Physiology of secretion.

THE PHYSIOLOGY

OF

SECRETION.

ALBERT P. MATHEWS.

Submitted in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

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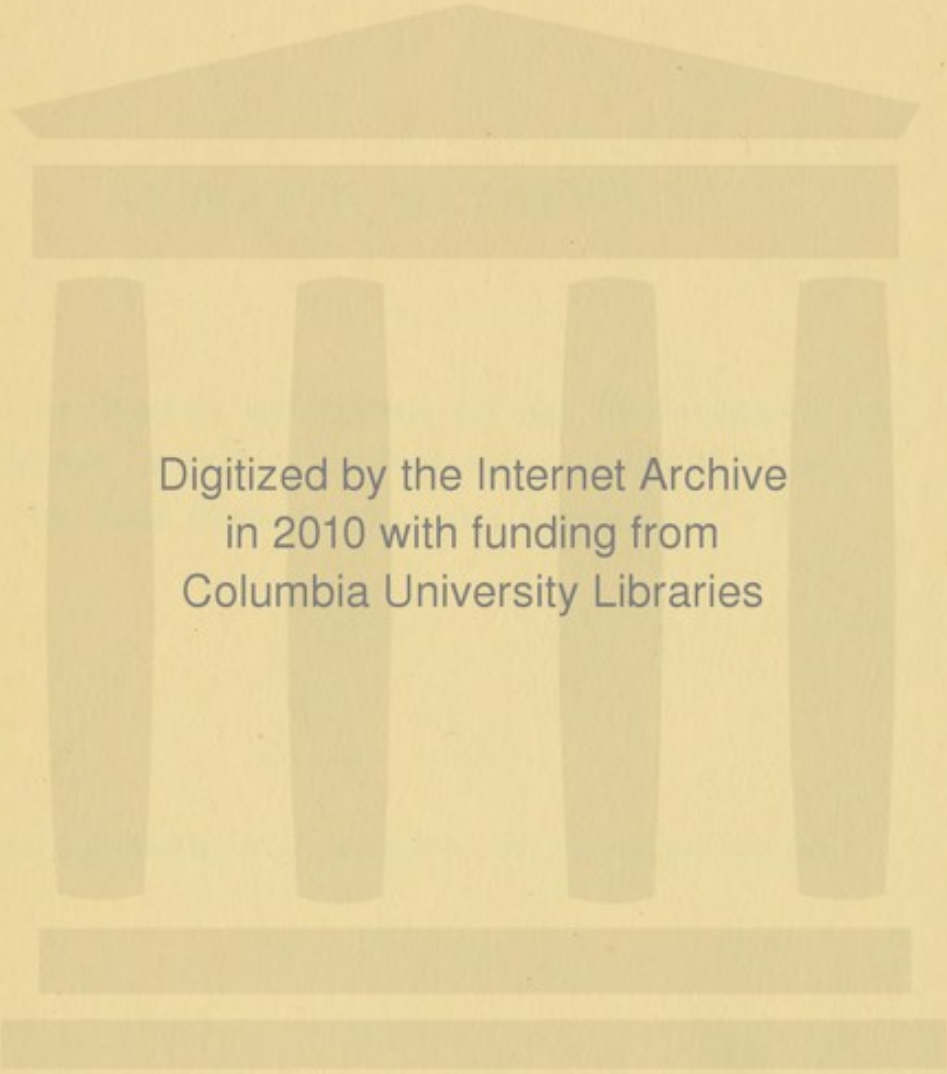

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THE PHYSIOLOGY OF SECRETION.

Albert Mathews.

(Read April 11, 1898.)

I. INTRODUCTION.

A Criticism of the Secretory-nerve Theory.

Nearly fifty years ago it was suggested by Ludwig[48] that secretion was a function of the gland cells controlled by the activity of special nerve fibres. Upon the gland cell, thus emphasized as the prime factor in secretion, and upon its relation to nerve action, most of the subsequent study of the physiology of secretion has been focussed. This study has unearthed such evidences of the truth of Ludwig's hypothesis that to-day few theories of physiology rest upon a foundation apparently firmer, or are more widely accepted, than the hypothesis of secretory nerves. Indeed, the recent discovery,[6] by means of the Golgi and Ehrlich methylen-blue methods, of the remarkably rich distribution of nerves to glands, and of the endings of these nerves about the gland cells, has seemed the final convincing demonstration of the truth of the theory which so many years ago foretold their existence.

The theory of secretory nerves did not long remain in the simple form suggested by Ludwig, for it soon received, at the hands of Heidenhain, a more complete and definite shape. First seriously worked out by him in 1868[21] the theory was further developed in 1878[22] and took its final form in his great treatise on secretion embodied in Hermann's Handbuch der Physiologie in 1880.[23] The Ludwig-Heidenhain theory, thus crystallized by Heidenhain, has been the lens through which the facts of secretion accumulated from 1868 to the present time, have been viewed. This theory may be briefly stated as follows :

Secretion is a specific function of the gland cells controlled by special secretory nerve fibres, acting directly upon these cells. There are two kinds of these nerve fibres : trophic fibres, which render the cell contents soluble ; and secretory fibres, which diminish the resistance to filtration offered by the lumen end of the cell. In consequence of this decreased resistance, the contents of the cell, which are under high endosmotic pressure, escape into the lumen. At the same time the cell imbibes liquid from the lymph space.

Heidenhain, R. Ueber secretorische und trophische Drüsennerven, Pflüger's Archv. f. d. gesam. Physiologie. Bd. XVII, 1878, pp. 60 and following: "The cell is normally under high endosmotic pressure. On nerve stimulation a molecular rearrangement takes place at the lumen end of the cell, so that the resistance to filtration is diminished and water flows out. This flow may be hastened by contractions of the protoplasm, as Kühne observed in the rabbit's pancreas under the microscope. The tension of the water within the cell being thus diminished, water begins to flow out of the lymph and capillaries into the cell. At the end of stimulation molecules are rearranged, the loss of water by the cell ceases, and secretion stops." "The attractive pull on the water comes from the protoplasm of the outer zone."

Before proceeding with the discussion of the evidence upon which this theory rests, it will make the matter clearer to recall the conception of secretion which the Ludwig-Heidenhain theory supplanted. For some of the facts brought forward by these authors are of value, not as direct evidence of the existence of secretory nerves, but because they disprove an alternative earlier conception. The prevalent conception of secretion, before Ludwig's time, was that liquid driven by intra-capillary pressure filtered out through the gland.[48] The chorda tympani was the principal secretory nerve then known, and it was believed to cause secretion by greatly increasing intra-capillary pressure by contraction of the veins or arterioles. The discovery of the vaso-dilator function of this nerve shortly thereafter by Claude Bernard re-emphasized the possibility of a high intra-capillary pressure being an essential cause of secretion. It is not surprising that many physiologists of that day believed that this striking correspondence between vaso-dilation and secretion could not be accidental, and it was natural for them to refer the secretory power of the nerve to its action on the blood vessels.

The first blows against the theory that the vascular system stood necessarily in a causal relation to secretion were dealt by Ludwig and his pupils. They discovered that stimulation of the upper end of the cut cervical sympathetic nerve caused a secretion from the submaxillary gland of the dog,[48] but this secretion, unlike that due to the chorda, was afterwards found to be accompanied by a pronounced vaso-constriction instead of dilation. They found that the pressure capable of being generated by the saliva flowing from Wharton's duct might considerably surpass

the pressure of the blood even in the carotid artery. They thus demolished, once and for all, the filtration theory. They found, further, that the temperature of the saliva secreted from the dog's submaxillary might surpass by 1.5 °C., the temperature of the blood in the carotid artery,[49] and as final evidence that the chorda tympani could induce secretion independent of the vaso-motor action, they brought forward the observation that stimulation of this nerve still caused a secretion, some minutes after the heart ceased to beat.[61] It is not strange that, in the face of such facts, Ludwig should have felt compelled to assume the secretory activity of the gland cell.

Heidenhain soon added other facts pointing in the same direction. He found that if the blood supply be cut off from the submaxillary gland by compression of the artery the chorda still caused a secretion analogous to the post-mortem secretion after the heart ceases to beat.[21] Giannuzzi[18] discovered that by the injection of sodium carbonate or a dilute solution of hydrochloric acid into Wharton's duct a pronounced vaso-dilation ensued, on stimulation of the chorda, but no secretion. Heidenhain[23] found that quinine sulphate injected into the duct had a similar action, and that atropine[24] effectually paralyzed secretion, while leaving the vaso-dilator power of the nerve unaltered. Heidenhain[25] also discovered, and Langley confirmed his observation, that after the chorda tympani had been paralyzed by the action of nicotine, either injected subcutaneously or applied directly to the submaxillary ganglion, the chorda tympani recovered its secretory function before its dilator function. He observed, also, that after the chorda had been cut and allowed to degenerate for 2–3 days stimulation of the nerve still caused an increase in secretion, without an increase in the flow of blood from the gland's vein. This evidence showed that vaso-dilation might ensue without a secretion, that secretion might take place unaccompanied by vaso-dilation, and that secretion might be caused by stimulating dilator nerves after cutting off the blood supply. If these facts were true vaso-dilation could not be the cause of secretion, and hence that cause must be sought in some other gland element than the blood vessels.

Evidence of a more positive kind of the direct action of nerves upon the gland cells was not long lacking. Heidenhain showed that stimulation of secretory nerves caused well-marked changes in the structure of the gland cells.[21] He discovered that the specific constituents of the secretion were accumulated in the cell during glandular rest, and discharged from the cell during secretion. That these substances were not simply dissolved from the cells by the water stream passing through them he endeavored to show by the fact that on passing from a weak to a stronger stimulation of the chorda tympani, or other dilator secretory nerve, not only the rate, but also the concentration of the secretion increased. Apparently the more rapidly secreted saliva, although in contact with the cell contents for a briefer time, nevertheless dissolved more of them than that more slowly secreted. This obviously would have been impossible if the contents of the cell had not been rendered more soluble by the action of the nerve during the stronger stimulus. He brought forward, also, still more convincing evidence.[22] In the dog's parotid gland stimulation of the cervical sympathetic causes, generally, no secretion, but if this nerve be irritated coincident with the dilator secretory nerve the saliva secreted under the influence of both nerves is more concentrated than that secreted during irritation of the dilator nerve alone. Apparently the sympathetic, though causing no secretion, must, nevertheless, act on the cells, so as to render their contents more soluble. That this effect of the sympathetic could not be due to any possible action of the nerve on contractile tissue of the gland, as suggested by Schiff,[65] Eckhard[13] and others, Heidenhain believed von Wittich[77] had conclusively demonstrated. That the well-known high concentration of the sympathetic saliva could not be referred to the nerve's vaso-constrictor action Heidenhain[22] showed by the fact that, if the gland artery be almost totally compressed, the following chorda saliva was not rendered more concentrated.

These facts undoubtedly furnish strong evidence that the sympathetic and other nerves act on the gland cells, not only increasing the flow of water through them, but also rendering their contents more soluble.

Most of these facts, brought out chiefly in the salivary glands, have been found to be true for other glands. The independence of blood pressure and secretion, the inhibitory action of atropine, and an increase in concentration of the secretion coincident with a more rapid flow, have been observed by Afanassiew and Pawlow,[3] Gottlieb,[19] Pawlow and S.[58] Simonoskaja in the pancreas, stomach and other glands, in which secretion is normally accompanied by vaso-dilation. Sweat may be secreted during vaso-constriction or vaso-dilation, and in the cat's foot, twenty minutes after ligaturing the artery or cutting the leg from the body.[47] The skin glands of amphibia can secrete in the total absence of blood supply.[11] Moreover, of recent years, the importance of the *condition* of the secreting cells, as a factor of secretion, has been clearly realized. The quick paralysis of some secretions during dyspnœa or by the action of drugs has emphasized this factor of secretion. Even in the kidney, where secretion apparently more nearly approaches a filtration, it has been shown that the condition of the capillary, or glomerular epithelium, and the character of the blood, exerts an influence on the secretion.[1] The possibility at once suggests itself that if the condition of the cells is so readily affected by external agents it may be modified by direct nerve action. The very rich nerve supply of many glands and the intimate association of nerve end and gland-cell undoubtedly bring strong confirmation to this supposition.

From this brief outline the extreme complexity of the problem of secretion will be manifest. Some secretions are accompanied by vaso-dilation; others by vaso-constriction. Some may persist twenty minutes after cutting off the blood supply; others are paralyzed within two or three minutes. Some are paralyzed by atropine and quinine; others are not. In the same gland stimulation of one nerve may cause the secretion of a large amount of watery secretion, while stimulation of another nerve causes the secretion of a small amount of exceedingly viscid secretion. There seems, in fact, to be no general rule of secretion true for all glands. The great difference between the phenomena of different secretions suggests that the mechanisms of

those secretions may be different in different cases. However probable it may seem, *a priori*, that there is everywhere one fundamental mechanism underlying all these secretions, a decent regard for truth forbids one accepting so far reaching a conclusion, unless it be supported by very strong evidence.

In the present paper, therefore, I wish to reopen the question whether all secretions are due to the activity of the gland cells, and to re-examine the evidence of the existence of nerves acting on those cells. The great theoretical and practical importance of Ludwig's conception is a sufficient excuse for a critical and experimental review, in the light of the physiology of the present day, of the evidence upon which that theory rests. Since the publication of Ludwig's and Heidenhain's work on secretion knowledge has been acquired of vaso-motor changes, osmosis, lymph formation as well as secretion proper, which might, possibly, cause even Heidenhain or Ludwig, if considering the subject at this time, to adopt a somewhat different interpretation of much of this evidence from that heretofore proposed. Such a review seems the more necessary for the reason that special applications of the theory have been, from time to time, questioned, and because, as will be apparent in the course of the following discussion, some of Heidenhain's inferences are unsound, owing to his having neglected to consider possibilities now known to be of importance. His recent extension of the theory to lymph formation, for example, has been seriously disputed by Starling,[68] Cohnheim and others. Starling especially has shown the uselessness of assuming any such secretory mechanism in certain special cases, and has thus thrown doubt upon the truth of the theory as a whole. Langley[37] has questioned the necessity for assuming distinct "trophic" fibres to explain salivary secretion, and for the kidney secretion special inferences of Heidenhain have been challenged by Senator, Adami[1] and v. Sobiranski.[67] The difference in pressure between blood and secretion observed by Ludwig may be readily accounted for on the basis of osmosis quite apart from any cell-activity.[28] The difference in temperature between saliva and blood has been denied by Bayliss and Hill,[5] working with bet-

ter methods. For some of the facts, also, errors of method greatly diminish the value of the testimony they offer, and some of that evidence depends upon the assumption that all secretions are probably due to the same cause. Hence, whether the theory of secretory nerves is true or not, it must be admitted, I believe, that little of the evidence which has hitherto been presented in support of that hypothesis can be accepted as it stands.

While fully aware, therefore, of the strong *a priori* probablity that nerves may act on gland cells so as to affect osmosis through them, and while appreciating the strength of the evidence that they do so act, I feel myself compelled, for the reasons presented in the following criticisms of that evidence, to question whether secretion is really controlled in this manner.

But not only is the evidence upon which the secretory nerve theory rests inconclusive; there are also certain weaknesses in the theory itself which deserve more attention than they have hitherto received. It is by no means easy to understand how the nerve can affect the cell in such a way as to cause a secretion. The mere discharge of liquid from the cells into the gland lumen would, as pointed out elsewhere, lead to no secretion from the gland ducts. To obviate this difficulty Heidenhain supposed that, while the secretory nerve diminished the resistance of the inner end of the cell, the outer zone imbibed water from the lymph and capillary. The outer zone exerted an attractive pull upon the lymph. By the imbibition of this lymph the secretion was forced along the ducts. This explanation leads at once to difficulties. Not only is the explanation exceedingly hypothetical, but it is difficult to see why, if the pull on the lymph comes from the outer zone, secretion should be slowest after long stimulation, or during paralytic secretion, when the outer zone is at its greatest development, and how secretion can take place at all, or with any rapidity, in glands in which the outer zone has almost, or completely, disappeared, as in mucous salivary glands, the stomach or pancreas, after a long rest. It is also difficult to understand sympathetic secretion, which takes place during a period of vascular constriction. Nor can we ig-

nore the extreme complexity of the theory. The assumption that each, or any, cell of the sub-maxillary gland has acting upon it four totally different nerve ends is, in itself, highly improbable. A further difficulty is encountered when we critically examine Heidenhain's assumption that the trophic and secretory fibres are unequally distributed to the chorda tympani and sympathetic. It seems simple enough to refer the small secretion ensuing on sympathetic stimulation to the presence of a small number of secretory fibres in this nerve, but if it be asked whether these fibres innervate all the cells, or only a portion of them, we are at once plunged into a maze from which there is no way out. If they innervate all the cells we may ask why, if a few fibres suffice, more should be present in the chorda, and why the secretion should not be as copious as the chorda's. If they innervate a part of the cells only, new assumptions must be made to understand why stimulation of the sympathetic should exhaust the constituents of the whole gland. If we abandon the trophic fibres and postulate one sort of fibre only, the secretory, acting on the cell, Heidenhain's facts become largely inexplicable. Furthermore, when Heidenhain[26] assumed secretory nerves to the capillaries he undermined much of the evidence accumulated by him of secretory nerves to glands. For many of the facts of gland physiology might be understood by reference to these capillary nerves. Atropine, for instance, might conceivably prevent secretion by paralyzing the ends of the secretory nerves of the capillaries, thus inhibiting the production of lymph and fluid necessary for secretion.

In the present paper I have considered chiefly the physiology of secretion in the salivary glands. The experimental work has been devoted chiefly to studying the exceptional features of that secretion which have seemed difficult of comprehension on any other than the cellular theory of secretion. I have ventured, however, to bring some other secretions into relation with the conclusions concerning the mechanisms of salivary secretion.

It may prevent confusion and reconcile what might appear to be contradictory statements, to give here the chief conclusion drawn in the present paper. This is, that there is no single mechanism of secretion. In some glands the stored metabolic products are driven out of the cells by the action of muscle, as in Amphibian skin glands and sudoriferous glands; in others they are removed by currents of lymph, which are probably the result of osmosis, as in the pancreas, stomach, salivary glands; in some cases the cells imbibe water until they burst, and their contents rush into the gland-lumen, as in the intestinal cells of Ptychoptera larvæ; in others the inner end of the cell crumbles to pieces, as in the mammalian milk glands. Two, or more, of these mechanisms may coexist in one gland, and it is this which has rendered the physiology of such glands as the salivary so confusing. In the submaxillary gland, for example, I believe we have a muscular mechanism, innervated by the sympathetic; and an osmotic mechanism, innervated by the chorda. The sympathetic, in other words, causes secretion as Eckhard,[13] Schiff,* [65] and others[20] have maintained, by its action on contractile tissue in the gland body, thus mechanically compressing the ducts and alveoli and squeezing out the secretion. The chorda probably causes secretion, by its dilator action on the blood vessels. The following pages present the evidence for these conclusions.

Before proceeding farther it is necessary to define the sense in which the word "secretion" is here used. At present the word has no very definite significance, as it refers to different processes. For the sake of clearness it would be better to designate these various processes by different names. I suggest that, in the future, the word secretion be used to indicate the process of extruding subtances from cells into the lumen of the gland, the process of expulsion from the ducts, and the substances secreted by the gland. By this use of the word cellular secretion will be generally coincident in time with glandular. For the

* Schiff, loc. cit., p. 304, I. "It is probable that the great sympathetic which causes constriction of the parotid vessels causes, at the same time, the tissue of the gland to contract, and that by this contraction the gland empties itself of its contents formed independent of nerve action."

process of the formation of substance by the gland cell—a different process, but one at present included under secretion—I propose the name "Hylogenesis" (Gr. *ὕλη matter* and *γένεσις generation*), and for the substances formed the name "Hylogens." Thus trypinogen, mucinogen, pepsinogen are hylogens. The secretions consist of the hylogens plus water, salts and other substances derived unchanged from the blood. The present paper deals solely with secretion proper. Hylogenesis is considered elsewhere.* This word seems to me preferable to that of "Mesastates," suggested by Mr. J. N. Langley. Ranvier[62] and Van Gehuchten[73] wish to call the process here named hylogenesis, "secretion." This seems to me inadvisable, as thereby cellular secretion would correspond with glandular rest.

The experimental work embodied in this paper has been carried on chiefly in the Physiological Laboratory of Columbia University, and I am particularly indebted to Professor Curtis and Professor Lee both for extending to me facilities of the laboratories and for suggestive criticism. A portion of the work was done in the physiological laboratories of Cambridge University, England, and Marburg University, Germany. I desire to express my hearty appreciation of the courtesy of Professor Michael Foster and Professor Kossel in placing the facilities of their laboratories at my disposal. To Mr. J. N. Langley I am indebted for critical suggestions.

II. SYMPATHETIC SALIVARY SECRETION.

Stimulation of the upper end of the divided cervical sympathetic nerve of the cat, horse, dog, sheep or rabbit generally causes a secretion from the salivary glands. This secretion has everywhere† the same characteristic features, indicating that it is produced in all salivary glands in the same manner. These common features are the following: The saliva reaches its maximum rate of flow in the first 10 or 20 seconds, and then generally ceases, although stimulation lasts for several minutes. If sev-

* Shortly to appear in the *Journal of Morphology*.

† Except in the resting parotid and submaxillary glands of the dog. See next page.

eral stimulations follow closely, one upon the other, the amount of saliva secreted at each stimulation rapidly diminishes and often becomes nothing. Stimulation becomes then again effective if the gland be allowed to rest, if the chorda be irritated, or if liquid be injected into the gland duct. Finally, sympathetic secretion is invariably accompanied by vascular constriction, and the saliva, with the doubtful exception of that of the cat,[35] contains more organic matter than that secreted from the same gland under the influence of the dilator nerve.

That there are deviations from the typical course of a sympathetic secretion just sketched need hardly be said. Such deviations are probably due (see p. 309) to the changing fluidity of the saliva. When the saliva is thin, as in the horse, rabbit, cat or sheep, the secretion follows a very typical course ; if the saliva be viscous, as in the resting salivary glands of the dog, the latent period is longer, and the secretion persists longer. These variations shed a not unimportant light on the mechanism of secretion.

To explain these typical phenomena, assuming the secretory activity of the gland cell, Heidenhain supposed that the sympathetic nerve carried three kinds of fibres : trophic, secretory and vaso-constrictor. The trophic fibres converted large quantities of mucinogen (submaxillary) into soluble mucin, making the juice rich in organic bodies ; the secretory fibres caused secretion ; the constrictor neutralized the secretory action and stopped secretion. The quick failure of the nerve on successive stimulations was referred to the exhaustion of nerve, nerve end, or gland cell.

The general features of sympathetic secretion seem to me, however, plainly to suggest that the secretion has been driven from the gland by a compression of the ducts and alveoli by some contractile tissue. I wish to consider these features separately, from this point of view, together with experiments bearing on their proper interpretation.

a. The Rate of Sympathetic Secretion.

Experiments I. and II.

Cat and dog. Submaxillary. Animals under ether. Canula in Wharton's duct, connected with a narrow tube graduated in millimeters, 250 mm. = 0.82 cc. Reading's every ten seconds

in mm. Chorda-lingual divided in each case. Cervical sympathetic divided and stimulated by tetanic shocks, secondary coil 180–100 mm. The chorda was first stimulated intermittently for an hour, so that the glands were secreting watery saliva.

		Cat.			Dog.	
		I	II	III	I	II
1st	10 seconds of sympathetic stimulation	10	9	10	25	17
2d	" " " " "	9	5	6	4	2
3d	" " " " "	0	0	0	3	2
4th	" " " " "	0	0	0	2	1
5th	" " " " "	0	0	0	2	2
		off	off		off	
6th	" " " " "	0	0	0	8	1
				off		off

By inspection of these figures, it is seen that on stimulation the secretion comes suddenly, reaches its maximum rate of flow in the first few seconds, and then quickly subsides. In the cat, it abruptly ceases after 20 seconds. In the dog, probably owing to the greater viscidity of the saliva and the resistance offered to its passage by the fine gland-tubules, it persists slightly throughout the stimulation.

Heidenhain attributes the abrupt cessation of secretion, after a few seconds, to the vaso-constrictor action of the nerve, in consequence of which the secretory mechanism is, as it were, suffocated.[23] That this explanation is incorrect may readily be shown by cutting off the blood by compressing the gland's artery, or by decapitation. In such cases, as the following experiments show, a perfectly typical secretion may ensue on stimulation of the sympathetic, ten or more minutes after ligaturing the artery, or decapitation.

Experiment Va.

(A full account of this experiment is given on page 343.)

Large dog, which had received 3cc. 1% morphine sulphate subcutaneously. Ether given through tracheal tube. Submaxillary dissected free, and remained attached only at the hilus and by its veins. Chorda-lingual and sympathetic cut. Canula connected with tube graduated in millimeters in Wharton's duct. Gland's artery exposed by extirpation of the digastric muscle. Tetanic shocks. Secondary coil at 150. The

secretion of the sympathetic is given in mm. at ten second intervals, 250 mm. = 0.82. cc.

Time.						Nerve Stimulated.	Secretion.
h	m	s		h	m	s	
3	25						The artery going to the gland was clamped close to the hilus.
3	25		–	3	30		Chorda (intermittent) — Copious at first, it gradually ceases.
3	30						" — 0
3	32						" — 0
3	35						Sympathetic — **16, 3, 2, 2, 0, 0,** off.
3	37						" — 0, 0, 0, 1, 0, 0, off.
3	40						" — 0, 0, 0, 0, 0, 0, off.
							Interval (see page 317).
3	42						Artery unclamped. Chorda stimulated intermittently for several minutes.
4	07	30					Artery clamped.
4	07	30	–	4	08		Chorda — 155
4	08		–	4	09		" (10 sec. int.) — 30
4	09		–	4	11	30	" — 16
4	12		–	4	13		" — 0
4	13		–	4	14		Sympathetic. — **17, 4, 2, 2, 0,** off.
4	15		–	4	17		Chorda — 0
4	17	30	–	4	18	15	Sympathetic. — **10, 4, 0, 0.**
4	20						" — 0, 0, 0.
							Interval (see page 317).
4	25						Sympathetic. — 0, 0, 0.
4	26		–	4	27		Chorda. — 0
							Interval (see page 317).
4	29	30					Artery unclamped. The gland secretes spontaneously. Chorda stimulated intermittently.
4	45	30					Artery clamped.
4	46	30	–	4	47	30	Chorda — 175
4	48	30	–	4	49	30	" — 30
4	50		–	4	51		" — 10
4	51	30	–	4	52	30	" — 2
4	53						0
4	53		–	4	54		Sympathetic — **8, 2, 1, 0.**
4	54		–	4	55		Chorda — 0, 0, 0, 0.
4	55	30	–	4	56	39	" — 0
4	57		–	4	58		Sympathetic — **0, 4, 3, 0, 0.**
5	02						Artery unclamped.
5	03		–	5	09		Spontaneous secretion.
5	09		–	5	10		Sympathetic. — **9, 3, 2, 0, 0.**

Experiment V.

Large dog under morphine and chloroform. Right submaxillary gland prepared. Chorda lingual and sympathetic cut. Each nerve causes a good secretion. Readings as in previous experiments. Canula in Wharton's duct. Secondary coil 150. Tetanic shocks.

TIME.					NERVE STIMULATED.	SECRETION.
h.	m.	s.	h.	m.		
5	49	30			Head cut off as rapidly as possible. Spinal cord and vertebral column not severed.	
5	50	30	– 5	55	Chorda (intermittent)	175
5	55				" (coil 70)	0
5	57				Sympathetic (coil 7)	**40, 20, 6, 2, 0.**
5	58		– 6	10	No stimulation.	
	6	10			Sympathetic	**7, 5, 2, 0, 0.**

Experiment VI.

Dog. Conditions of experiment the same as in Experiment V. Submaxillary. Both nerves active.

TIME.					NERVE.	SALIVA SECRETED IN MM.
h.	m.	s.	h.	m.		
	4	30			Head completely severed from body.	
4	31	40	– 4	35	Chorda intermittent	65
	4	35	– 4	38	Chorda.	0
	4	38			Sympathetic.	**14, 3, 2, 2, 0.**

The foregoing experiments, demonstrating that a sympathetic secretion may be obtained ten minutes after all fluid and oxygen have been cut off from the gland shows, I think, that Heidenhain was wrong in ascribing the quick normal cessation of secretion during sympathetic stimulation to the nerve's action on the blood vessels. It is obvious that vascular constriction can have nothing to do with such cessation, because the changes produced in a normal gland by vascular constriction, namely, diminution of water and oxygen, have existed in all three experiments at least seven minutes before the nerve was stimulated, and continue during that stimulation without in any way affecting the course of the secretion.

Even a normal gland secreting a very viscous saliva furnishes evidence against the truth of Heidenhain's explanation. In the

resting submaxillary of the dog the sympathetic secretion may have a latent period of many seconds and persist for minutes. An instance of such a kind is the following :

Experiment III.

Large morphinized dog, receiving chloroform. Both chorda lingual and sympathetic cut. The submaxillary has not previously been secreting. Sympathetic stimulated by tetanic shocks. Secondary coil 15. Readings every 10 seconds in millimeters as before. *The saliva was extraordinarily viscid.* Total stimulation 2 minutes, 40 seconds. *Latent period 45 seconds.*

Amount of secretion : 0, 0, 0, 0, 5, 7, 7, 5, 5, 5, 4, 5, 5, 4, 4, 3 ; off, 3, 1, 0.

If secretion can begin after 42 seconds, and endure for two minutes, during a period of vascular constriction, as was the case in this experiment, it can hardly be assumed that vaso-constriction is the cause of the normal failure of that secretion within twenty seconds.

Heidenhain seems to have overlooked the fact that a sympathetic secretion may be obtained after cutting off the blood supply, at least five minutes after the chorda becomes inoperative. He referred the quick loss of the chorda's power in these experiments, to the suffocation of the gland cell.* If the loss of the chorda's secretory power is due to the paralysis of the gland cell by suffocation, the sympathetic must cause secretion in some other way than action on the cell, since this nerve causes a normal secretion long after the chorda has been paralyzed.

The quick gush of saliva and its abrupt cessation, as well as the anomalous cases represented by Experiment III, clearly indicate a muscular mechanism of secretion. They are probably to be explained as follows : On sympathetic stimulation the ducts

* Heidenhain, R. Hermann's Handbuch der Physiologie V, p. 46 : "Die Ursache der Verlangsamung der Absonderung bei hochgradiger Gefässverengerung oder Gefässverschluss liegt nicht in dem Sinken des Capillardruckes, sondern in der, mit der künstliche Anämie der Drüse verbundenen Verlangsamung des Blutstromes, bei welcher sich das Secretions Material, und namentlich der Sauerstoff für die Drüsenzellen allmälig erschöpft so dass der secretorische Apparat erstickt."

and alveoli are compressed and the liquid in them ejected. If that liquid is thin and runs readily, as in most albuminous glands, for example the parotid and submaxillary of the rabbit, sheep and horse, and the cat's submaxillary, or in mucous glands after long stimulation, the latent period is short, and the saliva is all expelled in from 10–20 seconds. Thereafter, although contraction persists, no more secretion escapes. If, on the other hand, the saliva is viscid, as in the first stimulation of a previously resting mucous gland (submaxillary and parotid of dog), it offers a great resistance in passing through the fine ducts and consequently requires a greater pressure and a longer time to start and to expel. Consequently the latent period is long and the secretion persists for some time. This explains the anomalous cases represented by Experiment III. In cases of very great viscidity, as in the parotid gland of the dog, the resistance may even be too great to be overcome by the compressing strength of the tissues. In this gland stimulation of the symyathetic either causes no secretion at all or very little, unless the saliva in the gland be previously diluted by the action of the dilator nerve. The muscular theory, too, readily explains why a typical sympathetic secretion can ensue in the total absence of blood supply.

b. The Decrease in the Amount of Saliva Obtainable upon Several Successive Stimulations.

If one sympathetic stimulation be followed by several others the amount of saliva obtainable on the second, or following stimulations, is much less than the first, and may be nothing at all.* If, however, the gland be allowed to rest, or if the chorda be stimulated, the nerve again produces a copious secretion upon sympathetic stimulation. This is shown in the following excerpts from experiments on the dog's and cat's submaxillary. Readings in mm. Stimulation in each case for thirty seconds. It is also clearly seen in Experiment VII, p. 311.

* This phenomenon has, of course, been often described. See among others Langley.[39]

	Cat. I.	Cat. II.	Dog.
	Amount.	*Amount.*	
1st stimulation	20	16	36
Rest	25 seconds	1 minute.	2 minutes.
2d stimulation	0	6	25
Rest	3 minutes	2 minutes	1 minute
3d stimulation	11	10.5	11
Rest			2 minutes
4th stimulation			10
Rest			1 minute
5th stimulation			11
Rest			1 minute
6th stimulation			2.5
Rest			Chorda stimulated
7th stimulation			25
Rest			2 minutes
8th stimulation			6
Rest			1 min. 40 sec.
9th stimulation			4

The great decrease in the amount of saliva obtainable on a second stimulation, closely following a first, even though a minute's intreval of rest elapse, might be explained on Heidenhain's theory, by assuming an exhaustion of secretory fibres, nerve ends or gland cells. Such an assumption is highly improbable. There is, I believe, no other example of a nerve end, or fibre, becoming exhausted by a weak stimulus of a minute's duration. That the secretory fibres of the chorda, their nerve ends and the gland cells are not exhausted or suffocated is shown by the fact that the following chorda stimulation is little, if at all, altered. The phenomena are clearly explicable, on the other hand, if the sympathetic causes secretion by compression of the ducts and alveoli. By the first stimulation the gland is largely emptied of its saliva. If no time be given for the ducts to be refilled, the following stimulation finds less available saliva, or none at all. The nerve appears, in fact, to have become inoperative until, through the resting of the gland, or the action of the chorda, the ducts be again filled. The exhausted element of the gland inferred by Heidenhain is the fluid in the ducts and alveoli.

c. The Augmentation of Sympathetic Saliva.

That the small amount of sympathetic secretion, in the cases just cited, is due to the presence of a small amount of fluid in the ducts and alveoli is indicated by the abnormally large sympathetic secretion, when the amount of liquid saliva in the gland is rendered abnormally large by stimulation of the chorda, or by the action of pilocarpine, nicotine and other drugs.

Langley[39] first observed the augmentation of sympathetic saliva by an immediately preceeding stimulation of the dilator nerve in the dog's parotid and submaxillary and the cat's submaxillary. The following experiments confirming Langley illustrates this augmentation.

Experiment VII.

Dog under morphine and chloroform, sympathetic and chorda cut. Canula in Wharton's duct. Secretion in mm. is given above the line for every 10 seconds, 250 mm. = 0.82 cc. Below the line is indicated the nerve stimulated; s, is the sympathetic; c, the chorda. If no letter is written, it indicates that at these intervals there was no stimulation.

10, 35, 31, 2, **25,** 4, 3, 2, 2, 8, 6, 4, **17,** 2, 2, 1, 2, 1, 3, 0
c s s s s s s s s s s s

3, 4, 1½, 1½, 1, 2, 1, 4, 4, 1, 1, 1, 1, 1, 2, 1½, 3, 1, 1, 0, 5, 1, 1, 0
s s s s s s s s s s s s s s s

½, 0, ½, ½, 8, 60, 38, 2, 1, **15,** 3, 1, 3, 3, 2, 2, 3, 2, 4, 1, 1, 2, 2, 1
s c c s s s s s s s

2, 1, 1, 2, 1, 45, 30, 3, **25,** 2, 4, 2, 3, 2, **3,** 1, 1, 1, 2, ———
s s s c s s s s s s s s c. c. c.

18, 7, 3, 3, 2, ½, 4, **2.** 2, ½, 1, ———— **39, 29,** 4, 0, 0,
s s s s s s s s s Chorda 1 minute s s s s

4, 3, 2, 2, 1, 1, 3, etc.,
s s s s s

It will be noticed, in this experiment, that the first secretion of the sympathetic, immediately following the chorda stimulation, is abnormally large, but that the augmentation effect rapidly passes off. The augmented saliva, as Langley pointed out, is

more watery than normal and has a shorter latent period. It resembles chorda saliva. A similar watery and copious sympathetic saliva occurs after the injection of nicotine,[24] or pilocarpine,[22] and during paralytic secretion.[42]

This augmented saliva may be explained, assuming that the nerve acts on the gland cell, as follows: If the chorda and sympathetic act as the same gland cells (Heidenhain) it may be said that stimulation of the chorda renders the cells more responsive to a sympathetic stimulation immediately following. If, on the other hand, the chorda and sympathetic innervate different gland cells (Langley), we are forced to the assumption that nerve impulses traverse glands outside of the nerve tracts. "When either nerve is stimulated," Langley says, "there is an irradiation of impulses of less intensity to the cells in the neighborhood of those directly affected; that on stimulation of the chorda tympani the cells connected with it are left for a time in a state of weak excitation, so that irridiation of impulses reaching the gland by the sympathetic is much greater than normal, and these irradiating impulses being weak lead to a more fluid secretion."[39] It can hardly be said, I think, that either of these explanations is satisfactory. That irritability of the gland cells probably has nothing to do with this augmentation, but that it is the simple result of the presence of an abnormally large amount of fluid saliva in the gland is shown by the injection of innocuous fluid into Wharton's duct. By this means we passively distend the ducts and aveoli, without the intervention of cell activities. Following stimulation of the sympathetic causes an augmented secretion. I have tried such experiments only in the case of the dog's submaxillary, a somewhat unsatisfactory gland, owing to the viscidity of the saliva. The experiment, particularly if tried on a fresh gland full of viscous saliva, is not always successful. The cause of the failures has not been investigated, but I suppose they are due to the unavoidable driving into the gland of the viscous saliva and partly to the use of too great pressure in such cases, causing an over-distension of the ducts and a consequent injury to the nerves. The positive results are, however, sufficiently conclusive.

Experiment VIII.

Small dog under morphine and chloroform. Left submaxillary duct and nerves prepared. Nerves cut. The chorda is first stimulated intermittently for an hour. The sympathetic is stimulated each time for 30 seconds. Secondary coil 70. Secretion in mm. as before.

Time.	Nerve	Secretion.
h. m. s.		
3 30	Sympathetic	10
3 32	"	4
Inject ⅓cc. 0.6% NaCl solution into Wharton's duct.		
3 34	Sympathetic	**15**
3 36	"	0
3 41	"	0
4 10	"	11
4 11	"	8
4 12 30	"	4
Inject ⅓ cc. 0.5% NaCl into duct.		
4 14	Sympathetic	**8**
4 15	"	6

Experiment IX.

Conditions of experiment as in 8. Dog larger. Sympathetic 30 seconds stimulation, unless otherwise indicated.

Time.	Nerve.	Secretion in mm.
h. m. s.		
5 20	Sympathetic	**40**
5 22	"	**15**
5 24 –5 25	"	20
5 26	"	10
5 27 –5 27 40	"	20
5 28 –5 28 40	"	18
Inject .4 cc. 0.6% NaCl into duct.		
5 30	Sympathetic	**40**
5 31	"	7
5 32	"	0
Inject .3 cc. 0.6% NaCl.		
5 34	Sympathetic	**17**
5 35	"	2
5 36	"	0
Inject .3 cc. 0.6% NaCl.		
5 38	Sympathetic	**11**

The results of these experiments, in conjunction with those following, are most readily explicable, I believe, on the muscular theory. The augmented saliva, in whatever manner produced, gives fairly conclusive evidence that the nerve causes secretion by compression of the ducts and alveoli. If these are filled with an unusually large amount of fluid saliva an unusually large secretion, characterized by its short latent period and watery character, is secreted. If there be little saliva present, or if it be very viscous, we obtain a small secretion of long latent period and lasting for some time.

(*d*) Paralysis of the Sympathetic by Emptying the Ducts and its Restoral to Power by Injection of Fluid into the Ducts.

Further strong evidence of the muscular action of the sympathetic may be obtained by preventing the passage of fluid into the gland and stimulating the nerve until all available saliva in the ducts has presumably been expelled. The nerve then appears to have lost its action, but it may be shown to be still active by the injection of fluid into the ducts. The passage of fluid into the gland may be prevented either by the use of quinine or by compression of the gland artery.

Heidenhain * showed that if quinine sulphate be injected into Wharton's duct the secretory action of the chorda is ultimately paralyzed, but the gland becomes œdematous. This indicates that, although liquid is present in the lymph spaces, it is prevented in some way from passing through the cell. If, after paralysis of the chorda, the sympathetic be stimulated, a copious secretion is obtained. After a few stimulations, however, the nerve appears to be paralyzed. If that paralysis is only apparent, due to the emptiness of the gland's ducts, we should be able to obtain a secretion on sympathetic stimulation, by the injection into the duct of more quinine sulphate. The following experiment proves this to be the case.

* Heidenhain, Studien aus Breslau, IV, 1868.

Experiment X.

Large dog. Operation as in other experiments. Secretion in mm. 250 mm.=0.82 cc., s=sympathetic ; c=chorda.

Time. h. m. s.	Nerve.	Coil in cm.	Secretion in mm.
12 24	s	15	72
12 25	s	15	12
Chorda stimulated for several minutes, then .5 cc. of saturated solution of quinine sulphate injected slowly into Wharton's duct.			
12 37	c	13	0
12 38	c	11	0
12 39	s	11	50
12 40	s	11	27
12 44	s	15	12
12 45	s	15	9
12 47	c	11	0
12 48	c	7	0
12 50	s	14	15
12 54	c	11	0
12 55	s	14	7
12 57	s	13	10
12 59	s	13	3
Inject mixture equal parts 0.6% NaCl and sat. quinine sulphate.			
1 03	s	13	24
1 05	s	13	4
1 09	s	12	0
1 10	s	9	1
1 11	s	10	0
Neither nerve produces a secretion, though stimulated from time to time.			
4 00	c	8	0
4 01	s	8	0
Inject 0.5 % NaCl into duct.			
4 02	s	6.5	32
4 03	s	6	14
4 06	s	6	3
4 09	Inject HCl 0.5% into duct.		
4 10	s	6	9
Chorda ineffective at any strength.			

In the foregoing experiment the chorda became completely ineffective at 12:30. The gland, however, was abnormally full of quinine fluid, and the first sympathetic stimulation after the

injection consequently gave a greatly augmented secretion at 12:39. Thereafter each stimulation yielded less and less, and finally at 12:59 only 3 mm. were secreted. The ducts may be assumed to be practically empty. Quinine solution was now again injected, and the next sympathetic stimulation yielded again a greatly augmented secretion. Finally at 1:11 the sympathetic failed to yield any secretion, and from then until 4 P. M. was totally ineffective. It would be said, at first sight, that the nerve was paralyzed. Such, however, was not the case, its seeming paralysis being due to the emptiness of the gland. This was shown by the injection of .5 % NaCl solution into the duct. The following stimulation of the sympathetic at 4:02 yielded a very large secretion.

This experiment in two ways furnishes very strong evidence of the muscular nature of the sympathetic secretion. The fact that sympathetic secretion may be obtained long after paralysis of the chorda is very suggestive. Heidenhain* maintains that the chorda secretion is paralyzed by the action of the drug on the gland cells. If this be true, and I see no reason to doubt it, it furnishes very strong evidence that the sympathetic produces its secretion in *some other manner* than action on the gland cell, for the sympathetic secretion is not materially affected long after the gland cells have been completely paralyzed. The fact that the nerve's effect soon passes away, but may be restored by the simple injection of more quinine solution or other fluid into the duct, I believe to be susceptible of but one explanation, *i. e.*, that the nerve causes this secretion by compression of the ducts and alveoli.

A similar phenomenon is witnessed if the gland artery be compressed and fluid thus cut off from the gland. A few stimulations of the sympathetic suffice to render the nerve inoperative, but by injection of fluid into the duct the nerve is shown to be still active.

* Heidenhain, Studien aus Breslau, IV, 1868, p. 85, "so wird die Erregbarkeit der absondernden Elemente bald herabgesetzt und nach kurzer Zeit ganz vernichtet."

Experiment Va (Continued; see p. 305).

TIME. h. m. s.	NERVE.	SECRETION IN MM.
3 25	Artery clamped close by the hilus.	
3 30	Chorda	0
3 35	Sympathetic	23
3 37	Sympathetic	0
3 40	Sympathetic	0
	0.2 cc., .5 % NaCl solution injected into duct.	
3 41	Sympathetic	**17**
3 42	Artery unclamped	
4 07 30	Artery clamped	
4 12	Chorda	0
4 13	Sympathetic	**25**
4 15–4 17	Chorda	0
4 17 30–4 18 15	Sympathetic	**14**
4 20	Sympathetic	0
4 23	.3 cc., .5 % NaCl injected into duct	
4 24	Sympathetic	**13**
4 25	Sympathetic	0
4 26–4 27	Sympathetic	0
4 28	.2 cc., .5 % NaCl injected	
4 29	Sympathetic	**8**

In this experiment the sympathetic appeared paralyzed at 3:40, 4:20 and 4:26, but the injection of normal salt solution into the duct was followed by a secretion little less than normal, on the next stimulation. In one case twenty minutes after the artery had been clamped, the sympathetic was thus shown still to be active. Heidenhain attributes the loss of the chorda's power to the suffocation and consequent paralysis of the gland cell. (See footnote, p. 308.) As already pointed out (p. 316) this would, if true, show that the sympathetic produces its secretion in some other way than by action on the cell. The fact that the nerve's power may be restored by the injection of innocuous fluid into the ducts is readily explicable on the muscular theory of secretion, but, with difficulty, on the cellular theory.

I found that a similar phenomenon may, at times, be seen in the cat's submaxillary, which has been paralyzed by just sufficient atropin to prevent chorda secretion. As was first pointed out by Langley, atropin paralyzes the sympathetic in the cat, but more atropin is required than to paralyze the chorda. The

sympathetic may appear paralyzed, wholly or in part, before it actually is. In this condition gently forcing the secreted saliva back into the gland restores the nerve's power.

Experiment XII.

Cat etherized. Canula in duct of left submaxillary. Both chorda and cervical sympathetic cut. Both nerves active. Inject .1% solution of atropin carefully into femoral vein until chorda just paralyzed. Sympathetic stimulated 30 seconds each time.

Time.	Nerve.	Secretion in cc.
h. m. s.		
3 50	Chorda	0.
3 51	Sympathetic	0. 1
3 52	"	0. 1
3 53	"	0. 1
3 54	"	0.05
3 55	"	0.05
3 56	"	0.03
	Blew the secretion gently back into gland.	
3 57	Sympathetic	0.13
4 00	"	0.15
4 06	Inject .1 cc. atropin into femoral vein.	
4 07	Sympathetic	0.10
4 08	"	0.10
4 09	"	0.10
4 10	Sympathetic	.10
	Inject .2 cc. atropin	
4 13	Sympathetic	**.07**
4 14	"	.01
4 15	"	.03
	Blew saliva into gland.	
4 16	Sympathetic	**.25**
4 17	"	.05
4 18	"	.04
4 19	"	.02
	Blew .1 cc. saliva back into gland.	
4 20	Sympathetic	**.12**
4 21	"	.04
4 22	"	.03
	Blew .1 cc. saliva back into gland.	

4 23 . . . . . Sympathetic . . . . . **.14**
4 24 . . . . . " 02
4 25 . . . . . " 04
4 26 . . . . . " 02

Blew .1 cc. saliva back into gland.

4 27 . . . . . Sympathetic . . . . . **.13**
4 28 . . . . . " 01
4 29 . . . . . " 06
4 30 . . . . . " 02
4 31 . . . . . " 03

Blew .1 cc. saliva back into gland.

4 32 . . . . . Sympathetic . . . . . **.10**
4 33 . . . . . " 02
4 34 . . . . . " 05
4 35 . . . . . " 04
4 26 . . . . . " 03

Blew back .1 cc. saliva.

4 37 . . . . . Sympathetic . . . . . **.12**
4 38 . . . . . " 04
4 39 . . . . . " 01
4 40 . . . . . " 04
4 41 . . . . . " 03

Blew back .1 cc. saliva.

4 42 . . . . . Sympathetic . . . . . **.09**
4 43 . . . . . " 03
4 44 . . . . . " 04
4 45 . . . . . " 02

Blew back .1 cc. saliva.

4 46 . . . . . Sympathetic . . . . . **.10**
4 47 . . . . . " 05
4 48 . . . . . " 03
4 49 . . . . . " 04
4 50 . . . . . " 02

Blew back .1 cc. saliva.

4 51 . . . . . Sympathetic. . . . . **.11**
4 52 . . . . . " 02
4 53 . . . . . " 04
4 54 . . . . . " 025

Blew back .1 cc.

4 55 . . . . . S . . . . . **.075**
4 56 . . . . . S 025
4 57 . . . . . S . . . . . .04 &c.

The most probable explanation of the apparent failure, partial or total of the sympathetic, in all the immediately preceding experiments, appears to me to be this: That by the injection of

quinine, or atropin, or compression of the gland's artery, liquid is prevented from entering the gland. A few stimulations of the sympathetic suffice to expell all, or most, of the available saliva in the gland, and the nerve thereafter appears paralyzed. If, now, the ducts and alveoli be passively redistended by the injection of liquid into the duct the nerve again causes a compression of the duct, and the fluid is again expelled and gives a secretion. This renewed secretion cannot, however, be referred to the action of the gland cell, because the latter has been in one case paralyzed by the action of quinine, and in the other case by suffocation. Nor could it be referred to the action of the cell, even were the latter not paralyzed, for the mere hypothetical taking-up of fluid into the cell from the duct, and its discharge again into the latter, would in no way alter the bulk of fluid in the ducts plus the bulk of the cell. There would, hence, be no pressure to drive the secretion from the gland.

e. The Character of Sympathetic Saliva.

Evidence that the sympathetic nerve innervates the gland cell has been derived from the character of the sympathetic saliva. This, as is well known, is richer in organic matters than the saliva secreted under the influence of the gland's dilator nerve. This greater richness Heidenhain attributes to the predominance in this nerve of so-called "trophic" fibres, the function of which is to render the stored-up metabolic products of the cell (hylogens) more soluble, and the juice consequently more concentrated. This assumption involves such consequences that by common consent it has been considered the most unsatisfactory part of the Heidenhain theory. It is, however, practically the only probable explanation, with one exception, which has been offered. The exception is the view suggested by Schiff, discussed below.

If the sympathetic simply drives out the saliva already present in the gland the sympathetic saliva must be of the character of that present in the ducts and alveoli at the moment of stimulation. There is evidence that this is the case. That the saliva in the ducts of the dog's parotid is very viscid has been shown by

Langley.[39] Sections show the ducts plugged with a viscous looking mass, and Langley suggests that the saliva is here too thick to be expelled. In one experiment Langley found a dog's parotid which secreted under the influence of the sympathetic 1.3 cc. Concerning this saliva Langley says :[40]

" The saliva was of the most remarkable nature ; it formed a thick jelly-like mass ; if allowed to collect at all in the canula it could be drawn out as a continuous clot. During the experiment the duct was frequently emptied by pressure to prevent its being stopped up." The saliva contained 7.8 % of organic solids. We can, moreover, artificially alter the fluidity of the saliva in the ducts, rendering it more dilute, by the action of the chorda tympani or pilocarpine. In such cases, as we have seen in speaking of the augmented secretion, sympathetic saliva is almost as thin as chorda saliva. By long stimulation of the chorda, moreover, we may exhaust the soluble constituents of the gland. In such cases it may be presumed that the gland saliva is thinner than normal. It is known that under such circumstances the sympathetic saliva may fall within the limits of density of chorda saliva.* A similar change occurs in paralytic secretions following division of the chorda. The gland then secretes a very thin saliva, and sections show the cells practically exhausted of their mucous. The sympathetic in these causes a very abundant and very watery secretion.

We may obtain still further evidence of the character of the saliva normally present in the ducts of the resting gland by a sudden, strong stimulation of the chorda tympani. The rapid inflow of fluid from the capillaries about the alveoli, taking place under the influence of that nerve, drives out the saliva in the ducts before it has time to become diluted. If we examine this saliva first appearing on chorda stimulation we find it in all respects typical sympathetic saliva. From this Schiff concluded† that sympathetic saliva was nothing more than the saliva normally present in the ducts, formed during glandular rest.

* Heidenhain, Studien aus Breslau, IV, 1868. After long sympathetic stimulations the saliva becomes " dünnflussig, hell, und dadurch dem chorda Speichel ganz und gar ähnlich."

† Schiff. Leçons sur la Digestion. Tome I., p. 296, 1867 ; also p. 304.

Schiff found that if the sympathetic nerve of the horse be stimulated the parotid secreted quickly 8–10 volumes of white saliva, and then, as in the cat's submaxillary, secretion ceased. If the horse be fed there ensued a copious, clear secretion of watery cerebral saliva. The gland was now, presumably, full of such saliva. If it be allowed to rest for twenty minutes without secretion on again feeding the horse the first saliva (8–10 volumes) *was typical, thick, white sympathetic saliva.* This was followed by the clear cerebral saliva. Schiff repeated this many times, thus showing that in the interval of rest the gland, uninfluenced by the sympathetic, converts the clear cerebral saliva into typical so-called sympathetic saliva. A similar phenomenon has been described, with a somewhat different interpretation for the dog's submaxillary, by Heidenhain.* I have repeated Schiff's experiment on the dog's submaxillary, fully confirming him. This is shown in the following experiment.

Experiment XIII.

Large dog, morphine and ether. At 10:30 A. M. canula in right Wharton's duct. Sympathetic and chorda-lingual cut. On the first stimulation of the chorda the first saliva was viscid, whitish and filled with corpuscles. The chorda was stimulated until 2 cc. of saliva were secreted. This saliva was thin, clear, typical chorda saliva. Gland rested without secretion until 11:30. Stimulated chorda. *The first saliva was thick, viscid, white saliva.* The gland then secreted 1 cc., clear chorda saliva. Rested until 2:30 P. M. Stimulated the chorda. *A very large amount of typical, sympathetic saliva* appeared first, followed by 2 cc. of watery chorda saliva. Gland rested until 4 P. M. Stimulated chorda. *The first saliva was viscid and contained many salivary corpuscles.* Secreted afterward 1 cc. clear saliva. Rested until 5 P. M. Stimulated the chorda. *The first saliva was again viscid, whitish saliva, filled with salivary corpuscles and lumps.*

* Heidenhain. Studien aus Breslau, IV, 1868, p. 52. "Die erste Speichel portion war sehr dick, fast gallertartig, reich an Schleimballen wie sie sonst im Sympathicus Speichel vorkommen, und ebenso an Speichelkörperchen die haufenweise bei einander lagen."

This experiment proves that after each stimulation of the chorda, the thin, chorda saliva filling the gland ducts is quickly converted, even in the absence of sympathetic influence, into typical viscid, sympathetic saliva.* It shows, also, that the ducts of the normal, resting mucous gland are filled with saliva, supposed to be characteristic of the sympathetic's action. This observation seems to me to render Heidenhain's assumption of special "trophic" nerve fibres to account for the character of such saliva, superfluous; and, also, to give additional evidence that sympathetic saliva is nothing more than this "saliva of rest," expelled by compression of ducts and alveoli. The correctness of the latter view is, in my opinion, strongly confirmed by the great variation in character of sympathetic saliva, with a variation of character of the saliva within the gland.

I wish to point out, also, that the influence of sympathetic stimulation upon the composition of the saliva secreted during coincident stimulation of the dilator nerve, upon which special stress has been laid by Heidenhain, is also readily understood on this hypothesis of the nature of sympathetic action. Langley's discovery[39] that the sympathetic produces a secretion from the dog's parotid unless the saliva be too thick for expulsion make Heidenhain's results clear.[22]

Heidenhain found, in harmony with all other observers, that stimulation of the sympathetic usually causes no secretion from the dog's parotid. He concluded from this that the nerve carried no, or few, secretory fibres.† He discovered, however, that if Jacobson's nerve be irritated so as to cause a secretion, and during this irritation the sympathetic be stimulated, the saliva secreted during simultaneous irritation of both nerves was far richer in organic solids than that secreted under the influence of Jacobson's nerve alone.‡ Denying that the sympathetic

* This is a pretty conclusive reply to the statement of Heidenhain that the simple contact of the water with the hylogens is not sufficient to dissolve them
We have here a demonstration that it is sufficient in the total absence of nerve influence.

† Heidenhain. Hermann's Handbuch d. Phys. V, p. 55. "Der Sympathicus des Hundes enthält für die Parotis nur trophische, für die submaxillaris daneben wenige secretorische Fasern."

‡ Heidenhain, Hermann's Handbuch d. Phys. V, p. 55.

exerted a secretory effect upon the gland, he considered the secretion to be due to Jacobson's nerve alone. He concluded, therefore, that stimulation of the sympathetic enormously increased the content of organic solids in the cerebral saliva. The sympathetic must hence act on the gland cells so as to render their contents far more soluble. From Langley's results, however, we can safely conclude that the saliva, secreted when both nerves are stimulated, is not pure cerebral saliva, but largely, if not wholly, augmented sympathetic saliva. Like all sympathetic saliva, it is more concentrated than the saliva secreted under the influence of the dilator nerve, because it is expelled without dilution.

f. Other Evidence of the Muscular Nature of the Mechanism of Sympathetic Secretion.

Very clear evidence, also, has been brought forward by Eckhard,[13] von Wittich[77] and Heidenhain[21] himself that the sympathetic causes at least the major part of its secretion, by a compression of the ducts and alveoli. The parotid gland of the sheep is an albuminous gland, capable of secreting against a pressure of 400–500 m. m. of water (Eckhard). If while secreting against a somewhat lower pressure (200–300 mm.) the cervical sympathetic be stimulated, the water rises suddenly in the manometer for some distance (30–100 mm.). *On ceasing stimulation the secretion rushes back at once into the gland nearly, though never quite, to its former level.* The higher the pressure the more sudden the flow backward. The quick rise at the beginning of stimulation and the abrupt back flow of the secretion at the end plainly suggest that the nerve caused compression of the ducts and alveoli, and thus pressed out the secretion. On ceasing stimulation these structures dilated, and the secretion, being under pressure, rushed back into the gland. I see no other explanation for the back flow, as it takes place too suddenly and at too low a pressure (200 mm. water) to be due to back filtration.

Heidenhain's observation is less striking, but it is similar to

the above. (Breslau Studien, p. 69, IV.) In taking the secretory pressure of the dog's submaxillary he stimulated the chorda until the pressure in the ducts was 271 mm. Hg. On ceasing stimulation the manometer gradually fell. *On stimulating the sympathetic the sinking became much slower*, and the manometer remained stationary at 160 mm. On breaking the stimulation the manometer sank gradually to 100. On stimulating the sympathetic it rose to 107, and on chorda stimulation to 271. It gradually fell during following sympathetic stimulation, *but on breaking the stimulation it fell with striking rapidity* (Auffälig beschleunigtes Sinken). Heidenhain thus records for the dog's submaxillary the same sudden back flow on breaking the stimulation of the sympathetic as Eckhard and von Wittich describe in the sheep.

Paradoxical though it may seem, the experiments just quoted of von Wittich and Eckhard have been cited by Heidenhain as conclusive evidence that the sympathetic does not simply drive out the secretion already in the gland. And it is this conviction which led Heidenhain, in the discussion of all experiments involving the sympathetic, to ignore the possibility of its having such an action. Heidenhain believed von Wittich was right in contending that the failure of the manometer to return to its former level on breaking stimulation proved that the amount of saliva in the gland had been increased. It will be instructive to consider von Wittich's explanation of the phenomena of this secretion. von Wittich[77] suggests that the back flow of the saliva is due to the saliva being pushed back into the cells. Let us examine this more closely. von Wittich and Heidenhain assumed that the cells, on stimulation, discharge their stored products into the lumen. Such a process, it need hardly be said, would lead to no secretion from the ducts, as the bulk of the cell would diminish to just the extent that the bulk of fluid in the ducts increases. Hence the bulk of cell plus liquid would remain unaltered. We must, therefore, make either one of two farther assumptions: First, that the alveoli are greatly distended owing to the turgor of the cells. Stimulation of the nerve might conceivably diminish the resisting power of

the inner end of the cell, and the secretion be expelled from the cell by intra-cellular tension, and from the ducts by the elastic tension of the distended alveolar wall. Or, second, it must be assumed that, as the fluid flows from the cell, new fluid enters the cell from the rear, so that the cell does not diminish in bulk to an extent aqual to the bulk of secretion it has lost. Either of these assumptions lands us at once in difficulties. If the first be true we cannot understand why the sympathetic secretion should be abnormally large, just in those cases, such as paralytic secretions, or after long-continued chorda secretion, in which the alveoli are not distended and are not presumably under pressure. The second assumption, besides being wholly imaginary, has to explain whence comes the fluid flowing into the cell, and why it should flow in during sympathetic stimulation at a time when there is a pronounced vaso-constriction.

With this difficulty of understanding how the nerve could cause a secretion by action on the cell, let us see how the sudden back flow could be understood. According to von Wittich and Heidenhain the diameter of the alveoli has remained constant. The secretion, manifestly, cannot upon this assumption return into the gland, unless there be a diminution in the combined bulk of the secretion in the ducts and the cells. There will be no such alteration in bulk, however, by the secretion passing into the cell as von Wittich assumes, for the cell will grow to just the amount that the secretion in the lumen diminishes. The only way a diminution in bulk could be brought about is by a back filtration. The fall is, however, much too sudden for this, and takes place at a pressure much less than the gland can sustain without becoming œdematous. It is also impossible to see why on ceasing stimulation the permeability of the gland to back filtration should suddenly increase. Easy though it seems at first sight, therefore, to ascribe such a back flow to a reabsorption under pressure of saliva by the cell, closer inquiry shows that it is impossible to account for this back flow except on the assumption either of a back filtration or that there has been an alteration in the diameter of the alveoli. I maintain with Eckhard that a back filtration is highly improbable, and there re-

mains only the alternative of an increase in the diameter of the alveoli, probably following an active compression.

But if the saliva is simply pressed out, why is it that it does not return to its former level on ceasing stimulation? This was supposed by von Wittich to prove that the nerve increased the amount of saliva in the gland. I fully agree with von Wittich in this contention, but I disagree with him entirely in referring the increase to the action of the nerve on the cell This increase may be readily understood on the muscular theory, without any assumption of nerve activity on the gland cell, as follows: On breaking sympathetic stimulation of considerable duration a temporary vaso-dilation occurs and the ducts and alveoli relax. It takes an appreciable time for the saliva to pass back into the fine tubules, and during this time the cells are absorbing water from the lymph and capillaries. Hence their bulk and the amount of saliva is increased and the saliva is never able to return to its former level. The proof of this is sufficiently clear. That vaso-dilation does occur temporarily on ceasing stimulation of constrictor nerves has often been remarked. I have myself often seen it in the rabbit's ear and in the cat's submaxillary. In the dog's submaxillary I have often seen, also, that coincident with this vaso-dilation a slight secretion may actually ensue (See Expt. VII, p. 311). It is, also, well established that the cells do imbibe fluid and food during or after sympathetic stimulation and thus increase the bulk of undifferentiated protoplasm.

In view of these facts, I believe that von Wittich's and Eckhard's experiments, instead of proving that sympathetic stimulation can not possibly be due to compression of the ducts and alveoli, demonstrates that it must be due to such compression; that it is impossible to account for the back flow on any other probable hypothesis, and that the fact that the saliva does not reach its former level is readily understood by reference to the nerve's constrictor action and the temporary vaso-dilation ensuing on breaking simulation. I do not believe that von Wittich ever endeavored to analyze in detail his own explanation, or he must have perceived its impossibility.

g. The Location and Nature of the Contractile Substance in the Gland.

The contractile tissue, responsible for the sympathetic secretion, resides neither in the gland capsule nor in the capillaries. Glands dissected free from the capsules secrete normally. The capillaries cannot be held responsible, as Vierheller[71] supposed, because, as one may readily see in the cat's submaxillary, the nerve may be still active on the blood vessels while producing no secretion, and von Wittich[78] records that after curare, the rabbit's sympathetic loses its secretory activity while still active on the blood vessels of the ear. Unna[70] has suggested that the basement membrane is contractile, and this may possibly be the case. There is, however, no evidence of it. That there is smooth muscle about some of the principal ducts of the salivary glands is well-known, but most histologists have failed to find any between or about the alveoli. However, Pflüger[60] and Schlüter[66] have each described isolated fibres, and strands of smooth muscle lying between the alveoli, distinct from the blood vessels, "so that the stroma is not entirely lacking in contractility."

Whether the contractile tissues thus far recognized histologically in the gland are those active in the production of this secretion appears to be doubtful. The physiological evidence is of itself so strong, however, that I believe we can safely assume the existence of such a tissue, even had we no histological evidence of its presence.

h. The Changes in Gland Cells upon Sympathetic Stimulation.

The changes in gland cells, induced by stimulation of the sympathetic nerve, are most clearly seen in the rabbit's parotid,[40] less clearly in the dog's parotid, where the nerve causes normally little or no secretion. The changes consist in the diminution in the size of the cell, the discharge of the mucous or secretory products, the formation of new undifferentiated protoplasm and

in the nucleus becoming round and moving toward the center of the cell. These changes are identical in kind with, though taking place generally more slowly than, those following stimulation of the dilator nerve or the injection of pilocarpine. Do they indicate the direct action of the nerve on the cell? Although they might be so interpreted, they may be readily understood without any such assumption, as follows: Stimulation of the nerve causes a compression of the cells and thus expels from them their stored-up metabolic products and liquid. By this means the cells discharge their products. On ceasing stimulation the alveoli and ducts relax, and the cells take up water and food from the lymph. The latter process is hastened probably by a temporary vaso-dilation ensuing when the sympathetic stimulation is broken. In virtue of the food, oxygen and lymph thus brought to them the cells form new undifferentiated protoplasm. On several successive stimulations the accumulated metabolic products are largely discharged, the cells become smaller and the nuclei, relieved from pressure, become round and move toward the center of the cells. The same explanation holds also for the changes following stimulation of the dilator secretory nerve, with the exception that the stored products are dissolved out of the cell, instead of being squeezed out, and as vaso-dilation accompanies this secretion the changes take place at a more rapid rate. These changes are discussed more at length in my paper on the Pancreas Cell.*

i. Summary and Conclusion.

The phenomena of sympathetic secretion, which have been considered, could hardly indicate more clearly, I think, the muscular mechanism of that secretion. The sudden gush of saliva; its sudden cessation, however prolonged the stimulation; the diminution in the amount of saliva secreted when the stimulations are rapidly repeated; the apparent paralysis of the nerve when the ducts are empty and its restoral to power if the ducts be passively redistended; the augmentation in volume of the secretion, when the ducts are abnormally full of fluid saliva, and the

* Shortly to appear in the *Journal of Morphology*.

diminution in amount of secretion when there is little saliva present; the dependence of the character of the sympathetic saliva upon that present in the gland at the moment of stimulation; the back flow of saliva into the gland on stopping stimulation when the gland is secreting against pressure; the presence of smooth muscle in the ducts and between the alveoli—these facts point unmistakably in one direction. A stronger chain of circumstantial and direct evidence that this secretion is caused by compression of the ducts and alveoli by contractile tissue would be hard to imagine. If some of these phenomena are susceptible of explanation upon the hypothesis that the secretion is due to gland cell activity, others of them, *i. e.*, the augmented salivary secretion, the back flow of saliva on breaking stimulation, the paralysis of the nerve when the ducts are empty, and its restoral to power if the ducts be redistended, are explicable, if at all, by that theory, only by means of improbable and unproven assumptions.

The surprisingly ready acceptance of the Ludwig-Heidenhain theory of secretory nerves, acting on gland cells, as an explanation of the sympathetic salivary secretion in the face of unmistakable indications of a muscular mechanism, has been due, largely, I believe, to the generally prevalent belief that there is but one mechanism of secretion. That this belief is erroneous, there has long been, I believe, many indications. For there is direct evidence in many glands, such as the poison glands of snakes, the skin glands of amphibia, many unicellular glands, sebaceous and sweat glands, that many secretions are due to muscular action. And in many other glands the phenomena of secretion have shown as clearly that here the mechanism was some other than muscular. There must evidently be at least two different mechanisms, a muscular and some other one. Once the idea that there is but one mechanism of secretion is abandoned, the salivary secretions will be found, I believe, to lose much of their puzzling character.

The facts which Heidenhain urges as showing that the sympathetic produces secretion by action on the gland cell are readily accounted for if the sympathetic cause compression of the ducts and alveoli and vaso-constriction.

III. OTHER SECRETIONS DUE TO MUSCLE ACTION.

Probably many other secretions are due to muscle action.

The unicellular glands of the carp-louse, Argulus foliaceus, are surrounded by muscle fibres. Nussbaum,[55] observing the living glands, states that they are emptied by the contraction of this musculature. Muscle surrounds the unicellular glands in the mantel of Aplysia,[8] and the glandular pedicellaria of the Echinoderms.[34] The gasteropod liver[4] possesses, beneath the serosa, an incomplete musculature, the contraction of which has been watched in the living gland. A similar sheath is found in the livers of Crustacea, land and water Isopods, Amphipods and Decapods.[74]

The poison glands of spiders have their alveoli enclosed in a tunic of spirally arranged muscular fibres.[51] In the salivary glands of Cephalopods[63] the cells rest on connective tissue, which is, in turn, surrounded by muscle fibres. An examination of the physiology of these glands leaves little doubt that the secretion is due to muscular action.[31] The amphibian skin glands are surrounded by a muscular sheath lying between the cells and the basement membrane. There is no doubt from observations on the living glands (Engelmann,[16] Drasch,[11] Ranvier[62]) that this muscle at times contracts, compresses the gland and thus causes a secretion. A similar muscular mechanism prevails in the mucous glands of Petromyzon, in which the cells are bodily extruded.

The poison glands of amphibia and reptilia and others of the salivary glands[76] are provided with their own musculature, or are emptied by surrounding skeletal muscles. Many anal and cloacal glands,[45] sweat[62] and sebaceous glands are provided with a musculature lying between the basement membrane and the cells. There is little doubt that the secretion of sebum is produced by the action of this muscle. The same can be said for the secretion of the oil gland of birds. Probably the most interesting secretion due to muscular action, outside of the salivary glands, is found in the mammalian sweat glands. From

the observations of Ranvier,[62] Joseph[29] and others certain secretions of sweat are probably due to the compression of the gland by this muscle. Probably the post-mortem sweat secretions, secretion after closing the artery, or the injection of strychnia are due to this cause. (There is, however, a second sweat mechanism associated with vaso-dilation.)

Many more examples of the muscular mechanism of secretion might be given, but these suffice to indicate the very wide distribution of such a mechanism. Muscular mechanisms are, possibly, more common among the invertebrates, but they play, also, a not inconsiderable part in vertebrate secretions. The vertebrate, however, with its delicately coördinated, closed vascular system, develops a second mechanism, that of osmosis, which we will now consider.

IV. SALIVARY SECRETION ENSUING UPON STIMULATION OF THE VASO-DILATOR NERVE.

That the general features of chorda secretion coincide with the phenomena of osmosis, regulated by the nerve's dilator action, is pointed out briefly on p. 356. I wish here to consider more particularly those facts which have hitherto been irreconcilable with such a theory, and have been generally considered evidence of a special action of the nerve on the gland cell. These facts are the most important evidences of a secretory nerves and so warrant a careful consideration. They are: (*a*) the increase in the percentage of organic solids of a secretion coincident with an increased rate of secretion; (*b*) the action of atropine; (*c*) the chorda-secretion after clamping the artery; (*d*) the action of nicotine.

a. The Increase in the Percentage of Organic Constituents coincident with an Increased Rate of Secretion.

Heidenhain * observed that on passing from a weak to a strong stimulation of the dilator nerve in the fresh submaxillary and

* Heidenhain. Hermann's Handbuch der Physiologie V. p. 50. Studien aus Breslan IV, 1868, p. 32.

parotid gland of the dog, not only was the rate of secretion increased, but also the percentage of solids. He obtained a simi-

No. of Stimulation.	Time.	Coil.	Am't. of Secretion.	Rate of Secretion in 1 min.	Solids.	Salts.	Organic Constituents.
	h. m. m.						
1	9 20–45	315—288	3.5	0.14	0.74	0.22	0.52
2	9 47–51	160—130	3.5	.87	2.10	.56	1.54
3	10 54.5–59	100— 60	3.0	.66	2.08	.45	1.63
4	10 19–40	264—245	2.8	.11	1.44	.36	1.07
5	10 45–48	160—130	3.0	1.00	1.41	.49	0.91
6	10 50–56	80— 65	3.0	.50	1.16	.39	0.76
7	11 9–27	270—250	2.5	.13	0.78	.30	0.48
8	11 30–34	150—120	3.1	.77	0.90	.38	0.51
9	11 35–44	80— 30	2.8	31	0.79	.36	0.42

lar result in the dog's pancreas, Gottlieb[19] in the rabbit's pancreas, and Pawlow and Schumowa-Simanowskaja[58] in the dog's stomach. In the sheep's submaxillary, on the other hand, there was little or no increase in the per cent. of solids on increasing the stimulus.

Heidenhain believed that this increase in solids meant that the cerebal nerve, besides quickening the flow of water through the cells, rendered the cell contents more soluble. How otherwise shall we explain the fact, he asks, that although given a shorter time of contact with these solids, the water passing through the cells, nevertheless dissolves more than during slow secretion. "Die blosse Berührung mit der aus dem Blute ausgeschiedenen Flüssigkeit ist zur Überfuhrung des Schleimes in das Secret nicht ausreichend, denn sonst musste das Secret um so reicher daran sein, je länger die Flüssigkeit in den Drüsenräumen verweilt, d. h. je langsamer die Secretion vor sich geht."[21] He further assumes that the trophic fibers require a stronger stimulus than the secretory. "Das cerebrale Secret wird, so lange die Drüse unermüdet ist, bei Reizverstärkung reicher an organischen Bestandtheilen, weil der Umsatz der organischen Substanzen in den Zellen unter den Einflusse der stärker gereizten trophischen Fasern schneller steigt, als der Wasserstrom unter dem Einflusse der stärker gereizten secretorischen Fasern."[23]

There are two possible fallacies in Heidenhain's argument. One fallacy probably lies in his tacit assumption that the gland secretes as a whole; that the secretion following a strong stimulus is derived from the same alveoli as the secretion following a weak stimulus. The other fallacy is the assumption that all of the organic constituents of saliva secreted from a fresh gland upon a strong stimulus are in solution. The true reason why the dilator-secretory nerve may cause an increase in the organic matter present in a secretion, coincident with an increased rate of flow, in passing from a weak to a strong stimulus, may be the following:

If a very weak stimulus be used, only a portion of the alveoli are aroused to activity. The supply of stored up products (hylogens) in these, becomes soon exhausted and the secretion derived from them is poor in organic constituents. On passing to a strong stimulus, the previously resting alveoli are thrown into activity and the secretion derived from them is rich in organic constituents. It is the secretion from these fresh alveoli, which increases the percentage of organic constituents in the whole secretion. On passing from a long continued weak to a strong stimulus in a fresh gland, one is really passing from an exhausted to a fresh portion of the gland.

Moreover, in Heidenhain's observation there is a second source of error which he has overlooked. Heidenhain treats all of the organic constituents of the rapidly secreted saliva as if they were in solution and considers that the liquid derived from the blood is in contact with the materials to be dissolved, only during the time of its passage through the cell. There can be little question, however, that saliva, and particularly the rapidly secreted saliva of a fresh gland, cannot be considered a true solution, for it contains many bodies in suspension. Heidenhain himself has been one of those to describe the microscopical appearance of the lumps of mucous matter, salivary corpuscles and occasional leucocytes found in this secretion. The presence of these bodies in saliva indicates that the rapidly secreted saliva carries out of the cell not only substances in solution, but viscous masses of mucous matter not in solution. Its swift cur-

rent is able to transport these masses, while a more slowly flowing secretion is not. Furthermore, in all probability the saliva keeps on dissolving them as it carries them along and hence becomes actually more concentrated, because it is in contact with them really for a longer time than the more slowly secreted saliva and not for a shorter time as Heidenhain thought. Heidenhain made no endeavor to distinguish between the matters in suspension and those in solution.

That any gland functions as a whole, as Heidenhain tacitly assumes in his explanation, can not be maintained.

The whole surface of the stomach, for instance, may be considered as one large gland. It has long been known that secretion can ensue in one spot, and not in another. Heidenhain himself, has called special attention to the marked differences in the condition of the various alveoli in the salivary glands. Even in the resting gland, here and there alveoli will be found possessing the structural features of secretory activity.[22] In the stomach he remarks that some glands show changes on stimulation before others,[23] and I have, myself, repeatedly observed glands in the Newt's stomach close together in very different stages of activity. Kühne and Lea[33] have observed this in the living rabbit's pancreas, a portion only of the gland being normally active. After pilocarpine all the alveoli passed into a condition of activity. In the kidney the independence of the various tubules in secretion has been remarked for the bird's kidney by von Wittich, and for the mammalian kidney by Ribbert,[64] and by Dr. Herter in conjunction with the author. Finally, in the case of the salivary glands, Langley says that even on prolonged activity of the chorda many alveoli show no change. "This is due, in some cases, to fibres escaping stimulation, fibres which leave the lingual later than usual." This histological evidence appears to me to be conclusive with reference to the idea that the gland does not function as a whole, but that the individual alveoli in the secreting gland may be here active, there passive.

The physiological evidence that the foregoing is the true explanation of Heidenhain's observation is hardly less conclusive. We can easily obtain evidence that the secretion obtained

during a weak stimulus is derived from a portion of the gland only in the following manner: Let us stimulate the chorda nerve carefully with a very weak current, until a large amount of secretion has been obtained. If this secretion has been derived from the whole gland a stronger stimulus should yield a secretion much less concentrated than a stimulus of equal strength before the weak stimulus. The glands should show, in other words, a considerable exhaustion of the gland products. If, on the contrary, the whole of this secretion has been derived from a portion only of the gland the rest of the alveoli must remain practically unaltered, and a stronger stimulus arousing these should yield a juice, little, if any, poorer in organic matters than was yielded by a stronger stimulus before the weak.

Werther[75] has unintentionally tried this experiment and found the latter possibility to be what actually occurs. A very weak stimulus, with the secondary coil at 300–240 mm., was employed for over three hours, and more than 20 cc. of saliva were secreted. The percentage of organic solids secreted in the slowly flowing saliva steadily fell, but the percentage of such bodies in the saliva secreted on a succeeding stronger stimulus was little if any less, after this long secretion, than it was with an equally strong stimulus before. If, however, a somewhat stronger stimulus was employed, the secretion from a still stronger stimulus was much poorer in organic solids, than the similar stimulus before the weak.

The fact that rapidly secreted saliva is not a pure solution, and the considerations just presented concerning the independence of the alveoli of the gland render this observatoin of Heidenhain of doubtful value as evidence of the existence of secretory nerves.

Moreover, there is good reason for doubting the truth of Heidenhain's statement, in the quotation on page 333, that the liquid derived from the blood is incapable of dissolving the constituents of the cells in the absence of nerve influence. As has already been pointed out, in treating of sympathetic saliva, (page 322), if the thin chorda saliva be simply left in the gland for twenty minutes, or more, it is converted into a dense, vis-

cous fluid having all the characteristics of sympathetic saliva. This conversion takes place with equal readiness whether the gland nerves be intact or divided.

Heidenhain's own explanation, also, will be found on analysis, I believe, to involve such assumptions as to arouse serious doubt of its truth. To explain this phenomenon on the basis of secretory cell activity, he assumed separate "trophic" nerve fibers acting on the cells. He thus necessitated the improbable conclusion, that at least many of the cells of the submaxillary gland received at least four different nerve ends, *i. e.*, trophic and secretory of the sympathetic, and trophic and secretory of the chorda; and at least two entirely different nerve impulses, *i. e.*, trophic and secretory. That such a consequence should not have aroused suspicion in his own mind of the truth of his explanation is difficult to understand.

b. Post-mortem Chorda Salivary Secretion.

Another strong argument that the chorda does not produce its secretion by its dilator action on the blood vessels, but by direct action on the gland cell, has been derived from the so-called post-mortem chorda secretion. Ludwig and Heidenhain found that if the gland's artery be completely closed, or if the head be rapidly cut off, and the chorda at once stimulated, a fairly copious secretion ensued. This secretion was most abundant in the first minute after section, and thereafter rapidly diminished, but a little could still be obtained four, and in some cases five, minutes after decapitation, or compression of the artery. Thereafter the nerve was ineffective. Heidenhain believed this secretion to be due to the action of the nerve on the gland cell, and its rapid failure to lack of oxygen and water. Both Ludwig and Heidenhain believed that by the conditions of the experiment they entirely eliminated the factor of the nerve's vaso-motor action, and hence thought it demonstrative evidence that the secretory and dilator functions of the nerve were independent.

I think it may be questioned, however, whether the conditions of the experiment do entirely obviate the vaso-motor action of the nerve, and whether it is not still possible that this dila-

tion may cause the secretion. It is conceivable that this post-mortem secretion might be due to the flow of blood from the veins and arterioles into the capillaries, owing to the active dilation of the latter during chorda stimulation. This explanation, it is true, necessitates the assumptions that the chorda tympani causes, on stimulation, an active dilation of the capillaries, or veins, as well as of the arterioles, and that that dilation in some manner makes it easier for the liquid to pass out into the secretion. Both of these assumptions are difficult of proof, and in the limited time at my disposal I have not been able to get demonstrative evidence, either of their truth or error. There is some reason to believe, however, that they may possibly be true.

That liquid passes out of the capillaries into the secretion of the submaxillary gland because of an attractive pull exerted upon it by some constituents of the gland cells, has been suggested both by Ludwig and Heidenhain. To the evidence presented in favor of such a view by Heidenhain, I have nothing to add, and in the normal condition of the capillary and gland wall, I presume that the hypothesis is true. Ludwig supposed that during chorda stimulation the attractive pull of the cell was increased, owing to the formation of substances in the cell possessed of a higher endosmotic equivalent. Heidenhain believed that the attraction of the cell for the liquid in the blood was constant, but that on stimulating the chorda, the turgor of the cell diminished owing to the passage of liquid into the gland lumen, and water was thus enabled to enter the cell from the blood. Both of these explanations, as will be noticed, assume that in some manner the effectiveness of the attractive pull of the cell is increased during nerve stimulation and water enters the cells independent of the state of the vascular system. The question which confronts us and which it was supposed this post-mortem secretion settled is this: Does stimulation of the nerve cause secretion by increasing in some manner the attractive pull exerted by the gland cells on the liquid of the blood, or does it indirectly render effective by vaso-dilation an attraction which is constantly exerted by the cell on this liquid? This is a very difficult point to determine. The endeavor

has been made to answer this question indirectly by showing that vaso-dilation may ensue without secretion, and secretion without vaso-dilation. But all the evidence which has hitherto been offered, that vaso-dilation may ensue without secretion, and that it alone is incapable of causing secretion, is invalidated by the fact that the conditions of such experiments produce an abnormal gland, or capillary wall, both factors which research on lymph formation have shown to be of importance. Quinine, hydrochloric acid, sodium carbonate, or atropine, drugs which enable vaso-dilation to ensue without secretion, probably alter the permeability of the capillary, or gland cell. So that inferences can be drawn from such experiments as to processes occurring in the normal gland only with the greatest caution. The evidence with the exception of the post-mortem secretion, that the chorda may cause a secretion without vaso-dilation is also unsatisfactory, as pointed out on p. 355. Attention may now be directed, hence, to this post-mortem chorda secretion.

It is probable from the considerations presented on page 338, that the liquid causing this secretion is derived from the blood. Can the chorda tympani act on the blood vessels in the absence of circulation, in such a manner as to facilitate the passage of that liquid from the capillaries to the gland cells? The only possible way in which it might so act, I believe, is by causing an active dilation of the capillaries or veins, as well as of the arterioles. Is there any evidence that the chorda has such an action?

Tiegerstedt[68a] states that the capillaries are contractile but that they have not hitherto been shown to be under nerve control. Roy and Brown have brought forward strong evidence that the capillaries are normally in a state of tonic contraction and that they may actively expand independent of the blood pressure. They observed in the capillaries of the web of the frog's foot that, although blood pressure might be diminished almost to atmospheric pressure, the application for an instant of chloroform to the web caused an enormous expansion of the capillaries. Interesting, also, in this connection, are the observations of von Frey. v. Frey[17] examined microscopically the capillaries of the

frog's tongue. He found that on stimulation of the dilator, hypoglossal nerve, a dilation of the capillaries ensued even after the blood supply had been cut off. If the artery be clamped, he observed that the blood streamed out of the capillaries both into the arteries and veins. If, now, the hypoglossal be stimulated the capillaries dilate and blood streams into them from the arterioles and veins. This movement persisted for from one to two minutes after clamping the artery. Furthermore, in experimenting on the blood flow from the veins of the submaxillary gland of the dog during stimulation of the chorda, v. Frey often observed that stimulation of the chorda was followed by a temporary decrease in the rate of flow of blood from the vein, before the ordinary increase. He suggests that this would seem to indicate a widening of the capillary area leading to a back flow of blood from the veins were it not more probable that the increased flow from the dilated arterioles would be more than sufficient to offset this.

These facts justify the conclusion, I believe, that on stimulating the chorda tympani in the severed head, the capillaries of the gland probably dilate, and that blood enters them from the veins.

How such a vaso-dilation might lead to a secretion is not clear, but two possibilities suggest themselves: (1) that the capillaries are thus brought into closer relation with the alveoli, and the constant attraction exerted by the gland contents for the water of the blood is thus rendered effective; or (2) that vaso-dilation may in some way increase the permeability of the capillary wall. The post-mortem chorda secretion can not, I believe, be accepted unconditionally as illustrative of a secretion independent of vaso-dilation, until these possibilities have been shown to be non-existent, or non-essential.

If it shall be found that vaso-dilation of itself is a cause of secretion in the normal gland, and that the gland cell is not the secretory agent, the facts of secretion in the submaxillary gland will probably necessitate the following conclusions, which are not without interest for those studying the physiology of the circulation: (1) That stimulation of the chorda causes an ac-

tive dilation of the capillaries, as well as a dilation of the arterioles. (2) That the sympathetic is able to overcome the chorda's action on the arterioles, but not its action on the capillaries. This is shown by the following fact: If, during strong stimulation of the sympathetic, the chorda be irritated by a current which by itself is barely able to arouse a secretion, a secretion ensues which is certainly as large, if not somewhat larger, than the chorda alone would cause. Such a weak stimulus of the chorda is, however, unable to neutralize the sympathetic's constrictor action on the arterioles, as shown by the observations of v. Frey. It will be necessary to assume, hence, that the arterioles have remained contracted, while the capillaries have dilated and blood has entered them from the veins producing a secretion analogous to the post-mortem chorda secretion.

I endeavored, in a variety of ways, to obviate with certainty all possibility of the chorda's dilator action. By the injection of supra-renal extract into the circulation I hoped to cause such an intense peripheral constriction as to neutralize the dilator action of the nerve. I am indebted to Dr. R. H. Cunningham for this suggestion. After division of the chorda I injected into the jugular vein the whole of a normal salt extract of two powdered supra-renal capsules of another dog. I found, however, that the injection was followed by a slow constant secretion of what appeared to be sympathetic saliva, and that this secretion was increased at all times by a very weak stimulation of the chorda. Indeed, the chorda caused a larger secretion after the injection than before, probably due to the vaso-constriction in other areas of the vascular system. This result was so discouraging that I did not attempt to repeat it.

Heidenhain remarks that large doses of physostigmin cause such an intense constriction of the arterioles of the gland after division of the chorda that stimulation of the latter nerve is unable to cause either a vaso-dilation, or secretion. Unfortunately, Heidenhain does not give a full account of the experiment. Were it true that the drug produces this effect within three or four minutes of its injection, it would be, I believe, conclusive evidence that secretion can not ensue in the absence of vaso-

dilation, and that the nerve does not cause secretion by action on the gland cells; for it is known that the drug does not directly paralyze the hypothetical secretory fibers, or the gland cell. To obtain the details of the drug's action, I injected into the jugular vein of a medium-sized dog 0.1 gr. of physostigmin sulphate. But although the chorda was divided, a spontaneous secretion began which stimulation of the chorda considerably increased. This discrepancy from Heidenhain's results is probably due, I believe, to the impure calabar extract he used.

I endeavored to ascertain whether the presence of blood in the capillaries was an essential condition of the post-mortem secretion by forcing the blood out with air. After ligaturing the carotid artery and placing in it a canula directed headwards I rapidly cut off the head and allowed air to pass into the carotid under a pressure of 100 mm. of Hg. The first experiment gave a positive result. On stimulating the chorda a brief, scanty secretion was obtained which quickly ceased. Examination of the gland showed it to be practically bloodless. In two other similar experiments the post-mortem secretion was greatly reduced in amount and ceased after 1 to 3 minutes, instead of lasting for from 3 to 5 minutes, as normally. The glands in these experiments still contained blood in the veins. The experiments indicate, I believe, that the presence of blood in the capillaries is an essential condition of this secretion. I regret not having been able to bring my experiments to a more satisfactory conclusion, but it is to be hoped that the important bearing of this post-mortem saliva upon the theory of secretion may lead to its being made the subject of careful investigation.

From the following experiments the following conclusions may be drawn relative to this post-mortem secretion :

1. After clamping the gland artery, or cutting off the head, a secretion may be obtained from the submaxillary gland on stimulating the chorda. This secretion is most abundant in the first minutes, and thereafter rapidly diminishes. After four or five minutes no more secretion can be obtained. The total amount of saliva secreted varies from 0.3 to 1.5 cc. (Experiments XVIII, XXII and LXIV.)

2. If the gland be left without stimulation for a minute after decapitation the total amount of saliva obtainable is considerably reduced.

3. If the gland be not stimulated until 3 or 4 minutes have passed a small secretion may be obtained 6 minutes after decapitation. (Experiment XVIII.)

4. If air be blown into the carotid artery, after cutting off the head, the secretion of saliva is reduced in amount and secretion ceases, either abruptly or after 2 to 3 minutes. (Experiments LXIII, LXVI and LXVII.)

5. If defibrinated blood be run under small pressure into the vein of the gland a small secretion may be obtained 20 to 30 minutes after clamping the gland artery.

6. If the blood supply be cut off for 30 minutes, on readmitting blood the arterioles dilate, arterial colored blood issues from the vein at a rapid rate and a spontaneous secretion begins. The rate of this secretion is not changed by stimulation of the chorda in the first minute. (Experiment Va.)

Experiment Va.

Large dog. 3 cc. 1% morphine sulph. subcut. Tracheotomy. Ether. Canulæ in both submaxillary ducts. Both chordo-linguals and both sympathetics cut. The left vagus subsequently divided also. The right gland is stimulated from time to time. See p. 305. The left is freed from its tunic and is attached only by the hilum. The vein on the upper surface is open and flows continuously. The only blood vessel coming to the gland is the hilum artery. The other artery was tied and cut.

Readings computed in cc.

Time.						Nerve.	Amount of Secretion in cc.
h	m	s	h	m	s		
3	25					Clamped artery going to gland.	
3	25		– 3	30		c	Gradually less.
3	30					c	None.
3	32					c	"
3	35					**s**	**.07**

3	37					s	.00
3	40					s	.00
						Inject 5 cc. .5% NaCl into duct.	
3	41					**s**	**.05**
3	42					Unclamped artery.	
3	43	30				c	Active secretion.
3	44					Gland secretions spontaneously .17 cc. per minute.	
						Cut left vagus.	
4	07	30				Clamped artery again.	
4	07	30	– 4	08		Chorda (intermittent).	.50
4	08		– 4	09		c	.18
4	09		– 4	11	30	c	.07
4	12					c	.00
4	13		– 4	14		**s**	**.08**
4	15		– 4	17		c-coil 12	.00
4	17	30	– 4	18	15	**s**	**.05** (very viscid)
4	20					s	.00
4	23					Inject NaCl. 5% into duct.	
4	24					s 30 sec.	**.04**
4	25					c	.00
4	26		– 4	27		s	.00
4	28					Inject ½ cc. fluid into duct. Most of it runs out before stimulation.	
4	29					**s**	**.025**
4	29	30				Unclamp artery (red blood rushes out of vein).	
4	30		– 4	31		*Gland secretes spontaneously.*	.1 cc.
4	31		– 4	32		" " "	.12 cc.
4	33	6				c	.30 cc. per minute.
4	35		4	32		Spontaneously secreting.	.08 cc. per minute.
4	37		– 4	38		c 1 mm.	.7 cc.
4	38		– 4	45		Spontaneously.	.5 cc.
4	45					c	.9 cc. per minute.
4	45	30				Clamped artery again.	
4	46	30	– 4	47	30	c (coil 12)	.5
						Gland still slowly secreting spontaneously.	
4	48	30	– 4	49	30	c	.1
4	50		– 4	51		c	.03
4	51	30	– 4	52	30	c	.005 in first thirty seconds, then no more.
4	53		– 4	54		**s**	**.03**
4	54		– 4	55		c	.00
4	55	30	– 4	56	30	c coil 10	.00
4	57		– 4	58		s coil 10	.015
5	02					Unclamped artery.	
5	02	30				c	Readily secretes.
						Blood rushes continuously out of vein a bright red on unclamping the artery.	
5	03		– 5	09		*Gland secretes spontaneously .5 cc.*	
5	09		– 5	10		s	.05

5	13	30				Clamped artery.		
5	13	40	– 5	14	40		c	.5
5	14	40	– 5	17	30	No stimulation.		
5	17	30	– 5	18	30		c	**.03**
5	19		– 5	20			c	.02
5	20						c	.00
5	22		– 5	23			s	.01
5	24						c	.00
5	25		– 5	26			s	.01
5	35						c	.00
5	35	30					s	.00
5	36					Unclamped artery. Red blood rushes from the vein.		
5	40					Chorda. Rapid secretion.		
						Gland secretes spontaneously.		
5	45		– 5	46		Right Sympathetic.		.1 cc.
5	47		– 5	48		Left Sympathetic.		.04 cc.
5	49	30				Cut off head as rapidly as possible. Was unable to saw through the vertebral column. All the muscles and skin severed.		
						Right gland.		
5	50	30	– 5	55		Intermittent stimulation of right chorda.		.530
5	55					Chorda (coil 5) muscular contractions. No secretion.		
5	57					Right sympathetic.		**.22 cc.**
6	10					Right sympathetic.		**.04 cc.**
5	56					Left gland; no secretion either from chorda or sympathetic.		

Experiment LIV.

Right submaxillary. Chorda and sympathetic cut. Dog under morphine and ether. Tracheotomy. The dog's respirations become very slow, and finally cease without any struggles, and without ether. There was considerable fluid in the trachea.

4.46. Stimulate the chorda while dying, chorda effective until 4.50. The secretion becomes less and less and finally ceases.

I then stimulated the sympathetic and obtained a very copious secretion of .2 cc. No more secretion from either nerve.

Experiment LXIV.

Before cutting. 10 seconds stim. Coil 24. Secretes .79 cc.

Begin to cut at 4.50. 1 minute to sever head completely. No secretion during operation.

h	m	s	h	m		Amount.
4	57	–	4	58	Stimulates 3 times, 10 seconds at a time.	.515 cc
4	59				" 10 seconds	.150 cc.
4	59	30			" 10 "	.021 cc.
					No more secretion.	
					Total time of stimulation 50 seconds. Total amount.	.686 cc.

From beginning to cut to end of chorda effect, 3 m. 30 s.

Experiment XXI.

Before cutting. Coil 20. 10 s. stimulation secretes .55 cc.
Begin to cut at 4.05. 1 minute to sever head completely. No secretion during operation.

h	m	s	h	m			Amount.
4	06		– 4	07	Stimulate 3 times, 10 seconds at a time.	1.	.235
						2.	.040
					Dog swallows.	3.	.090
4	07		– 4	08	" 3 times, 10 seconds at a time.	1.	.070
						2.	.040
					Swallows.	3.	.060
4	08	15			Coil to 10, muscular contractions, 10 sec.		.100
4	09				30 seconds stim. off and on (muscle).		.030
4	09	15			No more secretion.		
4	10				Coil 4. Heavy contractions (escape of current).		000
					Total time of stimulation, 85 seconds. Total amount,		.665 cc.

Time from beginning to cut until end of chorda effect, 4 m. 15 s.

Experiment XVIII.

Before cutting. Coil 11. Stimulate 10 seconds.
Right gland secretes .64 cc. Left gland, .61 cc.
5.24.30 begin to cut head. Head severed in 30 s.

h	m	s	h	m	Right gland.		Amount.
5	25		– 5	26	Stimulate 3 times, 10 seconds at a time.	1.	.125
						2.	.100
						3.	.080
5	26		– 5	27	" 4 " " "	1.	.070
						2.	.050
						3.	.020
						4.	.010
5	27		– 5	28	" 40 seconds.		.040 cc
5	28	30			" 10 "		.000

			Left Gland.	Amount.
5	30		Stimulate left chorda 10 seconds.	.070
			next 10 "	.010
5	30	30	" " chorda (strong muscular contractions).	.070
5	31		Left chorda. No more effect except on muscular contraction.	

Summary.

Right gland.

Total time of stimulation, 120 seconds. Total secretion, .495 cc. From beginning of cut to end of chorda effect, 4 minutes.

Left gland.

Total time of stimulation, 20 seconds. Total amount, .080 cc. Time from beginning to cut to end of chorda effect (2) 5 minutes, 30 seconds.

Experiment LXIV.

Before cutting. Coil 18. 30 sec. stimulation. Secretes 2.1 cc. Cut head at 4.30, 1½ minutes to sever completely.

h	m	s	h	m		
4	31	40 –	4	36	Intermittent stimulation. Secretes	.250 cc.
					No more secretion after 4.35.	
4	38				Stimulate sympathetic for two minutes, secretes	.065 cc.

Time from beginning of cut to end of chorda effect 5 minutes.

Experiment XXII.

Before cutting. Coil 18. 10 sec. stim. Secretes .2 cc. Cut at 6.07. 30 seconds to sever head completely.

h	m	s	h	m	s		
4	07	30 –	6	9.		Stimulation, 1st 10 seconds	.225 cc.
						40 seconds stim.	.060 cc.
6	09	20 –	6	19	10	Stimulate coil 18. 30 sec. stim.	.150 cc.
6	10	30				Chorda no mre effect	
6	12					Coil to 14. Muscular contractions	.050 cc.
						Total secretion	.375 cc.

Time from cuttiug till chorda ineffective, 3 m. 30 s.

Experiment LXIII.

Small dog, Irish terrier, under ether. Canula in left Wharton's duct. Tracheotomy. Chorda-lingual nerve cut. Pro-

tected electrodes on chorda. Vago-sympathetic not cut. Canula connected with air reservoir in the head end of the left carotid artery.

Before cutting, stimulation of the chorda, with secondary coil at 200, causes a secretion of 0.15 cc. in 10 seconds.

Head rapidly severed at 4.17 P. M. As soon as it was severed I opened the cock, letting air into the carotid. I then stimulated the chorda tympani at 4.18. Stimulation of the chorda causes a secretion of .02 cc. Secretion then stops and no more can be obtained by any strength of stimulus.

Experiment LXVI.

Conditions of the experiment as in Experiment LXIII. Before cutting off the head stimulation of the chorda for 10 seconds with secondary coil at 180 causes a secretion of .17 cc.

Head rapidly severed from body at 3.03. Chorda stimulated at 3.03.45 for 20 seconds. Gland secretes .20 cc. Air then forced into the carotid artery.

3.04.30–3.05.30 stimulation of the chorda with secondary coil at 130 causes .07 cc. Thereafter no secretion with a stimulation of any strength.

Experiment LXVII.

Conditions of experiment the same as in Experiment LXIII. Before decapitation stimulation of the chorda for 10 seconds with secondary coil at 230 yields a secretion of 0.2 cc.

Dog decapitated at 10.49. Air forced into carotid as soon as cutting began. Head severed in 30 seconds.

h.	m.	s.				
10	49	45	Chorda	10 seconds.	Coil 230	0.1 cc.
10	50	30	"	" "	" 200	0.05
10	52		"	20 "	" 180	0.05

Thereafter no more secretion.

Post-mortem examination shows the gland veins to be filled with blood. The air does not seem to have penetrated the gland.

c. The Nature of the Action of Atropine and Pilocarpine.

Atropine permits vaso-dilation, on stimulation of the chorda, but prevents secretion. The drug has been supposed to act, not on the gland cell, but on the ends of the secretory nerve fibers. The reasoning for this is as follows: In the dog's submaxillary, atropine paralyzes the chorda secretion, but not the sympathetic. If the sympathetic innervate the gland cell and cause its secretion by action on the latter, the gland cells connected with this nerve have evidently not been paralyzed. As there is no reason to suppose these cells different from those connected with the chorda, it is probable that the cells connected with the chorda have not been paralyzed. But if the gland cells have not been paralyzed, and the dilator action of the nerve remains unaffected, we must assume that there is some third element connected with the nerve which has been paralyzed. This must be the element causing secretion, *i. e.*, the secretory nerve fiber. The latter must be paralyzed at the nerve termination, since, as far as known, atropine does not act on the nerve fibre. This argument is true only for the dog and not for the cat[35] since, in the cat, atropine paralyzes the sympathetic as well as the chorda. The argument, as will be seen, depends on the assumption that the sympathetic causes secretion by action on the gland cells. This, as pointed out, is probably incorrect. The sympathetic produces its secretion by action on contractile tissue. There is, hence, no longer any reason to suppose that the gland cells have not been paralyzed by the drug. How it acts upon the cell is unknown, but the effect of that action is to prevent or diminish the passage of fluid through the cells. The variation in the susceptibility to its action of different glands in the same animal (compare the pancreas, salivary glands and kidneys of dog), or of the same gland in different animals (compare the pancreas of the dog and rabbit) points, I believe, toward an action on the gland cell itself, the variations in its action being due to variation in the chemical composition of the cells.

That atropine does act on the gland cell is, perhaps, indicated also by the action of its great antagonist pilocarpine. Pilocarpine, namely, produces a secretion of sweat two to three weeks after cutting the sciatic of the cat, when the nerve is totally inactive.[72 52 46] Luchsinger,[47] in commenting on this, says that this secretion must be due either (1) to action on the secretory cells themselves, or (2) to the non-degeneration of the nerve ends. The second possibility is impossible since these nerve ends are not provided with nuclei. A similar secretion may be obtained in the dog's salivary glands, fourteen days after cutting both chorda and sympathetic. The evidence is here not so conclusive since the submaxillary ganglion does not degenerate. In the sweat secretion, however, I believe the evidence is fairly strong that pilocarpine does act directly on the gland cell. It thus strengthens the evidence that atropine also acts on the cell.

There is also reason for believing that atropine acts in some manner on the capillary wall, thus reducing, or preventing the transudation of lymph. It might, in this way effect secretion from glands. This possibility has not received the attention it deserves.*

The evidence that atropine checks lymph transudation is as follows:

If atropine permitted the transudation of lymph normally ensuing on vaso-dilation, it would be expected that, after its injection, stimulation of the chorda would render the submaxillary gland œdematous, since fluid no longer passes into the secretion. Quite the contrary is the fact. I have repeatedly stimulated the gland all day, after the injection of atropine, without producing a trace of œdema. Heidenhain[25] himself says: "After atropine on stimulation of the chorda tympani no in-

* Heidenhain's reasons for rejecting the possibility that atropine checks lymph transudation and thus secretion will be found in Hermann's Handbuch. A striking instance of failure to consider this possibility is the following quotation from Langley:

"Atropine prevents the stimulation of the hilum from producing a secretion. Nicotine does not do this, therefore, atropine acts upon structures more peripheral than those acted upon by the nicotine. Since nicotine acts on nerve cells, and atropine does not act on gland cells, atropine must produce its paralyzing result by action on the secretory nerve endings."

crease in lymph flow occurs, even when during stimulation of the chorda the medulla is stimulated and the blood pressure greatly increased." Brunton in commenting on this says: "It appears to me that this circumstance can hardly be explained otherwise than by supposing that atropin not only paralyses the secretary fibres of the chorda, but acts upon the blood vessels in such a manner as to greatly diminish or prevent the exudation which would usually take place from them into the lymph spaces."

Heidenhain[23] supposed that lymph normally left the blood vessels on account of the secretory pull exerted by the gland cell. Atropine prevented lymph transudation by paralysis of the secretory chorda nerve ends. He was led to this conclusion chiefly by the following facts: (1) No more lymph normally leaves the blood vessels than passes into the secretion, and (2) if one inject 4.9% solution of sodium carbonate, 0.5% hydrochloric acid or quinine sulphate into Wharton's duct the chorda's secretory power is annihilated, but on stimulation the gland becomes highly œdematous. If, however, atropine be injected into the blood before the chorda is stimulated and after the injection of quinine into the duct no œdema ensues, however long the nerve be stimulated. I have fully confirmed these observations. The most probable interpretation of these facts, it seems to me, is that quinine prevents the passage of fluid through the glands by action on the gland cells, but does not prevent lymph transudation. That atropine, however, acts directly on the capillary wall, as well as upon the gland cell, in such fashion as to prevent lymph transudation and secretion.

A further indication that atropine checks lymph transudation is the diminution in thoracic lymph flow after its injection. Tschirwinsky[69] found that in morphinized animals thoracic lymph flow fell from 3.75 cc. to 1.5 cc. and from 10 cc. to 4.2 cc. in a given time. Atropine neutralized, also, the increased flow due to curare. In the latter case it fell from 9 and 10 cc. to 2.5 and 5.3 cc. in a given time. As there is reason to believe (Adami) that curare increases lymph transudation by direct action on the capillary wall, the inhibiting action of atropine may

be referred to an opposite action on the same structure. Not knowing of Tschirwinsky's work, I had already performed similar experiments on the lymph flow, comparing it with pancreatic flow on vagus stimulation and after pilocarpine. I found (Experiment V that atropine temporarily neutralizes the large increase in lymph flow which occurs concomitant with increased panceas secretion during rythmic stimulation of the vago-sympathetic after division of the cervical cord, and also neutralizes the increased lymph flow due to pilocarpine.

Experiment Vb.

Medium-sized dog. Ether. Temporary pancreatic fistula. Tracheotomy. Cervical cord cut. Artificial respiration. Thoracic duct prepared. Lymphatics of head and neck ligatured. Readings every minute in cubic centimeters :

Thoracic Duct.	Pancreas.	Thoracic.	Pancreas.	Thoracic.	Pancreas.
Vagi uncut.		.050	.009	.197	.009
.220	.02	.110	.013	.180	.004
.220	.02	.115	.012	.180	.008
.200	.02	½ hour interval.		.150	—
.200	.015	.120	.013	.190	.006
.180	.015	.119	.012	Rt. Vagus. Ryth. Coil 9.	
.180	.010	.090	.009	.200	.000
.190	.015	.130	.011	.180	.000
.160	.013	.120	.010	.100	.002
.180	.017	.110	.010	**.300**	**.068**
.155	.017	.100	.008	—	.025
.155	.018	.100	.009	—	.015
.170	.015	.102	.004	—	.015
Cut vagi in neck.		.100	—	Off.	
.280	.015	Clot.		.160	.020
.220	.010	1 shock per second.		.140	.010
.160	.005	Rt. Vagus. Ryth. Coil 10.		.150	.005
.100	.003	.150	.009	—	.010
.120	.007	.220	.006	Rt. Vagus. Ryth. Coil 9.	
.100	.009	.250	.010	.360	.006
.100	.010	.170	.005	.200	.009
.060	.015	.230	.010	.240	.005
.050	.020	Current off.		Coil to 4.	
.090	.010	.200	.005	.200	.005
.120	.015	.190	.007	—	.008
.120	.003	.220	.007	Off.	
.120	.007	220	.005	Clot.	0.15
.065	.010	.310	.002	"	.011
.125	.010	.210	.001	Left Vagus. Ryth. Coil 9.	
.100	.011	.180	—	.550	.030

Thoracic.	Pancreas.
.290	.005
—	.005
—	.005
—	.010
Coil to 6	.015
—	**.060**
—	**.090**
.240	**.100**
—	**.090**
Off. Then on by accident.	
.230	.060
Off.	
.140	.035
.170	.030
.160	.030
.120	.015
.170	.015
.130	—
.170	.010
Left Vagus. Ryth. Coil 6.	
.140	.007
.130	.002
.060	.009
.140	.090
.200	.120
—	**.130**
.290	**.140**
.235	**.110**
.280	**.130**
.235	**.130**
.250	**.080**
Off.	
.340	**.154**
.210	.116
.190	.052
.160	.043
.190	.020
.190	.020
.170	.025
—	.011
—	.014
.155	.015
—	.010
.150	.010
.150	—
Left Vagus. Ryth. Coil 6.	
.210	.010
.190	.000

Thoracic.	Pancreas.
.120	.005
—	.010
.175	.025
.225	.045
.250	**.055**
.220	**.110**
—	**.120**
.320	**.140**
.300	**.130**
Off.	
—	.115
.170	.065
.200	.030
.150	—
.200	.030
—	.020
—	.015
.140	.015
.140	.010
.145	.016
.135	.009
.130	.005
.160	.017
Left Vagus. Rythmical.	
.160	.002
.250	.008
.210	.000
.240	.001
—	**.015**
.300	**.075**
.300	**.035**
.270	**.045**
—	**.100**
.350	**.100**
.300	**.110**
—	**.140**
Left Vagus. Ryth. Coil 6.	
.220	**.110**
.280	**.070**
Off.	
.200	.070
.200	.050
.230	.020
.180	.025
.180	.030
.155	.005
.145	.005
Left Vagus. Ryth Coil 6.	

Thoracic.	Pancreas.
.270	.015
—	.005
.230	.005
.240	.000
— suddenly	.120
.250	.080
Inject .5 cc. atropin into supra-scap. vein	
Stimulation continued.	
.250	.050
.200	.070
—	.030
.180	.020
.140	.015
.145	.015
.155	.015
.110	.010
.120	.015
Off.	
—	.007
.120	.008
.130	.010
.5 cc. atropin.	
.080	.010
.040	.010
.090	.005
.100	.007
.100	.008
.120	.012
.100	.007
.100	.005
.110	.005
—	.006
Stim. Left Vagus. Coil 6.	
.070	.010
.100	.008
.120	—
.160	.002
.160	.000
.230	.000
.200	.000
.260	.000
.170	.000
.200	.000
Off.	
.250	.000
.170	.000
.190	.000

This experiment is of interest, not only as a clear confirmation of Pawlow and Mett, but because of the invariable increase in thoracic lymph flow occurring on stimulation of the vagus. I have repeatedly sought to obtain other experiments like it, but never with such success. The operation is long and apt to miscarry at some point.

Experiment XI.

Dog, etherized. Canula in thoracic duct. Readings in cc. every minute.

Thoracic duct.
.150, .220, .200, .180, .300, .230, .250.
1 cc. 1% pilocarpine into left femoral vein. Dog perfectly quiet.
.250, .300, .500, .600, .400, .460, .400.
1 cc. pilocarpine.
.490, .410.
1 cc. 1% atropine 1%.
.240, **.090, .060, .070, .170, .110,** .120, .090, .090.
Moved head.
.220.
1 cc. atropin.
.130, .100, .070, .060, .040, .120.
2 cc. pilocarpine.
.100, .080, .120, .130.
1 hour interval.
.160.

It is not without interest in this connection that pilocarpine, contrary to atropine, increases lymph flow. This was first observed by Tschirwinsky.[69] My own experiments have yielded a positive result generally, but not invariably. In all cases the dogs had divided cervical cords, and generally divided vagi. They were all under artifical respiration. The lymph was measured in cc. for equal intervals of time.

Experiment.	Before pilocarpine injection.	After the injection of 1–2 cgs. of pilocarpine.	Remarks.
11	1.53	3.00	7 minutes. Dog motionless.
29	2.44	6.09	Some movements of abdomen.
14	0.50	1.72	Motionless. 9 minutes.
4	1.55	10.40	Movements.
62	1.41	1.69	No movements. Pancreas did not secrete either.

In experiments 11 and 14 there were no visible movements. The flow of the seven minutes after injection in No. 11 was

double that of seven minutes before, and in experiment 14 was three times as great. In experiment 62, however, there was scarcely any difference.

The evidence presented in the foregoing pages, if not conclusive, certainly indicates that atropine restricts and pilocarpine increases lymph transudation. They may in this manner affect secretions. In any case, if the sympathetic causes its secretion by action on contractile tissue in the gland, there is no longer any reason against assuming that atropin acts directly on the gland cell, in such manner as to check the passage of fluid through it, and thus to prevent secretion.

d. The Action of Quinine and Nicotine.

We have considered the three main objections which have been raised against the chorda salivary secretion being an osmosis. There are, also, certain other phenomena which have been thought indicative of the independence of the secretory and dilator action of this nerve, and, hence, are worthy of a short criticism.

The first is the action of quinine, which when injected into the gland duct causes a temporary vaso-dilation, but no secretion. If, however, the chorda be stimulated, still greater dilation ensues and secretion takes place. This secretion is less than normal. Heidenhain[21] interprets this to mean that vaso-dilation cannot of itself produce a secretion, but that the secretory fibres must be aroused. (See literature reference No. 21, p. 85. Also reference No. 23, p. 45.)

The facts may, however, be otherwise understood. Quinine prevents the passage of liquid through the gland cell. This is shown by the fact that ultimately it prevents chorda secretion, even though the gland become œdematous. If the permeability of the gland membrane be thus diminished, the slight vaso-dilation caused by the drug may be insufficient to cause a secretion, whereas a larger vaso-dilation on stimulating the chorda might overcome this resistance. Another possibility is that the quinine reaches a portion only of the alveoli, poisons these, and throws their capillaries and arterioles into dilation.

On stimulating the chorda the secretion may be derived from unpoisoned alveoli of which the blood vessels have not hitherto been in dilation.

The value of Langley's and Heidenhain's observation, that the secretory fibres of the chorda tympani recover, after nicotine poisoning, before the dilator fibres, is seriously impaired by a defective method of determining whether vaso-dilation did, or did not, occur. If we admit that the rate of flow of blood from the gland's vein is a criterion by which we can determine whether vaso-dilation has or has not occurred their conclusion is justified. But reflection shows that if vaso-dilation be slight the amount of water passing out into the secretion might so reduce the bulk of blood flowing through the gland as to mask entirely all effects of the increased flow due to vaso-dilation. In fact, the flow of blood from the vein would be a safe criterion of dilation, only if there were no escape of liquid through the capillary wall, a condition which manifestly does not here exist. Langley's and Heidenhain's conclusion that the secretory function recovers before the dilator is, hence, unjustified. The same criticism applies, also, to Heidenhain's observation that after the chorda tympani has been cut and allowed to degenerate for three or four days stimulation still causes an increase in the paralytic secretion, but no increase in blood-flow from the vein.

c. Evidence of the Osmotic Character of the Salivary Secretions which are Accompanied by Vaso-dilation.

wish now to summarize briefly those features of secretions, accompanied by vaso-dilation, which indicate that they are of an osmotic character.

(1) In structure the salivary glands have all the requirements of an elaborate osmotic mechanism They are, essentially, extraordinarily thin-walled bags, possessing an enormous surface, containing a mass of hydroscopic indiffusible substances. The outer surface of this bag is in intimate association with a mesh work of capillaries so coördinated by the nervous system as to permit an almost instantaneous flooding of the gland mem-

brane. Plainly here are all the requisites of a delicate osmotic mechanism adapted to the most rapid osmosis.

(2) Chorda secretion is closely dependent on blood supply. (Compare p. 342.) Heidenhain has shown that partial occlusion of the artery diminishes the rate of secretion (p. 88, Breslau Studien IV.)

(3) If the osmotic equivalent of the blood be increased by the injection of strong salt solutions the secretion is diminished or altogether inhibited.[54 38]

(4) If the osmotic equivalent of the blood be decreased by the injection of water the rate of secretion is increased.[38]

(5) The rate of secretion is increased, other things equal, by an increase in the rate of blood flow through the gland.[38 23]

(6) The rate of secretion diminishes when the hylogens are washed out of the gland. (Paralytic secretions, secretion after long stimulation.)[23]

(7) Substances may be absorbed with extraordinary rapidity when injected into the duct (nicotine, atropine).

(8) If the percentage of salts in the blood be increased the percentage of salts in the saliva increases also. If the percentage of salts in the blood be decreased, the percentage of salts in the saliva decreases also.[38 54 14]

(9) If the artery of the gland be clamped for 20–30 minutes, and the blood thus completely cut off from the gland, on readmitting the blood a vaso-dilation ensues, so that the blood rushes red from the gland veins, and this vaso-dilation is accompanied by a spontaneous secretion. Stimulation of the chorda in no way alters this secretion during the first minute, nor until the dilation has somewhat diminished. This spontaneous secretion is a close duplicate of that observed by Levy in the secretion of sweat. [Experiment V (a).]

Although this spontaneous secretion might, perhaps, be explained by supposing that a direct stimulation of nerve-end or cell by the oxygen has taken place, it seems more probable to me to class it with the spontaneous secretion of sweat in the horse, following section of the cervical sympathetic, and to refer it to the direct effect of vaso-dilation.

f. Conclusion. The Physiology of Salivary Secretion.

If the sympathetic salivary secretion shall be found to be due to the action of contractile tissue, and if the criticisms of the objections to considering the salivary secretion, coincident with vascular dilation, an osmosis, be sustained by subsequent work, the following conclusions concerning the physiology of this secretion may be drawn.

The salivary glands may be caused to secrete, either by the action of contractile tissue under control of the sympathetic nerve or by osmosis under control of the vaso-dilator nerve. Probably in normal secretion both of these nerves come into play, but of this evidence is as yet lacking.

Drugs, or other reagents, may arouse secretion by action on either or both of these mechanisms. I would suggest that secretion following strychnine injection, camphor, pikrotoxin, physostigmin (after division of the chorda) are due to the contractions of the contractile tissue. All of these drugs stimulate the nerve centers and cause a pronounced vaso-constriction. On the other hand, pilocarpine, nicotine, muscarine, curare and chloral hydrate, or other drugs with a similar action on the vascular system, probably cause secretion partly by vaso-dilation and partly by increasing the permeability of the gland membranes. Such drugs work through an osmotic mechanism. A third class of drugs, such as quinine, atropine, hydrochloric acid or sodium carbonate may produce vaso-dilation, but probably act, also, on the gland cells in such manner as to diminish their permeability. Most of the work which has hitherto been done upon the action of drugs on salivary secretion needs to be repeated with the possibility in mind that the chorda and sympathetic induce secretion in these different ways.

The osmotic mechanism of secretion in the salivary glands is probably dependent on the condition of the gland and capillary membranes, upon the composition of the blood, upon the rate of flow of the blood and the character and amount of hylogens present within the gland. The evidence that the course of osmosis is controlled by the action of nerves directly on the gland

cells is open to serious criticism. That chorda salivary secretion can ensue without vaso-dilation may be seriously doubted, not only for the reasons already stated, but because in the pancreas there is good reason to believe that secretion can not take place without vaso-dilation. (See p. 361.)

V. SOME OTHER SECRETIONS.

The submaxillary gland, considered in the foregoing pages, may be taken as a type of all the salivary glands, as each possesses a dilator secretory nerve, and a constrictor, sympathetic secretory nerve. I wish now to consider some other secretion in the light of the conclusions derived from the physiology of the submaxillary.

a. The Physiology of Sweat Secretion.

There is reason to believe that the mammalian sweat glands also have a double mechanism of secretion, a muscular and an osmotic. These glands are surrounded by a sheath of muscle fibres lying, like those of the skin glands of amphibia, between the cells and the basement membrane. From the observations of Ranvier, Joseph and others, who have shown that upon stimulation of the sciatic this muscle contracts, there can be little doubt that a secretion may thus be formed. Probably sweat secretions ensuing coincident with vaso-constriction, upon the injection of strychnine, upon stimulation of the sciatic in the amputated limb or after compression of the blood vessels is due to this mechanism.

On the other hand, certain secretions of sweat are too copious to be due to muscular constriction of the gland. That those secretions probably fall under the second, or osmotic, mechanism is shown by the following facts:

(1) The coincidence of vaso-dilation and sweat secretion. Most sweat secretions are normally accompanied by vaso-dilation. If the cervical sympathetic of the horse be severed, strong hyperæmia and sweating occurs on the side of the neck the nerve governs. This sweating ensuing after nerve division

can hardly be explained, I think, on the basis of secretory cell activity.

(2) Pilocarpine, which does not cause contraction of the muscular sheath, causes a profuse secretion.

(3) The vaso-motor and secretory fibres in the cat follow the same paths.

(4) Pilocarpine causes sweat secretions fourteen days after nerve degeneration.

(5) If the blood supply be cut off, on readmitting the blood after 30 minutes, a spontaneous secretion occurrs.[44] The similar secretion in the submaxillary is invariably accompanied by vaso-dilation.

(6) Increasing the capillary blood pressure or drinking large quantities of water increases secretion.

The facts, as far as they go, are the same as those observed in the cerebral salivary secretions and pancreatic secretion. They justify us, I believe, in classing all three secretions in the same category. That these sweat secretions are of an osmotic character would thus be indicated. That other sweat secretions are due to muscle there can be little doubt.

b. The Secretion of the Pancreas.

Secretion of the pancreas is normally accompanied by vaso-dilation. In its relation to atropine, its increased content of organic bodies coincident with an increased rate of flow, and in taking place after compression of the aorta, pancreatic secretion resembles the submaxillary secretion on stimulation of the chorda tympani. There is reason to believe, however, that the pancreas cannot secrete unless the blood vessels dilate. Thus the means employed by Pawlow,[57] Mett[53] and Kudrewetsky[32] to give the vagi a secretory function are just the means used by Bowditch, Luchsinger and others[56] to give the sciatic and other mixed dilator and constrictor nerves a dilator action. These authors either cut the vagi and splanchnics, and allowed them to degenerate three or four days, or else they stimulated them with rythmic induction shocks, at the rate of one per second after division of the cervical cord. There are two possible ex-

planations of the fact that stimulation of the normal nerve with the cord undivided causes no secretion. Either the nerve carries inhibitory secretory as well as secretory fibres, or stimulation of the nerve is unable to cause a secretion without vaso-dilation. The first alternative Heidenhain has particularly combatted in the case of the submaxillary, and it appears to me lacking all proper experimental basis. The second alternative is probably the true explanation, for the reason that stimulation of the *normal* nerve below the cardiac branches causes no alteration in blood pressure, and for the reason that the treatment to which the nerve is subjected is calculated to give it a dilator action. If this be true the pancreas would appear fundamentally different from the salivary glands, unless, as I have endeavored to show, the latter are, also, in reality, unable to secrete on stimulation of the chorda or other cerebral nerve, unless vaso-dilation ensues.

Further evidence of the dependence of pancreatic secretion on vaso-dilation is furnished by the action of pilocarpine, chloral hydrate[19] and curare, drugs which cause vaso-dilation and secretion, and by strychnine,[19] or digitalis, drugs which cause vaso-constriction and inhibit secretion. Heidenhain,[23] also, has observed a close correspondence between vaso-dilation and secretion, and between vaso-constriction and the cessation of secretion. This parallelism between vaso-dilation and secretion can not be accidental. It indicates, I believe, that the dilation is the cause of the secretion, other things being normal.

VI. GENERAL CONCLUSION.

We have now considered the evidences of the existence of secretory nerves, and the reasons for believing that secretion is a function of the gland cells. While readily admitting the possibilities that secretion may in certain instances be a function of the gland cell, controlled by the action on it of secretory nerve fibres, we have seen reason to believe that certainly many so-called secretions are due not to the gland cell, but to the action of contractile tissue either within or about the gland. Among

such secretions are the salivary secretions following stimulation of the sympathetic, certain secretions of sweat, the secretion of the cephalopod salivary glands and of the skin glands of amphibia.

Whether those secretions which are normally accompanied by vaso-dilation, such, for instance, as the salivary secretions following stimulation of the cerebral nerves and the secretions of the alimentary tract and its appendages, are governed by nerves acting directly on the gland cells, or indirectly through the vascular system, cannot with certainty be said. But I believe it has been shown in the present paper that the evidence which has hitherto been offered that such secretions are controlled by nerve action on the gland cell is open to serious criticism. The remarkable parallelism between the hypothetical secretory and vaso-dilator fibres, the close dependence of such secretions on the vascular system, the general features of such secretions and the structure of glands, all indicate, I believe, that osmosis is the essential cause of these secretions, and that they are controlled by the action of nerves on the vascular system. No one would deny that the course of these secretions is modified by the condition of the gland or capillary wall, and that that condition is easily affected by drugs, but that nerve action directly affects that condition, I do not believe the evidence entitles us to say.

Probably the study of these secretions from the standpoint of osmosis will bring to light facts difficult to reconcile with our present knowledge of osmosis. But while our knowledge of the latter process through membranes undergoing chemical change, such as gland membranes, remains in its present fragmentary state, I do not believe that we are justified in assuming a special sort of secretory activity on the part of the gland, or capillary cell, unless the facts are certainly irreconcilable with any other hypothesis.

In short, while fully admitting the possibility that nerves may act on gland cells, in some way affecting osmosis through them, it appears to me that, in the present state of our knowledge of secretion, the assumption of a particular secretory function of

cells, and of special secretory nerves, is unwarranted, unnecessary, and, in certain particular cases, opposed to the phenomena of the secretion itself.

SUMMARY OF RESULTS.

(1) The sympathetic nerve induces salivary secretion by acting on contractile tissue in the glands and thus causing a compression of ducts and alveoli.

(2) The chorda tympani, or other dilator salivary, secretory nerve probably causes secretion by its dilator action on the blood vessels, thus increasing osmosis.

(3) The evidence that the chorda tympani acts on the gland cells is open to serious objections, as follows :

(*a*) Atropine probably acts directly on the gland cells and capillary endothelium, diminishing their permeability.

(*b*) The post-mortem chorda salivary secretion is possibly due to a back flow of blood from the veins owing to a dilation of the capillaries.

(*c*) The increased content of organic matter in a secretion coincident with an increased rate of secretion is of little value as evidence of secretory nerves, because (1) saliva is generally not a true solution, and (2) a weak stimulus probably arouses but a portion of the gland.

(*d*) The evidence derived from the action of nicotine and the degenerated chorda tympani that secretion may ensue on stimulation of the chorda without vaso-dilation is of doubtful value, because of an erroneous method of determining that vaso-dilation had not occurred.

(4) The sweat glands and the amphibian skin glands, like the salivary glands, receive a double nerve supply and probably possess a double mechanism of secretion, *i. e.*, a muscular and an osmotic.

(5) Whether secretory nerves exist or whether secretion is ever a function of the gland cell must be considered at present an open question.

(6) The thoracic lymph flow in dogs reacts to nerve stimula-

tion and drugs very similar to pancreatic secretion. It is increased by rhythmical stimulation of the vagi after division of the cervical cord and by pilocarpine and chloral hydrate, and decreased by atropine.

COLUMBIA UNIVERSITY, April, 1898.

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