and so forth, varies greatly in different pieces even if they belong to the same animal. Moreover the sensitiveness of

a certain loop is by no means constant during the course of an experiment; usually there is a tendency to an increased sensitivity as the experiment proceeds. Hence it was not advisable to try to find exact minimum active doses for the drugs under investigation. We knew from a great many experiments on isolated catgut in Tyrode solution that this organ will, as a rule, react to 0.005 to 0.01 mgm. of pilocarpine hydrochloride added to 75 cc. of Tyrode solution. The effect of a dose of pilocarpine, which gives a marked contraction of the gut can be influenced antagonistically by 0.0001 to 0.001 mgm. of atropine (7). As it appeared after the first experiments with the isolated gut of fowls that also in the organs of this animal great differences in susceptibility are to be found, we contented ourselves with the investigation whether the sensitiveness of the gut of the fowl would be about the same as that of the cat. This indeed proved to be the case as in several experiments 0.005 to 0.01 mgm. of pilocarpine was active (in one case also 0.001 mgm.) whereas this action could be influenced antagonistically by doses of atropine corresponding to the above-mentioned active doses for the cat.

Histamine was active on the gut of the fowl in doses of 0.01 to 0.05 mgm. ergamine added to 75 cc. Tyrode solution. These doses fall into the same range as those found in the cat.

Choline was active on the gut of the fowl in doses of 0.05 to 1 mgm. added to 75 cc. Tyrode solution. It was not attempted to determine the exact minimal active doses.

On the *isolated esophagus* of the fowl only a few experiments were performed. In one experiment it reacted to 0.1 mgm. of pilocarpine added to 75 cc. Tyrode solution with a fairly strong contraction whereas the contraction was inhibited by 0.01 mgm. of atropine (smaller doses would presumably have been active also but they were not tried).

Experiments on fowls suffering from avitaminosis

Investigations were made on 9 fowls. They were not experimented upon until the symptoms of polyneuritis were fully developed. Some animals were so ill at the beginning of the experiment that it was hardly possible to narcotize them. For

this reason it was not possible to make all the necessary determinations on every animal because sometimes they died during the experiment.

Blood pressure. The blood pressure at the beginning of the experiment was as a rule lower in the animals suffering from avitaminosis than in the normal ones. In 3 cases very low pressures were found (50 mm. of Hg at the beginning and down to 10 to 20 mm. at the end of the experiment) but in other cases we found 140 to 145 mm. Hg.

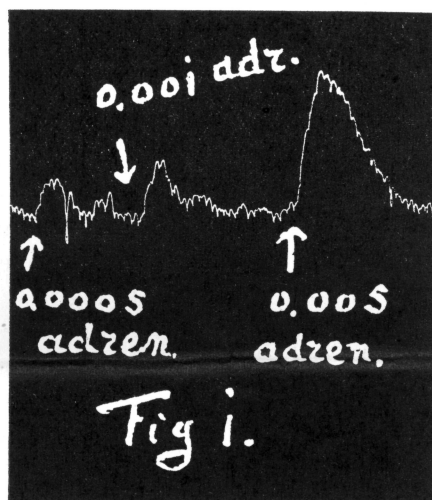


FIG. 1. INFLUENCE OF ADRENALINE (PARKE, DAVIS AND COMPANY) ON BLOOD PRESSURE OF A FOWL SUFFERING FROM AVITAMINOSIS

Blood pressure 90 mm. of Hg. 0.0005 mgm. of adrenaline dissolved in 1 cc. of NaCl solution and injected in twenty seconds with constant rate intravenously gives very slight reaction. 0.001 mgm. causes slight rise in blood pressure. 0.005 mgm. gives moderate rise in blood pressure.

The blood pressure could be experimentally raised by stimulation of a sensible nerve (ischiadus f. i.). Stimulation of the vagus with currents of the same strength as in the normal gave a definite fall in pressure.

Action of adrenaline. Exact information on the adrenaline action could not in all cases be obtained, as in those cases where

the blood pressure was very low, there was a continuous tendency to clotting. One animal (fowl VIII) seemed to be very resistant to adrenaline. The blood pressure however was low at the beginning of the experiment (50) and went down to 20 mm. Hg during the first ten minutes, in fact this animal was moribund so that, in view of the results obtained in other animals, we incline to disregard this experiment. In 5 cases where exact determination could be made the active dosis varied from 0.0003 mgm. to 0.001 mgm. of adrenaline dissolved in 1 cc. and injected into the vena femoralis at a constant rate, the entire injection taking exactly twenty seconds. Figure 1 gives an instance of the action of 0.0005 mgm. of 0.001 mgm. and of 0.005 mgm. of adrenaline in the blood pressure of fowl V suffering severely from polyneuritis at the time of the experiment.

Choline was active in one case in doses of 0.2 to 2 mgm., but as stated above we do not lay much stress on the cholin experiments.

Histamine. Ergamine was active in all the cases (6) where it was tried in doses of 0.01 to 0.05 mgm. In one case a drop in blood pressure was obtained with 0.002 mgm.

Atropine on effect of vagus stimulation. The atropine dosis necessary to inhibit the effect of vagus stimulation was determined in 3 cases. The doses were 0.005 mgm., 0.01 mgm. and 0.1 mgm. It is not certain whether in the last mentioned case a smaller dosis would not also have been sufficient.

Action on isolated gut

The action of pilocarpine on the isolated gut was tested in 8 cases. The active doses varied from 0.001 to 0.01 mgm. pilocarpine hydrochloride added to 75 cc. Tyrode solution.

Atropine. The inhibitory effect of atropine on pilocarpine contraction was studied in 8 cases; the active doses varied from 0.0001 to 0.001 mgm. of atropine sulfate added to 75 cc. of Tyrode solution.

In one case (fowl VI) 0.00005 mgm. was also active.

Figure 2 a gives an instance of the action of 0.005 mgm. of pilocarpine on the gut of a normal fowl suspended in 75 cc. Tyrode solution; the action is inhibited by 0.0001 mgm. of atropine sulfate.

Figure 2 b gives the action of 0.01 mgm. of pilocarpine in the gut of a fowl (V) suffering severely from polyneuritis. The pilocarpine action is inhibited by 0.0001 mgm. of atropine.

Histamine. Ergamine was tried in 3 cases; it was active in doses of 0.02 to 0.05 mgm. In one case (IX) only 0.1 mgm. of

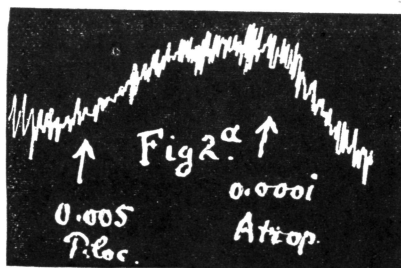


FIG. 2A. INFLUENCE OF PILOCARPINE HYDROCHLORIDE AND ATROPINE SULFATE ON ISOLATED GUT OF NORMAL FOWL

0.005 mgm. of pilocarpine added to 75 cc. Tyrode solution in which the gut is suspended gives contractions which are inhibited by 0.0001 mgm. of atropine.

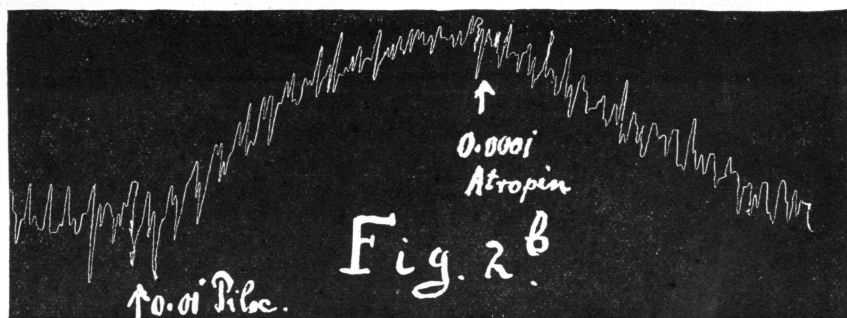


FIG. 2B. INFLUENCE OF PILOCARPINE AND ATROPINE ON ISOLATED GUT OF FOWL SUFFERING FROM EXPERIMENTAL POLYNEURITIS

ergamine was tried. It was very active. Smaller doses were not tested in this experiment.

Figure 3 a gives an instance of the action of 0.05 mgm. of ergamine added to the 75 cc. of Tyrode solution in which the isolated piece of gut of a normal fowl was suspended.

Figure 3 b gives the action of the same dosis of ergamine on a piece of gut of a fowl suffering from polyneuritis. This action can easily be inhibited by 0.01 mgm. of atropine. Very likely smaller doses would have been sufficient in this case.

Choline. Choline was given to three pieces of gut; 1 and 2 mgm. were active.

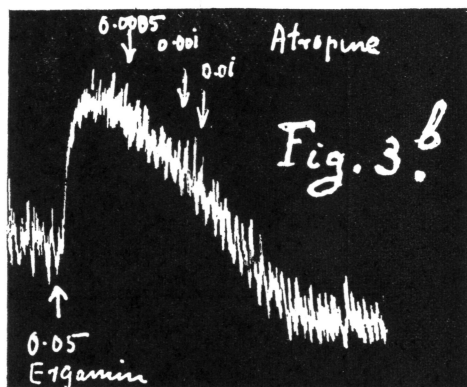
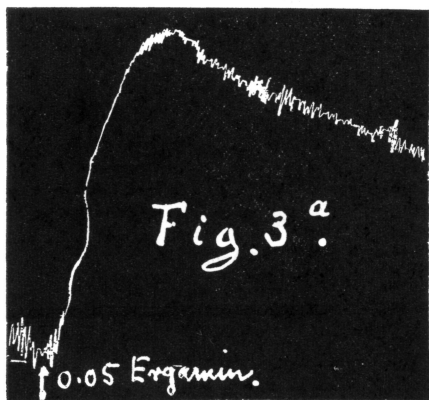


FIG. 3A. ACTION OF 0.05 MGm. OF ERGAMINE (BURROUGHS, WELCOME AND COMPANY) ON ISOLATED GUT OF NORMAL FOWL

FIG. 3B. ACTION OF 0.005 MGm. OF ERGAMINE ON ISOLATED GUT OF FOWL SUFFERING FROM EXPERIMENTAL POLYNEURITIS

Action of ergamine inhibited by atropine

Action on the esophagus

Pilocarpine in doses of 0.1 to 0.15 mgm. gave contraction of a isolated piece of esophagus in all the 4 cases where it was tried. 0.001 to 0.01 mgm. of atropine inhibited this pilocarpine contraction.

Figure 4 gives the action of 0.1 mgm. of pilocarpine on an isolated piece of the esophagus of a fowl suffering from polyneuritis; this pilocarpine action is partly inhibited by the addition of 0.001 mgm. of atropine. The complete data of the experiments related here are given below in tables 1 to 11.

From these tables and from the description given above it will be clear that the result of our investigation is an entirely negative one. As stated above, the sensitiveness of different individuals and even of different pieces of isolated organs of the

same individual—to the drug used varies greatly. Hence it is very difficult to get very exact values for the minimum active doses, and we agree that a slight difference that might exist between the normal fowls and those suffering from polyneuritis might have escaped our attention. We are of the opinion however that if the very severe symptoms that all our polyneuritis cases showed had been caused by a lack of susceptibility to stimulating chemical agents, very great differences in sensitiveness were to have been expected. And great differences were certainly absent in our cases.

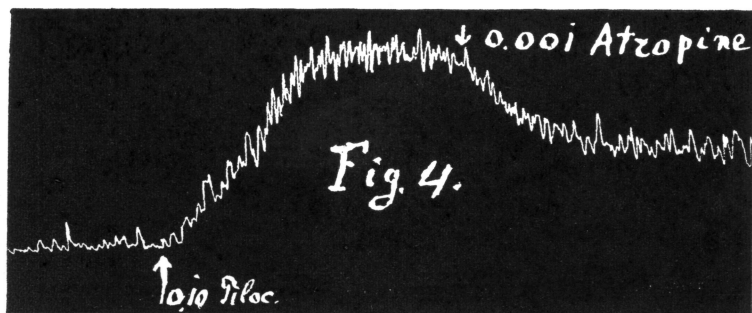


FIG. 4. ACTION OF 0.1 MGm. OF PILOCARPINE ON ISOLATED ESOPHAGUS OF FOWL SUFFERING FROM EXPERIMENTAL POLYNEURITIS

Pilocarpine action partly inhibited by 0.001 mgm. atropine

TABLE 1

Blood pressure at the beginning of the experiment

	I	II	III	IV	V	VI	VII	VIII	IX
Normal fowls.....	135	152	145	128	110	—	—	—	—
Polyneuritis cases..	145	140	124	54	90	—	140	50(20)	145

TABLE 2

Minimum active dose of adrenalin, in milligram of adrenaline (Parke, Davis and Company). Dissolved in 1 cc., injected in vena femoralis in 20"

	I	II	III	IV	V	VI	VII	VIII	IX
Normal fowls.....	0.0005	0.005	0.001	0.005	0.0005	—	—	—	—
Polyneuritis cases..	0.001	0.0003	0.001	—	0.0003	—	0.003	0.005*	0.0005

* Very slight reaction. The animal did not react to further doses of adrenaline and died soon afterwards.

TABLE 3

Doses of ergamine in milligram (Burroughs, Welcome and Company) which give definite fall in blood pressure

	I	II	III	IV	V	VI	VII	VIII	IX
Normal fowls.....	—	—	—	0.01*	—	—	—	—	—
Polyneuritis cases..	—	—	—	0.05	—	—	0.01	—	0.002 0.02

* In 3 other cases not belonging to this series the same dose of ergamine was active.

TABLE 4

Effective dose of choline on blood pressure in milligrams.

Normal fowls.....	2.0
Polyneuritis fowls.....	0.2 to 2.0

TABLE 5

Inhibition of effect of vagus stimulation—minimal effective atropine doses in milligram

	I	II	III	IV	V	VI	VII	VIII	IX
Normal fowls.....	—	0.01	0.01	0.01	0.02	—	—	—	—
Polyneuritis cases..	—	0.01	0.1	—	—	—	—	—	0.005

TABLE 6

Minimal effective dose of pilocarpine in milligram on isolated gut

	I	II	III	IV	V	VI	VII	VIII	IX
Normal fowls.....	—	—	0.005	0.01	0.001	—	—	—	—
Polyneuritis cases..	0.02	0.001	0.05	—	0.001	0.005	0.01	0.01	0.01

TABLE 7

Minimal dose of atropine in milligram which inhibits pilocarpine action

	I	II	III	IV	V	VI	VII	VIII	IX
Normal fowls.....	—	—	0.0001*	—	—	—	—	—	—
Polyneuritis cases..	0.001	0.001	0.001	—	0.0001	0.00005	0.0001	0.0001	0.001

* In a large series of normal cases on cat min. effective dose 0.0001 to 0.005 mgm. atropine.

TABLE 8

Effective dose of ergamine in milligrams on isolated gut

	I	II	III	IV	V	VI	VII	VIII	IX
Normal fowls.....	—	—	—	0.05	—	—	—	—	—
Polyneuritis cases..	—	—	—	0.02	—	—	0.05	—	0.1

TABLE 9

Effective dose of choline in milligrams on isolated gut

	I	II	III	IV	V	VI	VII	VIII	IX
Normal fowls.....	0.05	1.0	—	—	—	—	—	—	—
Polyneuritis cases..	—	—	—	1.0	—	2.0	—	—	2.0

TABLE 10

Effective dose of pilocarpine in milligram on isolated esophagus

	I	II	III	IV	V	VI	VII	VIII	IX
Normal fowls.....	—	—	0.1	—	—	—	—	—	—
Polyneuritis cases..	—	0.1	0.15	—	0.1	—	—	0.15	—

TABLE 11

Dose of atropine in milligram which inhibits pilocarpine action on isolated piece of esophagus

	I	II	III	IV	V	VI	VII	VIII	IX
Normal fowls.....	—	—	0.01	—	—	—	—	—	—
Polyneuritis cases..	—	0.01	0.005	—	0.005	—	—	0.001	—

Experiments on cats

The experiments on cats were performed in the same way as those on fowls. The animals were only fed on meat heated for three hours in the autoclave at 120°C. (Voegtlin and Lake (8)). Marked symptoms of polyneuritis were present fifty to sixty days after the beginning of this diet. The cats were not used for the experiment until they were very ill; two animals died on the operating table so that only the sensitiveness of the isolated organs could be studied. With two cats we were able to make

a complete investigation of the susceptibility to drugs. As it was noted that in these 4 animals there was (as with the fowls), no change in sensitiveness to drugs demonstrable (with one exception to be mentioned below) we abandoned further experiments.

A short description of the investigation on cats will be given here.

Blood pressure. The blood pressure at the beginning of the experiment was low in both cases (very light ether narcosis), 66 and 70 mm. of Hg.

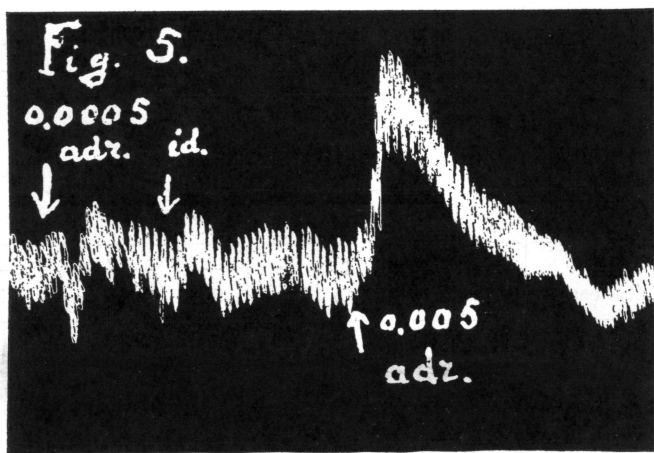


FIG. 5. ACTION OF ADRENALINE ON BLOOD PRESSURE OF CAT SUFFERING FROM EXPERIMENTAL POLYNEURITIS

0.0005 mgm. of adrenaline gives fall in blood pressure; same dose two minutes later hardly any reaction; 0.005 mgm. of adrenaline gives definite rise in blood pressure.

Reaction to adrenaline. The reaction to adrenaline was normal. Cat II gave a drop of blood pressure after injection of 0.0005 mgm. of adrenaline, hardly any reaction after another dose of 0.0005 mgm. and a distinct rise after 0.005 mgm. of adrenaline (fig. 5). The adrenaline (Parke, Davis and Company) was dissolved in 1 cc. of NaCl solution and injected in the vena femoralis at a constant rate, the duration of each injection being exactly twenty seconds.

Cat III gave a distinct rise in blood pressure after 0.0003 mgm. of adrenaline.

These adrenaline doses fall within the range of reactions of a large number of normal animals studied by us in this respect; the minimum active doses of adrenaline varied in these normal cats from 0.0005 to 0.005 mgm.

Reaction to histamine. Ergamine (Burroughs, Welcome and Company) gave a fall of blood pressure in doses of 0.01 and 0.05 mgm. This reaction corresponds completely with that found in

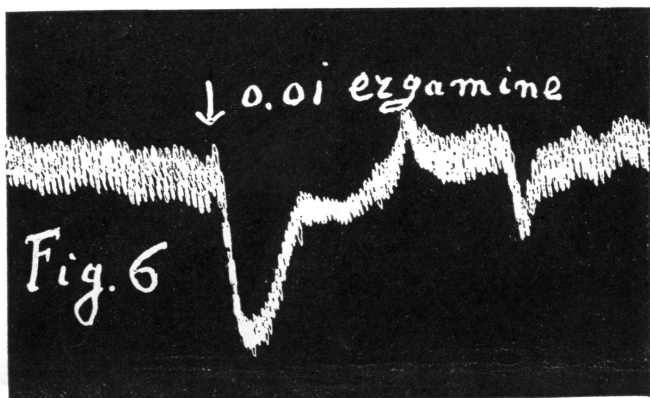


FIG. 6. FALL IN BLOOD PRESSURE CAUSED BY 0.01 MGm. OF ERGAMINE IN A CAT SUFFERING FROM EXPERIMENTAL POLYNEURITIS

normal cats. Figure 6 gives an instance of the action of 0.01 mgm. of ergamine on a cat suffering severely from polyneuritis.

Action of atropine on effect of vagus stimulation. The reaction to atropine was normal in one case, 0.005 mgm. giving a temporary inhibition of vagus effect, lasting for three or four minutes; a second equal dosis then gave the same effect. In a second case 0.0008 mgm. of atropine was active but the effect was doubtful and of very short duration so that we are inclined, especially in view of the results obtained with fowls, to disregard this finding.

Action on isolated gut

Pilocarpine gave normal reactions; doses varying from 0.005 to 0.1 mgm. of pilocarpine hydrochloride added to 75 cc. of Tyrode solution in which the gut was suspended gave a normal contraction which could be inhibited by doses of atropine varying from 0.001 to 0.005 mgm. These doses are exactly equal to those usually found on the gut of normal cats. Figure 7 gives an instance of the action of pilocarpine on the isolated gut of a cat

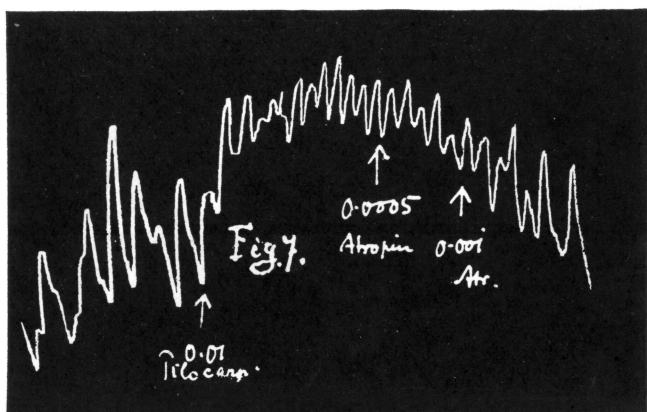


FIG. 7. ACTION OF 0.01 MG. OF PILOCARPINE ON ISOLATED GUT OF A CAT SUFFERING FROM POLYNEURITIS

The pilocarpine action is inhibited by 0.0015 mgm. of atropine

suffering severely from polyneuritis. 0.01 mgm. pilocarpine gives a moderate contraction. 0.0015 mgm. of atropine acted antagonistically and brought back the contraction to the normal niveau.

Ergamine was active in doses varying from 0.02 to 0.05 mgm. and choline in doses of 1 to 2 mgm. These doses also fall in the range of those which cause contractions on normal animals.

DISCUSSION

The object of our investigations was to make out whether a decrease of sensitiveness of smooth musculature to chemical agents normally present in the body could be responsible for

part of the very severe symptoms which occur in animals fed on a deficient diet. We found that the reaction of fowls and cats, suffering from avitaminosis, to adrenaline, histamine and choline (action on blood pressure), to atropine (inhibition of vagus stimulation) and the reaction of isolated gut and esophagus of these animals to pilocarpine, atropine, histamine and choline did not differ materially from the reaction of normal animals or of isolated organs of normal animals.

Since it is quite sure that the function not only of striped musculature, but also of smooth musculature is greatly damaged in animals suffering from avitaminosis and since—as we have shown—the sensitiveness of the smooth musculature to drugs has not been changed it must be deemed very probable that the decreased activity of smooth musculature in avitaminosis is caused by a lack in the body of these animals of the normal stimulating chemical agents. This view is in agreement with the conception of Abderhalden, Bang, Uhlmann and others who ascribe to the vitamins an action very similar to those of pilocarpine, viz., a stimulating action on smooth musculature.

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