Physiology. — *"A new form of correlation between organs."* By Prof. H. J. HAMBURGER.

(Communicated at the meeting of May 26, 1923).

Thus far we were acquainted with two forms of cooperation between organs. As to the eldest known form, here the central nervous system plays an important rôle. If any one pricks my finger unexpectedly with a needle, I immediately withdraw my arm; a cooperation has taken place between the skin of the finger and the muscles of the arm, and well by means of the spinal chord. Here we have to deal with a reflex.

Some years ago we got acquainted with a second form of correlation between organs; this one is not effected by means of nerves, but here the bloodcurrent is the mediator of the cooperation. For instance, the glandula thyroidea produces substances, which are carried through the body by the bloodcurrent and influence the metabolism and growth of distant organs.

That nerves here don't play an essential rôle appears from the fact, that the glandula thyroidea still exerts its influence, even when it is detached from its nerves and transplanted to another part of the body.

Now, in the last years experiments, performed in our laboratory, have clearly demonstrated *a third new form*[1]) *of correlation between organs*. The starting point of these researches, carried out by Dr. R. BRINKMAN, Miss E. VAN DAM and Dr. L. JENDRASSIK, was the following experiment of O. LOEWI in Graz. The vagus nerve of an isolated frog's heart, which is filled with a salt solution, is for some time stimulated so that the heart stops its beat. Then the content of the heart is removed and transferred into another frog's heart, which was isolated in the same way. Then the well-known pharma-

[1]) See my lecture at the opening of the Biological Buildings of Mc. Gill's University in Montreal (Canada) in September 1922. See also: H. J. HAMBURGER. The increasing significance of permeability problems for the biological and medical sciences; the Charles E. Dohme Memorial Lectures. First Course, 10, 11, 12 October 1922, delivered in Baltimore; printed in: Bulletin of the Johns Hopkins Hospital, June 1923.

cologist saw, that the second heart often showed slower contractions. Experiments with the sympathetic nerve gave analogous results.

Now the purpose of our experiments was in the first place to control the results of LOEWI's researches under more physiological conditions.

In the vena cava of a frog A a glass tube is inserted and in this way a suitable saltsolution is conducted through the heart. A similar small tube is introduced into the aorta. Then we see, that the saltsolution will leave the heart in a rhythmical manner. If then the fluid, leaving the heart, is led to the vena cava of another frog B, the fluid will run through the heart B, and after leaving it by the aorta of this second frog, it may be taken up again by the vena cava of the first frog A. Thus we obtain a circulation of saltsolution through both frog's hearts. This method of socalled "crossing circulation" was first introduced by Prof. J. C. HEMMETER.

Now, if the sympathetic of the first frog A be stimulated electrically, causing acceleration of the heart beat of this frog, it can be observed that already after a few seconds, the heart rate of the second frog B is also quickened, *although the sympathetic of this animal has not been stimulated.* How to account for the acceleration of the second heart? Evidently in no other way than by assuming that in the first heart A, in virtue of permeability of course, substances were liberated which had a similar effect upon the second heart as if this had been directly stimulated. I shall presently come back to the probable nature of these substances.

How it is possible that substances, liberated by a physiological action of an organ, here the heart of the frog A, may also stimulate the same organ of the second animal B, I shall not discuss here. It is sufficient to say, that there is an analogy between this case and the secretion of saliva. If we allow a salt solution to percolate through the salivary gland, as J. DEMOOR has demonstrated some years ago, no saliva is secreted. However it does occur if a small quantity of saliva is added to the saltsolution. The product formed during the activity of the salivary gland is, it seems, a stimulus again to further secretion of saliva. The substances, formed in the stomach during conversion of protein, excite gastric secretion. It is therefore not strange that the substances, liberated in the first heart during stimulation of the sympathetic, should have a stimulating action on the second heart.

Dr. BRINKMAN and Miss VAN DAM made yet another experiment that in a still more convincing and striking manner demonstrates, that the transmission of stimuli can take place by means of fluids,

in other words that there exists a humoral transmission [1]), I say "in a still more convincing manner", for by the just mentioned experiment the remark could be made, that with the movement of the second heart hydrodynamic influences might have played a rôle.

For this reason for the second organ not the heart of the frog B was taken, but the *stomach* of this animal.

It is well known that stimulation of the sympathetic nerve is followed not only by an acceleration of the heart beat, but also it slows, even inhibits the spontaneous movements of the stomach. Now the question arose: if the fluid of the stimulated heart of frog A is transferred into the arteria gastrica of the frog B, will it then cause the spontaneous movements of the stomach of this last frog to grow slower, even to stop? This proved to be the case, as the experiments of Dr. BRINKMAN and Miss VAN DAM showed us. *In other words, on sympathetic stimulaiton of the first heart substances were liberated which influenced the movements of the stomach in an inhibitive way.*

Analogical phenomena as occur in stimulating the sympathetic nerve could be observed by stimulation of the vagus nerve.

As it is well known, stimulation of this nerve affects the rate of the heart beat and also influences the strength of the contractions of the stomach, but in an antagonistic sense. Stimulation of the vagus slows the heart, but causes the contractions of the stomach to become more powerful, contrary to what happens when the sympathetic nerve is stimulated. Now the experiment was repeated by crossing the circulation of the heart of the first frog with that of the stomach of the second frog; in other words, the salt solution coming from the heart of the first frog, is conducted to the stomach-circulation of the second frog. On stimulating the vagus of the first frog, the heart slows its beat and when the solution has passed through this heart and reached the stomach of the second frog, this organ shows typical vagal contractions, though the vagus of frog B has not been stimulated electrically. From this we may infer that stimulation of the vagus of the first frog sets free in its heart vagus-substances, which may cause the stomach of the second frog to contract, as if its own vagus nerve had been directly stimulated.

We are therefore in presence of two kinds of substances liberated by the vagus and sympathetic nerve respectively, which may be called vagus- and sympathetic substances.

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[1]) R. BRINKMAN und Frl. E. v. DAM, Pflüger's Archiv. Bd. 196, S. 166, 1922.

That really such substances exist, could be directly proved by the fact that the salt solution, leaving the heart after stimulation of the vagus, contains substances, which lower the surface-tension of the original salt solution, socalled capillary-active substances. On the other hand we find that the surface-tension of the salt solution, coming from the heart after the sympathetic nerve has been stimulated, is slightly increased [1]). Further it appeared that the vagus- and sympathicus-substances were able to neutralize each other in capillary-active sense, i. o. w. they were able to neutralize each other's influence on the surface-tension.

I shall not enter here into further particulars. It is an established fact now, that as an effect of stimulation of the vagus nerve, a liberation of vagus-substances takes place, and that on stimulating the sympathetic nerve, sympathetic-substances are set free. However the nature of these substances has not yet been determined; perhaps, at least with the vagus-stimulation, we have to do with cholin-compounds, which cooperate with the potassium.

As for the method to determine the surface-tension of very small quantities of fluids, we refer to two articles, which appeared last year [2]). There it is shown that a very simple apparatus will do for this purpose. By means of a torsion balance, well-known to the clinicians, the force is determined which is necessary to pull off a small platina-ring from the surface of the fluid which is to be examined.

The experiments discussed here, give rise to many questions. So the clinician will think of the bearing of these results on the nature of vagotonia and sympathicotonia and will ask himself under which conditions an excess of vagus- and sympathicus-substances will exist in the circulation and influence different organs; and also he will put himself the question how it will be possible to make this surplus harmless for the body.

The physiologist will ask himself whether the latent period and the after-effect in vagus-stimulation can be explained by the time, which is necessary for the liberating and the disappearing of the vagus-substances; further he wants to know whether the vagus-substances are specific for one and the same animal. And what will be of interest both for the physiologist and the clinician is the question: can we observe the same phenomena, seen in the frog,

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[1]) See the article of Dr. BRINKMAN and Miss VAN DAM, in the Journal of Physiol., still to appear.

[2]) R. BRINKMAN und Frl. E. VAN DAM. Münch. Med. Wochenschr. 1921. S. 1550.
R. BRINKMAN, Arch. Néerl. d. Physiol. VII 1922, p. 258.
R. BRINKMAN und Frl. E. VAN DAM VIII, 1923, p. 29.

also *in warmblooded animals?* With this question Dr. L. JENDRASSIK has occupied himself very recently. The results obtained untill yet, can be summarized in a few words. If the surviving heart of a rabbit is perfused with a suitable salt solution, and we stimulate the vagus nerve, then the liquid, leaving the stimulated heart is able to accelerate in a high degree the contractions of an isolated piece of gut, taken from the same animal.

I cannot enter into these researches on this place. Dr. JENDRASSIK will describe them in a short time in the Biochemische Zeitschrift. Here we will only point out that the experiments proved, that on stimulation of the vagus nerve not only in the heart of coldblooded animals but also in those of warmblooded animals substances are produced, which are able to influence other organs in the very same way, as if the vagus of those organs were stimulated by an electrical current. Here the gut proved to be the most suitable object for the researches.

Further I might draw the attention of the readers to three remarkable facts. In the first place it appeared that an extract of the atrium of a rabbit's heart in saltsolution was also able to accelerate the contractions of the isolated piece of gut. This experiment was made in considering that it would be very probable, that the atrium still contained vagus-substances, which were formed there during the life of the animal. Secondly it appeared that if atropine, which, as is well known, inhibits the influence of vagus-stimulation, was added to the active extract, this was turned into an unactive one, i.o.w. then it had no more influence on the movements of the gut. In the third place it was found, that the extract of the ventricle-muscle of the heart has a sympathetic effect on the movements of the gut instead of a vagus-influence.

The experiments on warmblooded animals described above, were all performed in a room of body temperature.

SUMMARY.

Thus far we have been acquainted with only two forms of correlation between organs, one, the eldest, established through interference of the central nervous system in cases where a quick response is needed (reflexes). The second form comes into play where slow processes are concerned; it may be exemplified by the influence of the glandula thyroidea on metabolism and growth. For the formation of hormons the influence of the nervous system is not needed, neither for the transport by the bloodcurrent. In *the third new form*

of correlation the action is neither quick nor slow; it is to be seen at work where functions, holding the medium between these two, are concerned. The essential thing here is, that *by nervous stimulation* substances are set free, which are conducted to other parts of the body.

There is much evidence to lead to the belief that the three forms may finally by reduced to one, but I cannot enter into this here. I have spoken about this possibility already in one of my HERTER-LECTURES, delivered in New-York in October 1922.

It may be of importance to lay stress on the fact that the formation of vagus- and sympathicus-substances is not only postulated, but *that it is proved directly in a physico-chemical way.*

There is no doubt that an analogous correlation between organs as described here for heart and stomach and for heart and gut will be established also between other organs[1]). We face here a wide field of new researches; we are only in the beginning.

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[1]) So it appeared very recently in our laboratory, that when stimulating the nervus vagus and the nervus sympathicus of the heart, substances are set free, which influence the *lumen of the small arteries* of another animal. (Note after the correction).