HUMAN PHYSIOLOGY

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HUMAN PHYSIOLOGY

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IN FOUR VOLUMES

VOL. II.—INTERNAL SECRETION—DIGESTION—EXCRETION—THE SKIN

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ERRATA

VOL. I

Page 6, bottom line, for "quantitatively" read "qualitatively."
,, 25, line 25, for "cornea" read "stratum corneum."
,, 35, line 3 from below, for "glycerin" read "glycerol."
,, 109, line 27, for "carbon disulphide" read "ammonium sulphide."
,, 127, line 3 from below, for "Connstein" read "Cohnstein."
,, 157, heading 3 should precede "Question."
,, 173, fig. 48, last word, for "distend" read "collapse."
,, 219, bottom line, for "rises" read "falls."
,, 238 is mispaged 328.
,, 239, fig. 90, for "Mosso" read "Marey."
,, 333, line 7 from below, for "afferent" read "efferent."
,, 415, line 13, for "inspiratory" read "expiratory."

VOL. II

Page 28, line 1, and page 52, line 5 from below, for "Christiani" read "Cristiani."
,, 73, line 10 from below, for "haemodrometer" read "haemodromometer."
,, 210, line 6, for "Ch." read "Cl." (Bernard).

CHAPTER I

INTERNAL PROTECTIVE SECRETIONS

CONTENTS.—1. Theory of glandular organs and secretory processes. Historical development (Malpighi, Ruysch, Haller, J. Müller). 2. Glands with no excretory ducts; their importance as organs of internal secretion. 3. Structure and mode of secretion of thyroid and parathyroid glands. 4. *Cachexia thyreopriva* after total thyroidectomy in man: analogy with spontaneous myxoedema and cretinism. 5. "*Tetania thyreopriva*" in man. 6. Varying effects of thyroidectomy in various animals. 7. Criticism of hypotheses put forward to explain effects of thyroidectomy. 8. Experimental basis for theory of auto-intoxication resulting from functional deficiency of thyroids. 9. Thyroid grafts: injection of thyroid juice and thyroid feeding in therapeutic treatment of *cachexia thyreopriva*. 10. Theory of specific functional independence of thyroid and parathyroids. 11. Specific protective function of pituitary gland (glandular portion of hypophysis). 12. Structure of suprarenal bodies (adrenals) and paraganglia. 13. Clinical observations and physiological experiments on protective function of the suprarenal bodies. 14. Double function of medullary (or paragangliar) and cortical part of suprarenals. 15. Experimental injection of suprarenal extract. 16. Active principles of suprarenal and paragangliar system (adrenaline, paragangline). Physiological action. Bibliography.

IN the last chapter (Vol. I. XIV.) we discussed the formation of lymph through the walls of the blood capillaries, and the physiology of the lymphoid tissues and organs (which continually pour out new cells, as well as the chemical products of their anabolism and katabolism, into the lymph and blood stream), and referred in general terms to the physiological concept of the so-called *secretory processes*. If *secretion* means every alteration by the tissue-cells of the medium in which they live—either by the removal from it of all the materials required for their nutrition, or by the return to it of all the products of their metabolism—we should obviously have to admit that every living cell, as such, exhibits secretory activity (Brown-Séquard). But the concept of secretion must be taken in a more restricted sense. The term *secretory* is not applied to the cells which form the nervous and muscular tissues, nor, speaking generally, to the active and passive mechanisms of sensation and movement, while it is used of the histological elements that participate actively in the production and purification of the blood and lymph, particularly the epithelia

of the tissues and glandular organs. This differentiation between the two kinds of cells arises from the fact that while in the former the exchange of materials with the medium (blood and lymph) is the means, or condition, of the development of other forms of energy, and is subservient to other special functions, in the latter, which are known as "secretory," this exchange is the specific function—hence it is more prominent, and assumes a distinctive character.

From this point of view the physiological concept of *secretion* is entirely independent of the morphological concept of *the gland.* In so far as the cells of the lymphoid or adenoid tissues and organs considered in the last chapter have a lymphapoietic and haemapoietic function, they are true secretory tissues and organs, though destitute of glandular structure proper. But they are intercalated along the lymph- and blood-vessels, with which they communicate directly, and into which they pour their cytological and chemical products, while *gland,* in the widest sense, implies a complex of *secreting epithelial cells,* which form the walls of cavities that are quite distinct from the lymph- and blood-vessels, and in which the *secretion, i.e.* the product of their secretory activity, accumulates.

The physiological study of the adenoid tissues and glands is thus logically succeeded by that of the glandular tissues and organs proper.

I. Midway in the eighteenth century, Albrecht von Haller, speaking of the functions of the glandular organs, observed: *multa in physiologia obscura; obscurius hac ipsa functione nihil.* So long as the structure of the glandular organs was imperfectly known, physiological theories as to the secretory processes were necessarily vague and confused, and highly speculative in character. To cite a classical example: the ancients long held that the *pituita,* or nasal mucus, was a secretion of the brain, that flowed through the lamina cribrosa of the ethmoid. The error was only corrected in 1660, when Schneider described the mucous membrane which bears his name.

At the same period the anatomy of the glands was more closely studied by Glisson, Wharton, Wirsung, Stensen, Rivini, Peyer, and Brunner. Malpighi (1665) was the first who investigated their internal structure. He stated that all the glandular ducts terminate in acini (*grana glandulosa*), which receive their juices from the minute blood-vessels by which they are surrounded, and that the juices collected within the acini were then poured out through the excretory ducts.

Ruysch (1696) disputed this theory, and maintained, on the strength of fallacious arguments derived from his celebrated artificial injection of the glandular vessels, that the gland substance proper is also composed of blood-vessels, and that the

finest terminal ramifications of these vessels (where no blood corpuscles can penetrate) are in direct continuity with the origin of the excretory ducts.

Haller (1757) decided the controversy between Malpighi and Ruysch in favour of the latter, and tried to re-establish the ancient doctrine, by which the arteries terminate in the form of open mouths, either in the excretory ducts, or in the so-called cellular tissue, in the lymphatic sinuses, the skin, etc. The argument on which he founded this unfortunate theory (which contradicted Malpighi's discovery of the capillary vessels as a completely closed system uniting the arteries with the veins) was the passage of injection masses, as performed by Ruysch, from the blood vascular system into the excretory ducts of the glands, and the haemorrhages simultaneously observed in the excretory canals. Haller's doctrine, based on imperfect morphological data, held its own for many years, until it was overthrown by the masterly monograph of Johannes Müller, *De glandularum secernentium structura penitiori* (Lipsiae, 1830). Müller's wide anatomical and embryological observations on the various secretory organs found in the different classes of vertebrates, laid the foundations of modern glandular morphology, and from this he deduced the physiological concepts of his classical treatise. Its most characteristic points are briefly as follows:—

(*a*) Whatever differences of structure exist in the glands of animals and man, they all obey the same laws, and present an uninterrupted series from the simplest follicle to the most complex gland.

(*b*) All glands present internally a large secreting surface, obtained in an immense variety of forms. In all, however, the surface extension is due to development of the excretory ducts in the form of internal cavities or blind canals, as held by Malpighi.

(*c*) In all glands, the blood capillaries behave in respect to the walls of the canals and extremities of the glands as to every other thin secreting membrane. They do not open by orifices into the secretory spaces or cavities, but form a close capillary network round them, which unites the dendritic ramifications of the arteries and veins, as held by Malpighi.

(*d*) Secretion is only a particular mode of the metamorphoses which the blood undergoes in circulating through the organs. The most complicated gland is but a large surface adapted to the smallest possible space, through which transformation of the blood takes place. Secretion does not occur only at the extremity of the glandular ducts, in the *acini*, supposed hypothetically to exist in every gland. Acini, in the sense of closed vesicles, are present only in a very small number of glands. Secretion takes place throughout the length of the glandular canals.

(*e*) The special characteristics and differences in the secretions depend not on any external and mechanical change, nor upon the anatomical form of the gland, but solely upon the specific character of the living organic substance (epithelium) which invests the internal secreting ducts. The difference in secretions depends, therefore, upon the same cause which determines differences of conformation and of life of the organs in general: there is but one difference, *i.e.* in the one case the altered blood is incorporated with the organ, in the other it passes beyond its limits, and appears externally to it, in the form of secretion.

(*f*) The chemical processes carried out in the secretory organs are twofold. On the one hand, they serve the nutrition, development, or formation of new cells; on the other, the formation of a heterologous product of secretion. The secreting cells differ chemically from the product secreted, although they may contain a small amount of the latter. Secretion cannot, therefore, be explained as a simple liquefaction of the pre-existing molecules of the secretory elements. We must assume that the products of secretion are gradually perfected in what may be a long journey through the canaliculi of the gland.

This conception of the general morphology and physiology of the secreting glands as formulated by Johannes Müller still holds good, and is a fitting introduction to the special study of the functions of the individual organs and mechanisms of secretion. Subsequent work has supplied a wealth of details, but all are in harmony with the general doctrine of the great master, which may be summed up in the statement that what fundamentally underlies each secretory process is *the specific physiological activity of the living substance by which the secreting surfaces are invested.*

After Schwann had established the Cell Theory in 1839, and it had been applied by Henle and Kölliker to the physiology of secretion, the idea of the *living substance*, as described by Johannes Müller in 1830, was more exactly conceived as the *living epithelial cells which clothe the internal cavities and the secreting surfaces.* Real knowledge of the intimate secretory processes of the gland cells only became possible, however, after the progress of histological technique enabled Heidenhain and his School to form a morphological comparison between glands in the state of rest, and those functioning actively.

A more palpable advance in regard to the specific nature of the secreting cells resulted from the chemical analyses of the various products of their secretory activity, undertaken by a host of observers. Advance in this direction has gone *pari passu* with that of chemical physiology. Much, however, in regard to the chemical composition of the secretions still remains incomplete and imperfect, and what we know at present is little in comparison with what remains to be learned—except for certain secretions

which it is possible to obtain in large quantities (*e.g.* urine, milk, bile), and which have accordingly been the subject of numerous and exhaustive researches.

The progress of physics again (particularly Dutrochet's theory of the phenomena of diffusion through permeable membranes, the kindred phenomena of imbibition, capillarity, filtration, the modern doctrine of osmosis through semi-permeable membranes, the molecular concentration of solutions, the isotonicity of animal fluids) has stimulated physiologists in the task of reducing the phenomena of secretion as far as possible to common mechanical principles. In this laudable attempt Ludwig is pre-eminent. As we shall see, he founded a mechanical theory of renal secretion that still holds its own in physiological text-books, and accounts for the fundamental phenomena that accompany the formation of urine. Generally speaking, however, it must be admitted that in the actual state of science we are very far from any mechanical concept of the secretory processes taken as a whole. All the forces brought into play with this object are confronted by the enigma of the *metabolic activity of the living cell*, so that the teaching of Joh. Müller stands firmer nowadays, after all the vigorous attempts that have been made to overthrow it, than in 1830 when it was first formulated.

II. The simplest glands, from both the morphological and the physiological point of view, are represented by epithelial tissues, which form alveoli or perfectly closed spaces, *i.e.* are destitute of excretory ducts by which the secretion is poured out either to the cutaneous surface, or to the inverted mucous surfaces (of the digestive tube, respiratory passages, genito-urinary apparatus). Since all *external secretion* is excluded by the absence of excretory ducts, it is evident that these closed glands are capable of *internal secretion* only. Their secretions collect in the glandular spaces, and in proportion as they acquire a certain tension pass through the pores or interepithelial spaces into the periglandular lymph spaces, or are directly absorbed by the network of blood capillaries that surrounds the epithelial layer.

These closed glands have therefore a structure and in all probability a function highly similar to that of the lymphoid tissues and organs discussed in the last chapter. Morphologically, they differ only in having epithelial cells as their essential substrate, while they do not communicate directly, and are not intercalated along the lymph and blood paths, but form quite distinct glandular spaces: physiologically, they differ because they do not contribute to the formation of the primary cytological and chemical elements of the blood and lymph, but represent special factors which modify the constitution of these two fluids, so as to adapt them to the normal life of the body as a whole.

The recognition of the vast importance of the secretory function

of this group of glandular organs constitutes one of the finest achievements of modern experimental physiology. It more particularly includes the physiology of the thyroid gland, the parathyroids, the hypophysis or pituitary gland, the suprarenal capsules, the paraganglia; to the same category belong also the pineal gland, the carotid glands, and the coccygeal gland, of which the functional significance is still unknown.

III. The Thyroid Gland (more correctly *glandula thyreoidea*) is in man a single organ, in colour dark red shading into yellow, which lies at the sides and in front of the larynx and the two first tracheal rings. Two lateral lobes and a median isthmus can be distinguished, above which rises a slender conical process (Morgagni's pyramid) which is attached to the thyroid bone by a

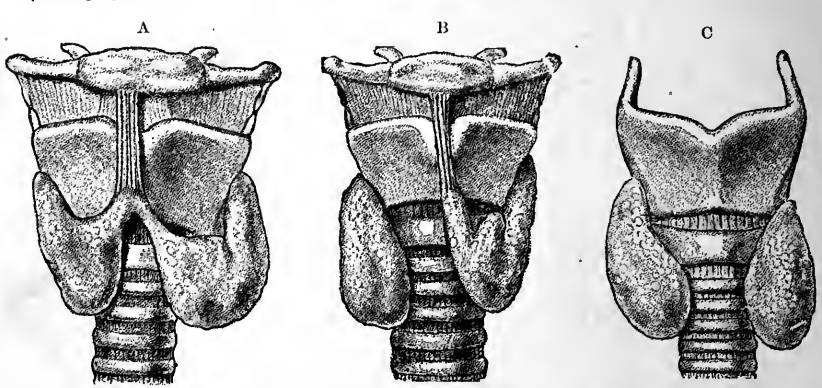

FIG. 1.—A, Human thyroid gland, showing bifurcation of lower end of pyramidal process, one part going to each lateral lobe. B, the same, with pyramidal process attached to left lobe of gland; isthmus absent. C, the same, with pyramidal process and isthmus absent. (C. F. Marshall.)

fibrous and muscular band (Fig. 1, A). It varies considerably in size, the weight seldom exceeding 30-40 grms. It is generally more developed in females than in males, and often swells at the periods of menstruation.

In the cat, rabbit, guinea-pig, and rat, the isthmus joining the two lobes is represented by a very slender band of thyroid tissue; in the dog, on the contrary, the two lobes are almost always separated, as, by a congenital anomaly, may also occur in man (Fig. 1, B and C). The isthmus is almost always well developed in the ape, as also in ruminants.

The thyroid is invested by a transparent capsule of dense areolar tissue which connects it loosely with the adjacent parts, and penetrates to the interior, separating the substance into small lobules of unequal form and size. When cut into, a yellow, sticky fluid escapes from the surface, which had previously been contained in a multitude of closed vesicles or follicles surrounded

by areolar connective tissue, and richly provided with blood and lymph vessels. The size of the vesicles varies considerably; the largest may be one millimetre in diameter, so that they are visible to the naked eye. They are rounded or oval in form, with a wall consisting of a single layer of cubical or columnar epithelial cells, which are the secreting elements (Fig. 2). According to Langendorff two kinds of cells can be distinguished: "Hauptzellen," which have sharp outlines and shining, finely granulated protoplasm; "Colloidzellen," which have indefinite outlines and protoplasm filled with large granules, shown by their affinity for certain pigments to consist of colloidal substance. The first are young cells that secrete by exudation;

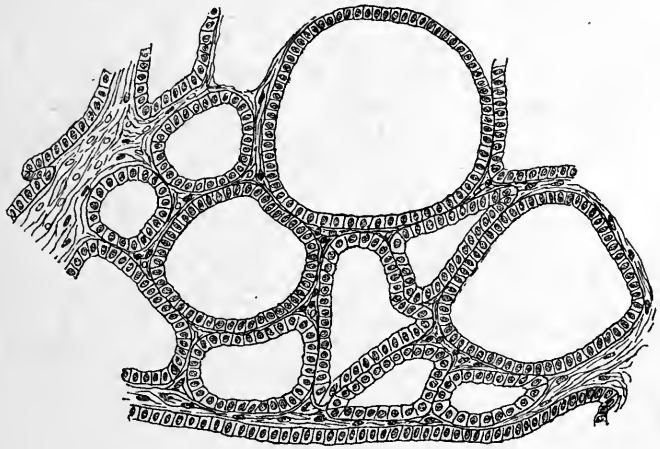

FIG. 2.—Thyroid gland of infant. Vesicles of various sizes, lined with single layer of cubical epithelial cells.

the second are older and exhibit a marked secretory activity, during which they liquefy and break up, so that both protoplasm and nucleus pass into the secretion. In fact, the colloid fluid of the alveoli contains both the old disintegrated epithelial cells, and leucocytes that have emigrated from the blood capillaries, as well as erythrocytes in process of destruction and discoloration.

Lübcke (1902) concluded from histological observations, more particularly of fresh preparations of the gland, that the so-called "colloid" cells are only artificial products, due to the diffusion of the contents of the vesicle in and around the atrophied epithelial cells. In any case they would not represent the secreting cells. According to this author the thyroid vesicles contain a homogeneous fluid, which is not shiny, and is quite distinct from the protoplasm, being watery or gelatinous in consistency. It can be washed out

with water, and coagulates after death, when it resembles the fixed content of the vesicles.

Lewandowsky (1902) came to the same conclusion from histological work on the thyroid of dog, cat, rabbit, ape, lamb, and hedgehog. He found that the secretion from the vesicular epithelium was quite fluid, and indistinguishable under the microscope from other protein solutions. According to this, there are no colloid cells which secrete preformed colloidal substances. This secretion first assumes the properties of a colloid in the vesicular lumen.

The blood-vessels, which are numerous and large in proportion to the size of the organ, penetrate the cavities of the interstitial connective tissue, where they ramify rapidly, and come into intimate relations with the walls of the alveoli, round which they form a capillary network that is in perfect contact with the epithelium. The lymphatics arise from the spaces of the interlobular and interalveolar connective tissue, forming a number of large trunks that anastomose into plexuses at the surface of the organ.

The nerves that supply the thyroid come from the two laryngeals, superior and inferior, from the vagus, and from the superior cervical ganglion of the sympathetic. Their mode of termination in the muscle cells of the vessels and in the epithelial cells is unknown.

Embryology shows that the thyroid originates from three epithelial diverticuli of the primitive intestine, two of which form the lateral lobes, and the third the isthmus and pyramid of Morgagni. The epithelial cells of the three diverticuli are grouped into small masses which are then transformed into vesicles or alveoli. The peripheral cells of each mass constitute the epithelium of the alveolus; the central cells become granular, and on breaking up form the colloidal content of the primitive alveolus.

The primitive epithelial masses are mainly grouped together to form the principal thyroid gland; but there are almost invariably certain nodules which do not fuse with it, and which give rise to small *accessory thyroids*,—these in the successive phases of embryonic development may wander to a considerable distance from their origin and enter into relation with various organs derived from the cephalic end of the foetus. On a careful computation of the accessory thyroids found in various places, they exist in the tongue and in the sub-maxillary, retro-pharyngeal, retro-oesophageal, laryngo-tracheal, hyoid, crico-thyroid, bronchial, aortic, and mediastinic regions (D'Aiutolo, 1890). The accessory thyroids are perfectly similar in structure to the principal thyroid body, and they also exhibit alveoli filled with colloidal substance, blood-vessels, lymph spaces and vessels, and nerve filaments.

The Parathyroids (*glandulae parathyreoideae*) differ completely

in structure (as well as function, *infra*) from the accessory thyroids. They were first described by Sandström (1880) in man and certain other mammals, externally to the lateral lobes of the thyroid body. Subsequent observations confirmed their constant presence in mammalia, adding to the *external* parathyroids other similar little glands situated on the mesial surface of the lateral lobes of the thyroid, the *internal* parathyroids, which, however, may be absent in certain species (Fig. 3).

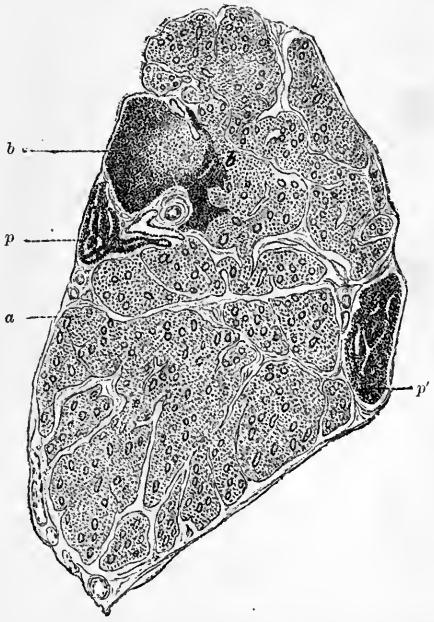

FIG. 3.—Transverse section of left lobe of thyroid from a two-months' kitten. (Kohn.) *a*, thyroid tissue; *b*, thymic tissue; *p*, *p'*, inner and outer parathyroids.

In man the outer (also called the inferior) parathyroids lie in front of the inferior thyroid artery and the recurrent nerve. Their position is not constant. For the most part they are situated at the inferior angle of the thyroid lobes, towards the lower part of the postero-external border, at a greater or less distance from it, and closely united by fine connective tissue. More rarely they are found at the level of the eighth and tenth tracheal ring (Fig. 4). It follows that in excising the thyroid body in man by the subcapsular method, the inferior or outer parathyroids are easily left *in situ*—a fact which, as we shall see, is of great clinical and physiological importance.

The inner (or superior) parathyroids are situated on the internal surface, towards the upper pole of the thyroid lobes, with which they are intimately connected, since they are wrapt in a common sheath of connective capsular tissue, and sometimes lie in the depth of the thyroid substance. In surgical thyroidectomy these must obviously be excised along with the thyroid body.

The structure of the parathyroids (both outer and inner) differs from that of the principal and accessory thyroids. They consist not of hollow vesicles, but of compact masses or columns of epithelium cells, which sometimes anastomose into branching cords. Between the cell masses there are septa of connective tissue, which convey the blood-vessels and nerves into the gland substance (Fig. 5).

The epithelial cells which form the specific substance of the parathyroids are columnar or polyhedral in shape; they have a

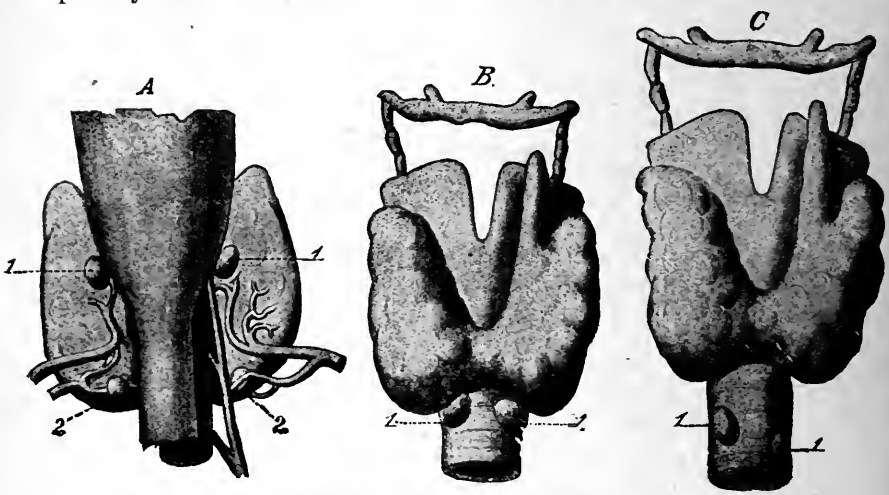

FIG. 4.—Human thyroid and parathyroid glands. *A*, from behind; *B* and *C*, from in front. *A* 1, Superior parathyroids; *A* 2, inferior parathyroids: *B* 1 and *C* 1, inferior parathyroids.

small roundish nucleus which may exhibit karyokinesis. According to Vassale and Generali the cytoplasm of the cells is sometimes

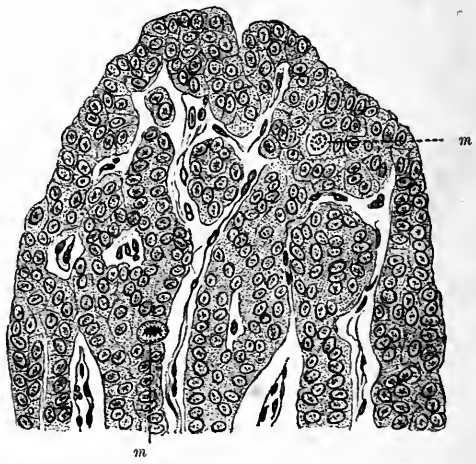

FIG. 5.—Part of external parathyroid of last figure. (Kohn.) $\frac{5}{9}$. Shows epithelial cells arranged in columns, with intervening septa of connective tissue; *m*, *m*, cells in mitotic division.

clear or finely granular and does not stain, sometimes it has coarse stainable granules. In all probability these represent two different stages of functional secretory activity.

Livini (1900) showed by histological methods that the parathyroids are fundamentally composed of epithelium cells, which are gland cells proper. These cells elaborate two different substances; one, the principal, appears in the form of granules or masses varying in size, which stain an intense green like colloid substances with Galeotti's method; the other, in the form of minute granules, stains bright red, like the chromatin of the nucleus. The parathyroid secretion is poured out into the pericellular lymph spaces, and reaches the blood by way of the lymphatics.

In certain animals small nodules of adenoid tissue with the structural character of the thymus gland (Fig. 3) are associated with the parathyroids, which suggests a common embryological origin. Livini, however, demonstrated that the cells of these masses (known as the *thymic lobules*) are epithelial cells for internal secretion, rather than lymphoid cells. He found, in fact, that they produce a substance which completely fills the thymic lobule, and usually increases its size. These modifications in the cell mass are attended by serious nuclear disturbances, which eventually lead to the dissolution of the cells. It is worth noting that this secretory product gives the same reaction as the principal product elaborated by the cells of the thyroid and parathyroid glands.

According to Prenant and Fusari, the *external* parathyroids have a common origin with the thymus, the *internal* with the lateral lobes of the thyroid. The mode in which this transformation of the structure and specific character of the epithelial cells is effected is unknown. In any case, we must exclude the idea (which in the abstract appears rational enough, and which was propounded by Gley) that the parathyroid is merely embryonic thyroid tissue, which in the course of its development may be transformed into the latter. The thyroid and parathyroid are two structures specifically distinct in character, and they cannot be vicariously substituted for one another (*infra*).

That both thyroid and parathyroid are secreting glandular organs, and that the colloidal substance collected in the vesicles is destined to be absorbed from the interfollicular lymph channels, has been established by the histological work of Biondi with Heidenhain (1889), Langendorff (1889), and a long series of other observers, among whom are Vassale and Brazzà, and Galeotti, in Italy. As early as 1839 King demonstrated on dead bodies that it is possible by exerting a certain pressure on the thyroid to express the colloidal content of the vesicles into the lymphatics that issue from the gland. Kohlrausch (1853) and Baber (1876) showed under the microscope the presence in the intervesicular lymph channels of colloid substances similar to that contained

in the vesicle. Later workers have tried by various modes of staining to determine the nature of the epithelial secretions and the paths by which the secretion penetrates the lymphatics. In this connection Langendorff's results are very interesting. He holds that the protoplasm of the colloid cells degenerates, passing into the secretion along with the nuclei, and leaving stellar interstitial spaces between the principal cells, through which the secretion passes freely into the lymphatics (Fig. 6). When the vesicle is emptied its epithelial cells close up again, and once more present a complete cavity, which in its turn forms outlets for the secretion by the above process. In the lymph channels the secretion is diluted by gradual admixture with the lymph, which carries it away to the circulation.

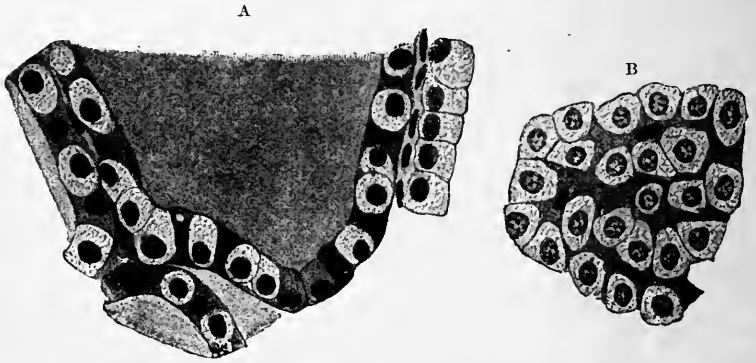

FIG. 6.—A, Segment of thyroid follicle from puppy. (Langendorff.) Treated with Friedländer-Zeiss osmic-haematoxylin method, homogeneous immersion. Numerous cells are seen in colloid degeneration, distinguished from the principal cells by their dark colour. B, same preparation. Superficial view of principal cells and colloid cells. The colloidal cells adhere together to form a network; they are attenuated, with occasional nuclei, which are flattened and stain more deeply than those of the principal cells.

According to Lewandowsky, as stated above, the secretion of the vesicular epithelium is not the colloidal substance but a mother substance, from which the colloid is formed. It is, he says, the mother substance that passes into the lymph or blood vessels. But the passage of true colloidal substance from the vesicle into the lymphatics has never been proved, while on the other hand it is not uncommon for a colloidal substance to form in the lymph spaces.

There are no glandular spaces in the parathyroids analogous to the vesicles of the thyroid. We must therefore conclude that the secretions from the epithelial cells are absorbed in the lymph channels as fast as they are formed. The observations of Mazziotti and Capobianco (1899), particularly those on the parathyroids of the cat, give interesting details in this connection. They find that the blood-vessels which irrigate the epithelial cells contain a

number of leucocytes in excess of the normal (as compared with the erythrocytes), and that perivascular lymph spaces exist round them, which are often wider than the vessels and show a network of connective filaments coming from the adventitia. They regard these perivascular spaces as the outflow of the parathyroid secretion, masses or lumps of a granulated substance being sometimes noted, which stain like colloidal substance.

IV. The physiology of the thyroid and the modern conception of it as a glandular organ of internal secretion, indispensable to normal life, is derived from surgery. After the introduction of antisepsis, thyroidectomy was attempted in cases of goitre, and the effects observed. As early as 1856-57, indeed, M. Schiff, in a series of experiments on total thyroidectomy in animals, noticed that it was frequently fatal in dogs after the first week, in guinea-pigs somewhat later, although death could not be referred to the state of the wound nor to lesions of the recurrent branch of the vagus, nor of the cervical sympathetic. But he gave no adequate account of the phenomena by which death is preceded, and abandoned his researches, owing probably to the inconstancy of the results, since he found that rabbits, some rats, a dog, and several guinea-pigs survived the operation.. It was not till after the publications of the two Genevese surgeons, Reverdin, and Kocher, a surgeon in Berne (who in 1882-83 described the effects of total excision of goitre), that these experiments were repeated. The credit of directing the attention of physiologists to this important subject is accordingly due to surgery.

We will first review the phenomena of *deficiency* of the thyroid gland, starting with all the best-known surgical cases, which may be regarded as so many physiological experiments performed on man.

Patients who have undergone total thyroidectomy, and have already been discharged from the hospital as cured, experience the initial symptoms of glandular deficiency either at once or at latest some weeks after the operation. They feel weak, complain of heaviness of the limbs, and more or less diffuse dull pains, particularly in the legs, which may become acute and assume the character of pains in the bones.

Other more serious symptoms are gradually associated with the preceding. After four to five months the face and the extremities swell and become cold, the muscles are torpid, sometimes rigid, often exhibiting muscular tremors, and are incapable of carrying out any delicate manual acts with precision. At first the swelling is variable; it is more pronounced in the morning than in the evening, but steadily increases, until it becomes permanent. It is not ordinary *oedema*, in which percussion with the finger leaves a depression; it is a hard and elastic swelling. It is specially localised in the hands, feet, and face, where it produces a

characteristic alteration of the countenance. The lower eyelids are the first to present a sacculated semi-transparent swelling, which is hard to the touch; then the infiltration spreads to the folds of the face, which become smoothed out; to the nose which gets rounded; to the lips which swell, and bulge outwards, saliva dribbling from them. The features are coarsened and expressionless like those of a *cretin*.

The mental functions accord with this appearance, since they are blunted, so that the patients lose their memory, become deaf, taciturn, melancholy, self-absorbed, and reply extremely slowly to questions. They further complain of slight but perpetual headache; feel an almost constant sensation of cold, which is most acute at the extremities; at times they are seized with vertigo, and may even lose consciousness.

All these symptoms become still further aggravated. The whole body may grow more bulky from the extension of the swelling. The skin loses its elasticity, can only be picked up in large folds, and becomes dry owing to defective capacity for sweating. The epidermis desquamates in more or less extensive lamellae, particularly on the hands and feet; the hair turns grey, falls out, and gets constantly thinner.

The heart functions weakly, but with ordinary rhythm; the pulse is small and thready. Examination of the blood shows nothing constant; but there is often a more or less pronounced and progressive oligocythaemia, which undoubtedly contributes to the characteristic pallor of the skin, this being of the earthy, yellow-spotted hue peculiar to cretins.

The respiratory rhythm is almost always normal; the digestive apparatus functions well, as also the urinary system. The spleen is not enlarged.

When thyroidectomy has been performed during adolescence, one of the most serious effects is the arrest of development. A boy on whom Sick operated at the age of ten, had at twenty-eight become a cretin whose height was only 1·27 metres; a similar case was described by Schmidt; and the same phenomenon appeared in a lesser degree on a third person, on whom Julliard operated at the age of seventeen.

This complex and characteristic syndrome of morbid phenomena, as described by Kocher, is now generally known by the name of *cachexia thyreo-* or *strumipriva*, *i.e.* cachexia consequent on complete ablation of the thyroid gland.

In 1874 Sir William Gull presented to the Clinical Society of London five cases of a disease which presented a morbid syndrome closely resembling that of cachexia thyreopriva. In 1878 W. M. Ord described five other cases of the same disease, to which he gave the name of *myxoedema*, derived from the constant symptom of thickening and swelling of the skin, as manifested especially in

the face and limbs, which he proved to be due to a pronounced accumulation of mucin in the subcutaneous connective tissue. He observed that the disease was accompanied by a shrivelling of the thyroid, and the destruction of its follicles by proliferation of the connective tissue; but he did not suspect that this degeneration of the gland was the internal cause of the myxoedema. He further noted the numerous analogies between myxoedema and *cretinism*; but did not regard the latter as dependent on the alterations of the thyroid.

It was the cousins Reverdin who recognised these relations, more particularly the great resemblance between the phenomena of *spontaneous myxoedema* and *cachexia thyreopriva*, to which they gave the name of *operative myxoedema*. Kocher, on the other hand, particularly emphasised the points of contact between *cretinism* and *cachexia thyreopriva*. In 75 per cent of the cases, cretins exhibit goitre with thyroid degeneration; and in cases in which there is no goitre, absence of this gland has been noted (Curling). In many non-goitrous cretins Kocher verified its absence by palpation, or at least such a diminution in its volume that it was not perceptible to touch. It is not surprising that the resemblance between cretinism and cachexia thyreopriva should be incomplete, seeing that cretinism is a congenital disease, and is almost always hereditary. But they may legitimately be grouped together, since in both the disease depends on a defective or insufficient function of the thyroid gland.

V. Following the initiative of the Swiss surgeons, the excision of the thyroid in cases of goitre was practised by many, notably by Billroth in the Vienna clinique. The results differed from those described by the cousins Reverdin and by Kocher, in that the morbid syndrome of slowly developing cachexia thyreopriva was frequently replaced or accentuated by acute phenomena of "*tetany*," which usually caused the rapid death of those operated on. Out of 53 cases of total thyroidectomy for goitre, reported on by von Eiselsberg in 1890, there were 12 cases of tetany, 8 with fatal results. In 8 cases operated on by Mikulicz 4 were attacked by tetany. Since the first 13 cases of tetany collected by Weiss were all very young women, it seemed as if this complication were peculiar to females. Subsequently this was found to be erroneous, cases of tetany having also been observed in young males by Kocher, Mikulicz, Hicquet, and Walkowitsch. Tetany is more frequent in women than in men, because cases of goitre are notoriously more frequent in females, and the majority of individuals operated on accordingly belong to that sex.

"*Tetania thyreopriva*" may appear on the day of operation; more frequently it commences on the second, the fifth or sixth, or at latest on the tenth day after the operation (Weiss). It begins with muscular cramp which is usually localised in the limbs, and

particularly in the flexor muscles of the hand and forearm; soon, however, the spasms invade other muscular groups, inducing lock-jaw, blepharospasm, cramp of the tongue, trachelismus, opisthotonus.

The tetanic spasms are preceded, accompanied, or followed by tachypnea and tachycardia, with a concomitant rise of temperature of 2-3° C. Sometimes the neuro-muscular super-excitation assumes the form of clonic-tonic epileptoid convulsions, consciousness being retained. This is generally the most serious symptom of tetania thyreopriva, and sets in shortly before death.

Unlike simple cachexia, post-operative tetany seldom exhibits sugar or even albumin in the urine.

The course and outcome of tetany varies. It may consist in one or more severe attacks, leading rapidly to the death of the patient. In other cases it may be protracted for many days and even months, when less acute attacks are observed from time to time, which may be followed by the slowly developing phenomena of cachexia thyreopriva. In other cases, again, tetany in a more or less intense form may appear much later, 3-4 years after thyroidectomy, when the phenomena of cachexia thyreopriva are already fully developed.

VI. These grave effects of thyroidectomy in man were the subject of much discussion and controversy at the Congress of German surgeons which took place in 1883. The observations of Reverdin, Kocher, Wölfler, and Bardeleben were confronted with not a few cases of goitre in which no subsequent morbid symptoms were apparent. We shall return later to the cause of this phenomenon. Meantime, experimental confirmation of the great physiological importance of the thyro-parathyroid system was not long wanting. The merit of its discovery is due to M. Schiff, who in 1884 published two Memoirs on the effects of removing the thyroid bodies in the dog, which indicated the true solution of this crucial question. Schiff was followed by a host of experimenters in Italy, Germany, and France, whose work threw much light on the subject, though it is still obscure.

Let us first consider the phenomena consequent on total thyroidectomy in the dog, on which many experiments have been carried out.

The total extirpation of both thyroid bodies in these animals produces effects no less complex and variable than in man: usually they present a combination of the phenomena of tetany and of cachexia thyreopriva. The operation is almost invariably fatal, after a period varying from 3-4 days to a month. Death more often occurs between the sixth and tenth days. The fatal issue is more rapid when acute symptoms of tetany prevail; it is retarded when the depressing and dystrophic symptoms of cachexia predominate. The phenomena of the first and second

groups, however, combine and succeed each other so variously in individual cases, that any separate description of them would be artificial and arbitrary.

Two to three days after the total ablation of the thyro-parathyroid apparatus, the dogs begin to exhibit signs of depression, and are sluggish in their movements, with a decided tendency to remain crouched. They are unwilling to eat (anorexia), swallow with difficulty (dysphagia), are inclined to vomit, and end by absolutely refusing all food. When they try to move, or are forced to stir themselves, they exhibit characteristic fibrillar tremors of the muscles of the thighs, shoulders, and back.

These symptoms gradually become aggravated and complex. The animals appear uneasy, they whine (as if in pain), rub their noses on the ground or wall, and shake their bodies as if they itched all over. At the same time, sensibility to painful and tactile stimuli seems to be objectively diminished or entirely abolished, while the pressure-sense is retained (Schiff). On the third or fourth day, more often on the fifth or sixth, trophic disturbances make their appearance in the skin, due in great measure to rubbing with diminished cutaneous sensibility. Conjunctivitis and keratitis next set in, and are first catarrhal and subsequently become purulent (Gley), if precautions are not taken by treatment with disinfectants (Lusena).

The muscular tremor becomes continuous; it is complicated by rigidity of the extremities, particularly the hind-limbs, in the form of tonic extension; twitches or clonic contractions of certain groups of muscles, particularly in the temporal muscle and the masseters, tonic contraction of the masticator muscles (lock-jaw), extending sometimes to the muscles of the back and limbs (opisthotonus), and assuming the form of true spasms of tetanic convulsions.

The convulsive spasms are not infrequently complicated by attacks of tachypnea of no long duration, during which there is a proportionate increase of temperature (Marchesi). Sometimes the tachypnea is so intense that the respirations can only be counted by the graphic method (Gley). Not infrequently, at the close of life, the respiratory rhythm becomes periodic (Cheyne-Stokes phenomenon), but this does not last long, and is irregular in form.

Along with tachypnea and hyperthermia there is regularly tachycardia, which may reach maximal intensity (150 beats to the minute). On the other hand, in the long intervals (sometimes whole days) in which there are no convulsive phenomena nor tachypnea, and the animal is in a drowsy, stupid state or in coma, the temperature may fall gradually to two degrees below normal (Ughetti), while the cardiac beats also become less frequent than the normal (Lusena). Investigation of the respiratory gas exchanges agrees with this fact, as they are found to be diminished after thyroidectomy (Baldoni).

Much work has been done with the object of determining the changes in the blood after thyroidectomy, but has led to no concordant results. The number of the erythrocytes and the amount of haemoglobin diminishes according to some authorities, according to others it remains approximately invariable. The quantity of oxygen fixed by the haemoglobin of dethyroidised dogs may diminish, or remain approximately unaltered, according to the nature of the pathological phenomena at the moment of investigation. The isotonic coefficient of the erythrocytes is somewhat reduced, owing probably to the altered metabolism (Bottazzi). The proteins of the plasma alter in their qualitative relations: at first there is a relative diminution of globulins and increase of serin; later, on the contrary, the serin diminishes, while the globulins relatively increase (Ducceschi). This fact depends probably on the state of almost complete inanition in which the dethyroidised dog exists, also on the *albuminuria* frequently observed in these animals (Herzen), owing to which a predominating amount of serin passes into the urine.

Coronedi's recent and systematic researches on this albuminuria have shown it to be a constant phenomenon, although it varies in intensity. It sometimes precedes the onset of characteristic symptoms of thyro-parathyroid deficiency, more particularly the convulsions. It is curious that this albuminuria can as a rule be detected most certainly by means of Esbach's citro-picric reagent.

In addition to albuminuria, glycosuria is often seen in dethyroidised dogs. It usually sets in two days after the operation (so that it is not the effect of post-operative traumatism), and lasts, sometimes intermittently, till death (Falkenberg, Gley). According, however, to the later and more accurate work of Coronedi, the reducing power of the urine is seldom due to dextrose. Coronedi and Luzzato further noted in dogs that the reaction of the urine became alkaline after parathyroidectomy, owing to the presence of free ammonia.

Such are the principal pathological features exhibited in dogs after complete ablation of the thyro-parathyroid apparatus. They present a less acute course than the typical cases of tetany in man, and a much more rapid course than Kocher's cachexia. This greater rapidity doubtless accounts for the absence of myxoedema in dethyroidised dogs, *i.e.* swelling owing to infiltration with mucin. In the dogs which, as a rare exception, lived for some time after thyroidectomy, Tizzoni and Centanni (1890) saw that trophic phenomena similar to myxoedema did make a tardy appearance. Coronedi and Marchetti have recently described two typical cases of experimental myxoedema in such animals, the psychical decadence being also particularly pronounced.

In thyroidectomy practised on monkeys (which by their greater

affinity to the human race might *a priori* be expected to show a greater likeness in pathological phenomena), Horsley (1885-86) reproduced and described the psychical decadence, the alterations in general nutrition, the special oedemas that were described for man by Reverdin, and which constituted the syndrome of *operative myxoedema*. Tetany was occasionally observed in apes as in man, and rapidly produced the death of the animal.

Fatal effects with phenomena similar to those in dogs were observed on cats (Schiff, Vassale, and Sacchi) and foxes (Sanquirico and Orecchia). In some of the herbivora, on the contrary, especially the rabbit, on which many experiments have been made, no particular effects were observed (Schiff, Colzi, Tizzoni and Fileti, Sanquirico and Orecchia, etc.) Later on we shall examine the reason for these negative results, as also for the rare survival of dethyroidised dogs, as noted by Albertoni and Tizzoni, H. Munk, and others. Thyroidectomy in birds yielded varying results to Moussu, negative results to Allara and Ewald. In reptiles and amphibia, on the contrary, the physiological importance of the thyroid apparatus was evident. The salamander usually died after a week (Gley, Phisalix, Nicolas). Lizards and snakes perished in 3-4 weeks (Cristiani).

VII. After this description of the phenomena, the first question to determine is whether the complex pathological effects observed after ablation of the thyroid bodies are really the direct consequence of loss of function in the glandular organ, or the indirect effects of the operation performed on man and other animals. We will shortly review the principal opinions in regard to this subject.

Prior to the observations of the cousins Reverdin and of Kocher on man, which were confirmed by Schiff for other animals, there was no really scientific theory of the specific function of the thyroid body. The current hypotheses were more or less gratuitous, or founded upon superficial observations. Among many such (which need not be recorded) was that formulated by Schreger (1791), which had a certain objective foundation. In view of the situation of the gland between the heart and brain, of the large arterial vessels with which it is provided, and of their origin in the arteries that carry the blood to the brain, he opined that the thyroid functioned as an organ for regulating the circulation in the upper part of the body, particularly in the brain: *Haec glandula sanguinis immodicos appulsus a cerebro aderceat et moderetur*. Rush (1806) supported this hypothesis, and explained the greater development of the thyroid in women by their greater predisposition to emotion, which is associated with cardiac excitement. The same doctrine was taken up more vigorously by Liebermeister (1864), who attempted to bring out the great importance of the regulatory mechanism represented by the

thyroid, in all cases in which there is danger of plethora or cerebral anaemia. In the first case, by dilatation of its vessels, the thyroid receives the excess of blood which would otherwise reach the brain; in the second, by contraction of its arteries, it determines a greater flow of blood to the cerebrum. Guyon (1868) adopted a more complicated, but analogous point of view, affirming that every increase in cerebral blood-pressure produces an augmentation in the volume of the thyroid (probably by passive vascular dilatation) which causes compression of the carotids, and prevents the blood from flowing in large quantities to the brain. Finally, Meuli (1884) attempted to give an experimental basis to the Schreger-Liebermeister theory, demonstrating by a series of measurements upon himself that the circumference of the neck varies considerably with the position of the body, these variations being maximal at the level of the thyroid region.

Without denying whatever may be true in this theory, as put forward by Liebermeister, its importance must not be exaggerated.

It is obvious that any regulatory or compensatory influence on the cerebral circulation which may be attributable to the thyroid arteries can have nothing to do with the specific function of the thyroid as a *glandular organ of internal secretion.*

The cousins Reverdin and Kocher (1883), who, as we have seen, were the pioneers of research into the physiology of the thyroid as a glandular organ, were not happy in their first attempt to explain tetany and cachexia thyreopriva in man. According to Reverdin, this characteristic syndrome depended on disturbances of innervation caused by lesions of the nerve trunks in the course of extirpating the thyroid organ. According to Kocher, on the contrary, the ligation of the great thyroid vessels in excision of this body produced on the one hand a considerable diminution in the lumen of the trachea, owing to deficient irrigation by the blood stream, on the other, a disturbance of the cerebral circulation by suppression of the thyroid system. The constriction of the trachea diminished the respiratory gas-exchanges, and indirectly produced anaemia, leucocytosis, cretinism, coma; the disturbance of the cerebral circulation (according to Liebermeister's theory) caused the convulsions, tachypnea, and tachycardia.

After Schiff's publications (1884) these hypotheses, which, as we shall see, were reared on an unstable basis, were abandoned even by their authors. According to Schiff the grave symptoms consequent on thyroidectomy are the direct consequences of deficiency of thyroid function, *i.e.* of the internal secretion of substances of unknown nature, which are of great importance in the normal nutrition of the nervous system. When deprived of these substances of thyroid origin the nervous system becomes disordered in its functions, and gives rise to the phenomena of tetany and cachexia thyreopriva. Schiff proved that the extirpa-

tion of one thyroid only was innocuous in the dog. On the other hand, he found that if the thyroid of one dog were grafted into the peritoneal cavity of another, and the two thyroids of the latter extirpated after a considerable period, the pathological phenomena were delayed, and the animal survived the operation longer. He observed that, generally speaking, the grafted thyroid did not take root, but was absorbed after a certain time. He explained the protracted survival of the animals on the assumption that during the disintegration of the thyroid introduced into the peritoneum, the substances necessary to the normal nutrition of the nervous system are absorbed and carried to the circulation. He conjectured that the same effect could be obtained by the periodic injection of thyroid juice into a dethyroidised animal,—as was subsequently demonstrated by other experimenters.

Another important fact stands out in Schiff's memoir. He states that if both thyroids in a dog are excised in two successive operations, at about a month's interval, no pathological symptoms appear in the animal. With a less interval between the two operations, the fatal symptoms are delayed; if the interval is reduced to one week they invariably set in. This suggested to Schiff the hypothesis that in the interval between the first and second thyroidectomy the activity of another organ, similar to or identical in function with the thyroid, might be progressively exaggerated, so as to act vicariously for the excised thyroid. The presumptive existence of another organ functioning vicariously for the thyroid, explains, he says, why total thyroidectomy in certain animals, *e.g.* rabbits and rats, and on rare occasions dogs also, may be innocuous. Later on we shall examine the value of this hypothesis. Meantime it may be stated that the fundamental fact on which it is based was immediately contradicted by the experiments of Sanquirico and Canalis (1884-85), who constantly obtained fatal results from the removal in two operations of both thyroids in dogs, whatever the period between the first and second operation. They also observed another enigmatical fact, the importance of which will appear below. Removal of the upper half of both thyroids is fatal in the dog, while removal of the two lower halves is innocuous.

Immediately after Schiff's publication, Colzi proposed that these experiments upon the thyroid should be repeated in our laboratory in Florence, in order to see, from an exclusively surgical standpoint, which minimal portion of the organ it was necessary to preserve in dogs in order to avoid the phenomena of "tetania thyreopriva." The results of his experiments, published in 1884, showed that if half the thyroid, or even half of one lobe were retained, the animal escaped death. In this case transitory phenomena of functional insufficiency were often apparent.

The rapid course and violence of the phenomena of tetany as

observed in the most robust dogs, after Colzi had excised both thyroids with a perfect surgical technique, led us to suspect that the whole pathological syndrome depended on an *auto-intoxication.* To prove this hypothesis we suggested that Colzi should perform direct reciprocal transfusion of blood between two dogs, one that had been operated on and was in the most acute period of tetany, the other perfectly normal. On joining a carotid artery of the first dog with a jugular vein of the second by glass cannulae united with rubber tubes, the vascular systems of the two animals completely exchanged their blood content, so that after a few moments the blood of each animal was perfectly mixed with that of the other. Previous experiment had shown that reciprocal transfusion can be borne for over half an hour, a period more than sufficient for the total mass of the blood of the two animals to be physiologically affected by the thyroids of the healthy dog, since we know that half a thyroid suffices for each dog.

The effects obtained by this experiment, as frequently repeated by Colzi, were what we had predicted. On suspending the transfusion after 20-30 minutes, the dethyroidised dog no longer showed symptoms of tetany, and seemed to have reverted to the condition it was in on the day of the operation. This more or less complete disappearance of pathological symptoms lasted only for two or three days, after which they set in with their former violence, and rapidly induced the death of the animal. The dog with intact thyroids appeared depressed for some hours after the transfusion, but soon recovered and became perfectly normal.

These results, as obtained for the first time in our laboratory, were the initial demonstration of the theory that *the thyroid apparatus has an antitoxic function,* a theory essentially different from that of Schiff, and confirmed, as we shall see, by subsequent researches. At the Session of the Medico-Physical Academy of Florence, July 13, 1884, we formulated our fundamental theory as follows, on the strength of Colzi's experiments. "The function of the thyroid secretion is to withdraw from the blood, and probably to destroy, a product of tissue katabolism that tends to accumulate slowly, and is capable, when accumulated, of producing a species of auto-intoxication analogous to the uraemia consequent on bilateral extirpation of the kidneys. The presence of the entire thyroid is not indispensable for this cleansing function, a half or quarter of it will suffice."

Although Schiff's experiments had established the fundamental fact that the pathological symptoms consequent on thyroidectomy were essentially phenomena of *glandular deficiency,* other authorities referred these phenomena to the operative lesions, more particularly of the nerves,—adopting the hypothesis of Reverdin. H. Munk, in repeated publications (1887-88, 1897), and contrary to the observations of other experimenters, maintained

that dogs often bear up well against the effects of bilateral thyroidectomy, provided there are no lesions of the sensory nerves of the region, and that the total occlusion of the thyroid vessels was equally without effect.

The direct confutation of Munk's opinion is given more particularly by the experiments on dogs of Fuhr (1886), Fano (1893), and Vassale (1893), which prove that lesions of the nerves and vessels of the neck, translocation of the thyroids and the grafting of them subcutaneously, have no sequelae, and that suppression or complete ablation of the gland are alone capable of producing the symptoms described by Schiff. Vassale proposed an *experimentum crucis*: if the thyroid lobe be excised from a dog on one side, and the sympathetic nerves divided on the other, this double operation is not followed by phenomena of cachexia and tetania thyreopriva.

At a later time E. Cyon (1897-98) formulated a new hypothesis to explain the effects of thyroidectomy. His theory at first seemed highly suggestive, but it proved fallacious in face of many facts that have received experimental confirmation. Cyon attempted to fuse the old theory of Schreger-Liebermeister with that which attributes a secretory antitoxic function to the thyroid, directed, *i.e.*, to the removal of some toxic matter from the body as a whole, and more particularly from the nervous system.

His hypothesis may be summed up as follows:—

(*a*) The function of the thyroid gland is to form and pour into the blood a special substance designed to stimulate or keep up the functional tonus of the nerve centres which regulate the beats of the heart. This substance is *thyro-iodine* (discovered, as we shall see, by Baumann among the active substances of the thyroid, *infra*, p. 30).

(*b*) In proportion as thyro-iodine is formed by the activity of the glandular epithelia, the iodine salts circulating in the blood which have a paralysing action upon the regulatory apparatus of the beats of the heart (Barbèra and Cyon), are withdrawn from the circulation and remain innocuous, forming organic combinations.

(*c*) By means of the depressor nerves and cardiac branches of the recurrent nerve, the heart exerts a direct control over the thyroid function, determining the formation of the amount of thyro-iodine that is necessary for its normal activity.

(*d*) The thyroid, which lies at the entrance of the carotids into the cranium, is a protection against an excessive flow of blood to the brain, since it can carry off a great quantity of blood through its vessels in a very short time. It therefore acts as a secondary circulation of low resistance.

(*e*) This regulatory function of the cerebral circulation attributed to the thyroid is also controlled by the heart, since the depressors are able to determine the active dilatation of the

thyroid arteries, by reducing the quantity of blood that flows to the brain.

The fallacy of Cyon's theory becomes obvious when we remember, on the one hand, that the effects of thyroidectomy are totally avoided in dogs by preserving the two upper halves of the two thyroid lobes (Sanquirico and Canalis), or even one upper half of one lobe (Colzi); on the other, the double clinical syndrome of cachexia and tetany exhibited in man after extirpation of the thyroid, with the various associations and successions of the two categories of phenomena consequent on thyroidectomy in dogs. The most direct and convincing refutation of Cyon's hypothesis, however, lies in other important experimental facts which must now be examined.

VIII. We have seen that the first generic proof of the theory which regards the sequelae of thyroidectomy as phenomena of auto-intoxication from accumulation in the blood of the katabolic products of the various tissues, resulted from the direct reciprocal transfusion between two dogs, one dethyroidised and the other normal, as performed under our directions by Colzi in our laboratory. The conclusion we arrived at of the *protective antitoxic* function of the thyroid gland, was too important for the work not to be taken up and repeated by many investigators and with various methods.

Rogowitsch (1886-88) was the first to verify these results. Next in order, with more variation in detail, came the experiments of Fano and Zander (1889), and of Lusena (1889).

Starting from these fundamental notions, Gley (1895) conceived the happy idea of comparing the degree of toxicity of blood serum from a healthy dog with that of a dog suffering from tetany and cachexia thyreopriva, by injecting these sera into frogs, guinea-pigs, and rabbits. He came to the conclusion that the toxicity of the serum of dethyroidised dogs, as compared with that of the normal dog, is exhibited in these animals by different and more acute symptoms, *i.e.*, by severe convulsions.

The toxicity of the urine in dethyroidised animals also increases relatively to that of the urine of healthy animals. This fact, which was at first denied by Alonzo (1890), was clearly established by Gley (1894), and was subsequently confirmed by Laulanié and by Maison (1894).

Reasoning from this fact, which shows that the toxic substances that accumulate in the blood after thyroidectomy are eliminated by the organism through the renal excretory system, Dutto and Lo Monaco (1895) were led to suspect that the intoxication consequent on thyroidectomy occurred by a process analogous to that which produces uraemia, more particularly as the symptomatology of the latter is no less varied, and presents not a few points of resemblance with cachexia thyreopriva. This suggestion was

tested in our laboratory by the so-called *washing of the blood* in dethyroidised dogs, *i.e.* the repeated injection into the veins of an isotonic solution of sodium chloride in quantities large enough to increase the urinary secretion and accelerate the elimination of all the toxic products accumulated in the blood. Our results were approximately identical with those obtained by Fano; after each injection the morbid symptoms were alleviated or entirely disappeared for some time.

This temporary cessation of all the symptoms is strictly associated with the increased diuresis, and thus with the normal functions of the kidneys. When the latter are affected and do not expel the excess of injected fluid fast enough, the symptoms of cachexia are not suspended.

Another important fact appears from the researches of Dutto and Lo Monaco. These authors found on methodical analysis of the urine that elimination of nitrogenous waste products diminishes in dethyroidised dogs, so that they accumulate in the body: the washing of the blood abolishes the symptoms of cachexia thyreopriva because it determines the elimination by way of the kidneys of these nitrogenous products, which had been retained and accumulated in the body.

These experimental results as a whole reinforce the hypothesis formulated by ourselves, to the effect that the toxic substances which determine tetany and cachexia thyreopriva are katabolic or waste products from the tissues, *i.e.*, they have the same origin, and, in part at least, consist of the same *urinary materials.* It appears from certain experiments of Vassale and Rossi (1893) that these toxic substances are largely derived from the muscles, which represent the tissue that predominates considerably over any other in the body. These authors studied the degree of toxicity of the juice prepared from the muscles of normal dogs, compared with that of the muscles of dogs killed when suffering from tetany and cachexia thyreopriva. The muscular extract of healthy dogs yielded negative results: the muscular extract of dogs in tetany, on the contrary, when injected into the veins of dogs that were normal or recently deprived of the thyroid, induced the gravest symptoms,—anorexia, vomiting, fibrillar contractions, and eventually convulsions.

If (as appears highly probable from what we have been stating) the phenomena of tetany and cachexia thyreopriva really depend on auto-intoxication; if the toxic substances by which this is determined are the waste products from the various tissues, notably from the muscles which form the predominating tissue; if these toxic katabolites are normally eliminated by the renal system as fast as they are formed, then the *protective, antitoxic* action of the thyroid secretion may validly be conceived as the direct or indirect effect of a physiological excitation of the renal epithelia. The

phenomena of thyroid insufficiency will thus consist mainly in the effects of the progressive accumulation in the blood and tissues of these products, owing to the altered or retarded secretory function of the epithelium.

That the kidneys do not function normally in dethyroidised animals may be argued from the albuminuria that accompanies tetania thyreopriva, as also from the lesions which are invariably found in the kidneys of dethyroidised animals, ranging from a simple albuminoid degeneration of the epithelia of the canaliculi to severe parenchymatous nephritis (Alonzo, Hofmeister, etc.).

Blum (1901) found nephritic alterations of greater or less gravity in dogs that had survived thyroidectomy for at least eight days. He, too, attributed the origin of these to auto-intoxication, which according to him is of an enterogeneous nature, due, *i.e.*, to the suppression of the antitoxic activity of the thyroid, which normally has the task of destroying the enterotoxins.

Bensen (1902), again, who particularly devoted himself to the histology of the lesions of various organs in the rabbit incident on thyroidectomy, arrived at a conclusion that coincides with the above. He admitted that, "after thyroidectomy, owing to the suppression of the thyroid gland, a poison is produced or retained in the body, which determines a characteristic degeneration of the cell protoplasm, especially in the kidneys, liver, and myocardium, leading eventually to the destruction of the cells. The products of protoplasmic degeneration appear in the form of colloidal spherules or cylinders in the renal canaliculi. When the morbid state is protracted an interstitial nephritis is readily set up, leading to the formation of scars, similar to those which Blum describes in dogs."

The theory of the intimate functional relations between the thyro-parathyroid apparatus and the kidneys, however, finds its fullest experimental confirmation in the studies of Coronedi (1907) and his pupils. In the first place, this author observed that the alterations of the kidney (consisting in inflammatory and degenerative processes) in animals exhibiting symptoms of a defective thyro-parathyroid system is a constant fact, certain to appear, and, at least within certain limits, proportional to the intensity and gravity of the pathological symptoms. It is worth noting that the lesions may be present even when the syndrome of symptoms has scarcely been initiated.

While the amount of katabolites increases after excision of the thyroid and parathyroids, and the elaboration of these products is never fully accomplished, the functional capacity of the kidneys diminishes *pari passu*. Hence a true intoxication of retention ensues, which, if not identical with, is at any rate highly similar to, *uraemia*.

Coronedi believes that among its other functions the internal

secretion of the thyro-parathyroid apparatus serves mainly as a *physiological diuretic* (stimulating the nutrition and specific activity of the renal epithelium). He arrives at this conclusion from studying the action of the gland-extract upon the kidney, and noticed that the salutary effects of thyro-parathyroid organotherapy and of the halogenated fats which are its equivalent, are entirely wanting or become less, with experimental alteration of the kidney.

IX. Schiff's ingenious idea of transplanting and grafting the thyroid to avert the fatal effects of thyroidectomy opened up a wide field of research, which is interesting both from the physiological and from the therapeutic point of view. After he had demonstrated that preventive intraperitoneal grafts of fresh thyroid are capable of prolonging the life of dogs that were subsequently deprived of their thyroids, it was natural to conclude that the same treatment might obviate the serious consequences of total thyroidectomy in man, and be a cure for spontaneous myxoedema.

Bircher (1889) was the first to graft a piece of human thyroid into the abdomen of a dethyroidised patient, who exhibited symptoms of cachexia. He obtained a temporary improvement which was repeated after a few months on renewing the graft.

Horsley (1890) attempted the cure of spontaneous myxoedema by grafting under the skin or in the peritoneum, the thyroids of sheep or monkeys (which are histologically very like those of man), after proving that thyroidectomy in these animals produces a syndrome which closely resembles human myxoedema. The results were so encouraging that this method of cure was repeated in a short time by many others, among them Lannelongue, Kocher, Bettencourt and Serrano, Merlen, etc.

The most interesting results were, however, obtained by Eiselsberg (1892), who repeated Schiff's experiments on cats, transplanting an excised lobe not to the peritoneum, but to the thickness of the abdominal wall, and then a month later—when the graft might be supposed to have taken—excising the other lobe. Of the many cats thus operated on, four long survived and exhibited no morbid symptoms. Three months after grafting, Eiselsberg exposed the transplanted gland, and found that it was attached by vascular adhesions; he then excised it again, and found normal glandular structure under the microscope. Two days after this second operation the animals developed acute tetany, and soon died. It is thus possible, even if exceptional, for the transplanted thyroid to become rooted in other than its normal surroundings. This is an *experimentum crucis*, by which the too-ingenious theory which Cyon founded entirely upon the peculiar nervous and vascular relations of the thyroid is invalidated.

These experiments have recently been confirmed by Christiani (1901) on a large number of animals.

He gives certain important details in regard to the method of performing the thyroid graft so that it shall take well.

No arbitrary quantity of thyroid can be grafted, but only such an amount as is required by the body in each individual case. If, *e.g.*, a whole thyroid is grafted on a completely dethyroidised rat, it may become attached as a whole, but if a whole thyroid, or several thyroids, are grafted on a partially dethyroidised rat, a part only takes root, corresponding, to a certain degree, with the deficit.

This shows that the action of the thyroid is, generally speaking, more useful to the body in proportion as the maximal intensity of its function is contained within physiological limits.

Graves' or *Basedow's disease*, which is characterised by a well-known complex of symptoms (tachycardia, oesophthalmia, increase of general katabolic processes, etc.) is now attributed by the majority of clinicians to exaggerated activity of the thyroid, whatever the conditions which initiated it. The same syndrome is also exhibited when thyroid preparations are administered to persons whose thyroid is normal, as, *e.g.*, with the therapeutic object of reducing obesity.

However efficacious in this direction, the cure is so dangerous owing to its tendency to produce the symptoms of Graves' disease, that it has now been generally abandoned (Strümpell).

Eiselsberg, having failed with other clinicians in the radical cure of spontaneous or operative myxoedema by thyroid grafting, owing to the difficulty of regeneration, put in practice Schiff's suggestion by preparing a thyroid extract, and injecting it beneath the skin of dethyroidised animals. His results, however, were not encouraging, either from the position of the injection, or from the amount of juice injected. Vassale was more fortunate. At the end of 1890, independent of Eiselsberg, seeing the therapeutic efficacy of certain drugs injected directly into the veins (Baccelli), he injected large quantities of thyroid juice into dethyroidised dogs, and obtained a beneficial, though transitory, action from such injections. These results were amply confirmed by Gley (1891), and applied very successfully by Murray (1893), both in a case of spontaneous myxoedema and in a monkey deprived of its thyroids.

A year after Murray's first cure of myxoedema Howitz, Mackenzie, and Fox substituted the administration of thyroid by the mouth for venous injections. This method is very simple, and within the grasp of all; and it gives surprising therapeutic results in cases of myxoedema which have gone on for years, and proved refractory to all kinds of treatment. This shows that the active principles of the thyroid juices are not decomposed by the action of the digestive secretions.

The salutary effect, both of injection of thyroid juice and of thyroid ingestion by the mouth, is probably owing to the fact that it facilitates the elimination of the toxic products accumulated in the blood. In this connection the following observation of Vassale is interesting: "After the injection of thyroid juice," he wrote in 1892, "the animal as a rule drinks water, sometimes in very large quantities; it subsequently excretes an excessive amount of urine, after which it returns to its normal condition, and remains well for at least twenty-four hours. It seems as though the animal drinks much water in order, with the large amount of urine it then evacuates, to wash the body free of a toxin that had previously accumulated in the blood and tissues." This gives weight to our hypothesis that the thyroid secretion normally has the function of directly or indirectly exciting renal secretion.

The work of Godard and Slosse, carried out under Heger's direction, also supports this point of view. According to these experiments, the thyroid juice has a lymphagogic action, analogous to that exhibited by the lymphagogues of Heidenhain's second category (Vol. I. p. 523 *et seq.*), which indirectly promote diuresis by transporting water and the products of katabolism into the lymphatic sinuses and vessels and the blood.

From the physiological point of view these results show that the protective action of the thyroid depends on the specific character of the chemical substances which it contains, and which normally pass into the blood by continual internal secretion. Many workers have therefore devoted themselves to research in this direction by chemical analysis of the thyroid juice. Their results are interesting, though inadequate for the solution of this difficult problem.

Notkin (1895) prepared a special substance from calf's thyroid which he termed *thyreo-protein*; this on injection into a dog recently deprived of its thyroid induced phenomena of tetany that subsequently ceased, to reappear at each fresh injection. He concluded that it was this substance (normally retained by the thyroid and rendered innocuous) which causes the auto-intoxication consequent on thyroidectomy. In addition to thyreo-protein, Notkin isolated another indefinite substance from thyroid extract which he termed *thyreo-gummin*; this acts upon the former and transforms it into an innocuous substance, necessary to the nutrition of the body. He was in fact able to neutralise the noxious effects of thyreo-protein by simultaneous injection of thyreo-gummin. These very suggestive results have not, so far as we know, been repeated or confirmed by other workers.

Fränkel simultaneously affirmed that the active principle of the colloid substance, or secretion, which the thyroid pours into the lymph and blood system, is a mucin, which he obtained from the watery extract of boiled and filtered thyroid. He called it

thyroid-antitoxin, and maintained that it was capable of inhibiting the appearance of cachexia when injected into dogs deprived of the thyroid.

These experiments of Notkin and Fränkel were abandoned as soon as the work of Baumann (1895-96) appeared. He proclaimed the discovery of *iodine* in the thyroid, and raised hopes that the active principle of the thyroid had been found in an organic compound of iodine, to which the name of *thyro-iodine* was given. Baumann, with Ross and with Goldmann, Hofmeister, Hildebrand and Irsai, maintained that the injection of thyro-iodine into the veins was able to compensate for the functions of the thyroid when that organ had been excised. The experiments of Gottlieb (1896), Wormser (1897), and Pugliese (1898) contradicted this vicarious action of thyro-iodine. According to Wormser, thyro-iodine is "neither capable of impeding the onset of an attack of tetany nor of arresting an attack that is already running its course."

On the other hand, by injection of the gland, as a whole, whether administered by the mouth or injected into the veins in the form of an extract, *in sufficient quantity*, it is possible to check the paroxysms of tetany, and to keep the dethyroidised animals alive for a long time, as was first demonstrated by Vassale.

Other facts tell against Baumann's theory. According to his own researches, the thyroid of dogs after a flesh meal contains either no iodine or the merest traces of it. Iodine is rarely found in the pig's thyroid; hardly any, or merely a trace, in the thyroid of sheep and horse (Töpfer). The human thyroid does not contain it constantly (Baumann). The subsequent researches of Neumeister and Malthes (1897) showed that iodine is frequently absent in the thyroid of adults and infants, and that while that of the ram and pig contains 50·9 mgrms. of iodine per gramme of dry gland, that of the dog, horse, and calf contains either none or merely traces of it. Thyro-iodine cannot therefore be the active principle required, although it is probable that the iodine, introduced in minute doses with vegetable aliments, is retained and fixed in organic form by the thyroid gland. It has been observed that the iodine of the thyroid increases after the medicinal use of iodides and iodoform.

On the other hand, the experiments of Coronedi and Marchetti on the biological importance of *halogens* to the function of the thyro-parathyroid apparatus have thrown new light on the subject. They actually succeeded in rendering animals (dogs and rabbits) perfectly immune against cachexia and tetany, and were able to cure them easily, when already attacked, by the administration of iodine or bromine in an alimentary form (halogenated fats), which can easily be stored in the adipose tissue of these animals, since, in comparison with normal animals,

they have a decided tendency to retain such halogens in the body. When the organic supply of halogen comes to an end, as may occur after months or even years, the characteristic symptoms of thyro-parathyroid deficiency reappear.

Bunge (1898), on the simple ground of analogy, propounded the hypothesis that the protective antitoxic substance secreted by the thyroid consists in an unstable protein compound, belonging to the enzyme group, with the property of producing large effects by infinitesimal doses. When poured into the blood along with the colloidal substances, this enzyme would influence the metabolism of the body and accelerate the elimination by the renal outlets of the katabolic products as fast as these are formed. But as yet no experiments are to hand in direct evidence of this hypothesis.

X. In order to explain the fact that some animals (rabbits constantly, and dogs in certain rare cases) can bear the complete ablation of the thyroid without injury, Schiff (*supra*) proposed the hypothesis that the body contains another organ capable of supplementing the functions of the thyroid. This hypothesis led to a number of ineffective researches, with the object of determining which this vicarious organ could be.

Fano (1893) showed that the removal of one suprarenal capsule, of the salivary glands, the ovaries, and a large portion of the pancreas, produced no modification in the sequelae of subsequent total thyroidectomy.

That no functional relation exists between the thyroid and the spleen was plainly shown by the experiments of Tizzoni and Fileti (1883-84), of Sanquirico and Canalis (1884), of Ughetti and Mattei (1885), and others. In 1893 Zanda revived the subject, and stated that thyroidectomy was not fatal in dogs, if performed about a month after splenectomy. Had these results been confirmed, they would have been of great importance, justifying the hypothesis put forward by Zanda, that the spleen pours toxic products into the blood, which the thyroid renders innocuous. Unfortunately, the later experiments of Fano, Vassale, and Di Brazzà proved that dogs and cats, deprived of their spleen, were liable more than a month afterwards to the effects of thyroidectomy, like normal animals.

The principal argument against the existence of any functional relation between spleen and thyroid rests on the recent histological work of Massenti and Coronedi on the first of these organs in the dethyroidised dog. The spleen undergoes a process of sclerosis and atrophy, which is the more advanced in proportion as the survival power of the animal to thyro-parathyroidectomy is greater.

Nor was the work of Marie and Möbius, of Cadeac and Guinard (1894), who sought to establish a functional relation between the

thyroid and the thymus, more successful. Gley (1894) demonstrated the fallacy of this theory.

Attempts to demonstrate a functional relation between the thyroid and the glandular portion of the cerebral hypophysis or pituitary gland succeeded better. These results will be referred to below, in their proper connection.

It is to Gley (1892) that we must ascribe the merit of having pointed out the importance of the *parathyroid* glands, previously discovered by Sandström. Along with the thyroids, he excised the two little glands of Sandström in rabbits, which died, under these circumstances, with symptoms of tetany, even when the removal of the parathyroids was effected a month later than that of the thyroids. But when the parathyroids alone were excised in rabbits, no pathological symptoms appeared. He concluded that the parathyroids acquire great importance only after the extirpation of the thyroids—probably because they have the function of vicariously replacing them. In confirmation of his hypothesis, Gley observed that the parathyroids become hypertrophic a month after the excision of the thyroids, and exhibit modifications by which their structure approximates to that of the thyroids, as if they were embryonic thyroids intended to supplement any functional insufficiency of the adult gland.

Subsequently, in collaboration with Phisalix (1893), he performed the same experiment on dogs, and came to the conclusion that these animals also survived the complete extirpation of the thyroids, when precautions were taken to spare the parathyroids and leave them *in situ*; while symptoms of tetany inevitably supervened, when the latter were also extirpated. Ablation of the parathyroids alone did not, according to Gley, produce morbid sequelae. This confirmed his theory of the supplementary function of the parathyroids.

His conclusions were, however, contested by Moussu (1893), Hofmeister (1894), and particularly by Vassale and Generali (1896). These authors disputed Gley's observations as to the structural modifications of the parathyroids after removal of the thyroids. But as Rouxeau (1896) confirmed the fact of the conspicuous increase of the parathyroids after thyroidectomy, and the innocuous effects of simple parathyroidectomy, many people adopted Gley's view of the functional interchanges between the thyroid and parathyroid glands.

Gley's hypothesis was first shaken by the accurate work of Vassale and Generali (1896), which showed that a specific functional importance distinct from, and even greater than that of the thyroids must be granted to the parathyroid glands. These authors excised the parathyroids only on numerous dogs and cats, and found that they succumbed rapidly, the cats usually in 5, the dogs in 3 to 4 days after the operation, *i.e.* the more rapidly in

proportion as the thyro-parathyroid excision was more complete. Sometimes the animals succumbed after incomplete ablation of the parathyroid glands, *i.e.* when one parathyroid only was left *in situ*, as usually occurs in the case of dogs that have more than four parathyroids. As a rule, however, the animals that survive partial thyroidectomy exhibit slight and transitory pathological symptoms. These are analogous to the effects of thyro-parathyroidectomy—acute phenomena of "tetania thyreopriva," which is speedily fatal, or slight and transient, according as the parathyroidectomy was complete or partial. When partial parathyroidectomy is associated with total thyroidectomy, the chronic phenomena of cachexia thyreopriva set in, with or without slight convulsions.

In view of their significance, the experiments of Vassale and Generali were at once repeated and confirmed in France by Moussu (1897). Of four dogs on which he performed total thyroidectomy, three died of tetany on the 2nd and 7th day, and the fourth survived because (as shown at the post mortem) it had a fifth supernumerary parathyroid.

Edmunds and Welsh (1898) independently repeated and confirmed the results of Vassale in England.

The same work was continued in Italy by Capobianco and Mazziotti (1899), and more extensively by Lusena (1899). The latter, in a fine series of comparative experiments on dogs, shows—

(*a*) That the (chief) characteristic symptom of thyro-parathyroidectomy is coma, the period from the operation till death being on an average 10 days;

(*b*) That the characteristic symptom of parathyroidectomy is tetany, the interval between the operation and death being usually 3 days;

(*c*) That the excision of the thyroid, including the two internal parathyroids (which, as we shall see, are included with them) is not fatal if perfect nutrition is maintained in the two external parathyroids which are left *in situ*.

Lusena, in order to confirm the fact that the presence of the thyroids aggravates the pathological syndrome of total parathyroidectomy, conceived the idea of excising the thyroids in dogs already deprived of their parathyroids, which were on the point of dying from tetany, and saw that the convulsive phenomena were gradually attenuated, and a state of comparative amelioration introduced, so that the fatal issue was postponed.

The effects of parathyroidectomy can also be attenuated by the so-called *substitutive therapeutics, i.e.* by hypodermic, or better intravenous, injections of aqueous extract of the parathyroids alone. These experiments were performed almost simultaneously by Moussu and by Lusena (1898). Moussu showed that such

injections, besides suspending the phenomena of tetany, effected a sensible prolongation of the life of the animal. Lusena added the further fact that injections of pure thyroid juice exerted no beneficial influence on the syndrome of parathyroidectomy or thyro-parathyroidectomy, and that the injection of the juice prepared from the thyroids of dogs that had tetany from parathyroidectomy, aggravated the symptoms of thyro-parathyroidectomy. This last result rests on a single experiment only, and deserves to be confirmed by further research.

Lastly, Lusena has established by the method of reciprocal transfusion, or that of the partial substitution of the blood by an isotonic solution of sodium chloride, that the phenomena of tetany in parathyroidectomy can be suspended or attenuated like those of thyro-parathyroidectomy. In the first as in the second case, accordingly, there must be toxic substances in the blood of the animals that have been operated on.

All these interesting data as to the functional importance of the parathyroids throw new light upon many obscure points, and subtract not a little from the value of the earlier conclusions as to the physiology of the thyro-parathyroid system.

We can now see why rabbits and other animals frequently survive complete extirpation of the thyroids, and why even dogs, on which the greatest number of experiments have been carried out with positive results, may also survive. This is evidently due to the fact that the external parathyroids are constantly in rabbits, and occasionally in dogs, distinct from the thyroid lobes, and are therefore left *in situ* when those lobes are excised.

So, too, we can explain why, after excision of goitre, the patient may only exhibit symptoms of a slowly progressing cachexia thyreopriva or operative myxoedema, while in other less frequent cases acute phenomena of tetany supervene. Previous to the investigation of the parathyroids, these two essentially distinct pathological forms were regarded as different steps of one identical process, due to the abolition of the function of a single gland, the thyroid. Cachexia thyreopriva is now held to be the effect of functional deficiency of the thyroid gland alone, and tetany the effect of inhibited function of the parathyroids. In excision of goitre by the subcapsular method, the surgeon in the majority of cases leaves the inferior parathyroids, which are distinct from the thyroid lobes; but in certain cases the inferior parathyroids are included in the ablation of the thyroid, being joined to the body of it. In the first case cachexia ensues, in the second tetany. Sometimes there may be transitory or intermittent tetany, in consequence of functional insufficiency of the parathyroids. This occurs, according to Vassale, when a single inferior parathyroid is left *in situ* during the operation. In order to avert this pathological consequence, it is necessary for the operator to spare

the lowest portion of the thyroid body, as well as the inferior parathyroids.

Opinions differ at present as to the functional relation between the thyroid and the parathyroids. Gley (1898) was inclined to admit the existence of such an association between them, and to think that the parathyroids prepared a substance which is subsequently taken up and poured into the circulation by the thyroids. According to Moussu, Vassalé, and Generali, on the other hand, the two glandular functions are independent and differ specifically from one another. The thyroids have an essentially *trophic* function, *i.e.* they secrete substances indispensable to good general nutrition, particularly to the nervous and skeletal systems; the parathyroids, on the contrary, have an *antitoxic* function, *i.e.* they neutralise or facilitate the elimination by the kidneys of the toxic substances formed during metabolism.

How, then, are we to explain the fact suspected by Vassale and established by Lusena, to the effect that after simple parathyroidectomy the convulsive nervous symptoms are more grave, and lead more rapidly to a fatal issue, while after thyro-parathyroidectomy they are less serious and run a more protracted course? In order to account for this difference Lusena assumes that in dogs deprived of the parathyroids only, the quantity of toxic substances circulating in the blood is greater than that circulating after complete thyro-parathyroidectomy. He believes that the thyroids normally have the property of subtracting from the blood the *materia peccans* of unknown character, to return it transformed and innocuous; and he holds this antitoxic function of the thyroids to be dependent on the normal function of the parathyroids, so that when the latter are removed a larger amount of poison circulates in the blood.

This bold hypothesis does not — it seems to us — explain the fact that the subsequent excision of the thyroids conspicuously attenuates the symptoms of tetany consequent on parathyroidectomy. If, after removal of the parathyroids, the thyroids are no longer capable of abstracting and transforming the *materia peccans* in the blood, it is difficult to see why their extirpation should diminish the symptoms of auto-intoxication.

Vassale's theory is simpler, and suggests a better interpretation. He holds the specific function of the thyroid gland to be that of pouring into the circulation a secretion that excites and promotes general metabolism. The myxoedema consequent on functional deficiency of the thyroid exhibits a complex of symptoms which clearly indicate a reduction or perversion of the metabolic exchanges, and the therapeutic action of thyroid juice or of ingestion of thyroid in spontaneous or post-operative myxoedema is characterised by phenomena of quickened metabolism. The parathyroids, on the contrary, have a specific *antitoxic* function.

This may be because they throw into the circulation a secretion that accelerates the renal elimination of the products of tissue consumption; and these in all probability constitute the *materia peccans*. The tetany consequent on parathyroidectomy is a necessary consequence of the accumulation of katabolites owing to the defective function of the parathyroids, and the therapeutic action of parathyroid juice is the proof that the parathyroids contain protective antitoxic substances.

On this assumption it is easy to understand why parathyroidectomy alone determines an acute auto-intoxication, and thyro-parathyroidectomy a less acute auto-intoxication, which runs a slower course. In the first case, where general metabolism is active, owing to the presence of the thyroid, the amount of toxic matters accumulating in the blood is larger; in the second it is, on the contrary, smaller, because metabolism is reduced owing to absence of the thyroid. This is the reason why the de-parathyroidised animal is attacked by morbid symptoms, when subjected at a later period to thyroidectomy.

In support of his views Vassale adduces the following experimental data:—

(*a*) The phenomena of "tetania parathyreopriva" are more serious in young than in very old animals.

(*b*) The said phenomena are more acute and more rapidly fatal to the animal, if it eats much, especially meat, after the operation.

(*c*) Fasting reduces the pathological syndrome consequent on thyro-parathyroidectomy.

(*d*) In animals deprived of the parathyroids alone, when metabolism is normal, cicatrisation of the wound in the neck occurs regularly by first intention; in animals deprived of the whole thyroid body it is on the contrary difficult—in spite of every antiseptic precaution—to obtain healing of the wound *per primam*, owing to the sluggish metabolism.

In conclusion, we must add that, according to the latest researches of Alquier and Theuveny (1907), and of Vassale's pupil Massaglia (1908), the renal lesions which are, as we have seen, inevitable on the extirpation of the entire thyro-parathyroid system, are in reality due solely to the suppression of the parathyroids, their secretion no longer being able to neutralise the toxic products of metabolism, which therefore injure the renal system, producing albuminuria and tetanic convulsions.

The pathological anatomy of man confirms the experimental data from other animals, *i.e.* it teaches us that the tetany of thyroid excision, the so-called "*tetania thyreopriva*," is only a "*tetania parathyreopriva*." We owe to Erdheim some careful notes on serial sections of the organs of the neck in three persons who died from tetany after excision of the thyroid. In two of these the parathyroids were entirely wanting, in the third, one only

remained, and that was necrosed. These three cases, therefore, verified what experiments on animals had indicated. To-day every surgeon agrees with Vassale's conclusions that in thyroid excisions it is essential, in order to avoid a fatal tetany, to spare at least one or possibly two of the parathyroids (the two inferior parathyroids).

Another form of human disease which is also characterised by violent convulsions, and which is known as *eclampsia gravidica*, has recently been attributed by Vassale and his pupils to functional insufficiency of the parathyroid apparatus. To support this theory Vassale invokes the following facts :—

In the first place, he observed and described a case of tetany of lactation and pregnancy in a partially parathyroidectomised bitch, in which after some five years of apparently normal life after the operation, suckling and pregnancy provoked violent convulsive epileptiform fits, which were cured by specific organo-therapy.

Other authors had already observed independently that the female of dogs or cats, in which the thyroid apparatus had been partially extirpated, are attacked during pregnancy and parturition with acute convulsions (Verstraeten and Vanderlingen, Lange). According to Vassale, the convulsions in this experiment also, in which thyroidectomy involved parathyroidectomy in the dog or cat, were due to parathyroid insufficiency.

Another no less valid argument in favour of the parathyroid theory of the pathogenesis of *eclampsia gravidica* is seen, according to Vassale, in the beneficial effects observed in certain cases of spontaneous *eclampsia gravidica* with specific organo-therapy, on administration of parathyroidine.

More recently, Vassale has found further evidence for the parathyroid theory of eclampsia in the following observations :—

(*a*) Pathological, the post mortem showing alterations or congenital loss of one or two parathyroids in the bodies of eclamptics (Pepere, Zanfrognini).

(*b*) Clinical, since it has been found possible to prevent and even overcome the spasm by the administration of parathyroiodine (Zanfrognini, Stradiviri, Brun, Vicarelli, Kaiser).

(*c*) Experiments on cats, on female rats, and gravid bitches, which show that in latent parathyroid insufficiency convulsive phenomena regularly break out in the final stage of pregnancy (*experimental eclampsia* of Zanfrognini, Erdheim, Thaler, and Adler, Vassale, Massaglia and Sparapani).

Lastly, it should be added that certain workers (Pineles, Chvostek and Yanase) express the opinion, on clinical and anatomical grounds, that all the varied pathological forms of tetany in man are in pathogenic relation with insufficiency of the parathyroid glands.

XI. The Pituitary Body (*hypophysis cerebri*) consists of two distinct parts or lobes (Fig. 7). The posterior lobe, which is greyish-yellow, is an outgrowth from the third ventricle of the brain; it has no glandular structure and is probably a rudimentary organ of no importance—in vertebrates at any rate. The anterior lobe, on the contrary, which is reddish in colour, and is much more highly developed than the posterior lobe, has quite a distinct function, and is derived from the primitive pharynx. At a certain point in embryonic development it appears as a pouch, which is empty at first, and subsequently fills by the development of

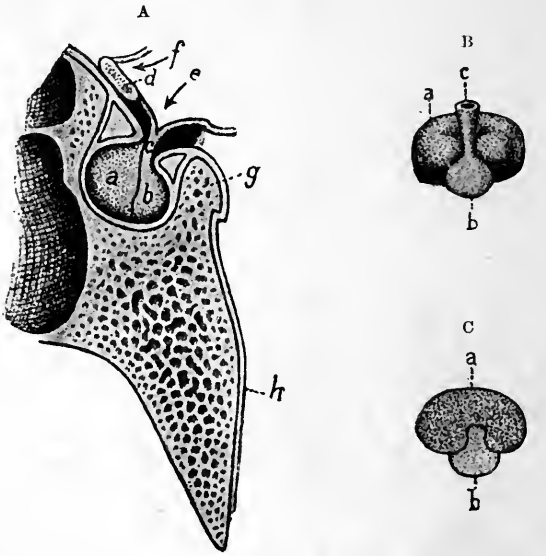

FIG. 7.—Hypophysis or pituitary body. A, lateral aspect, showing relations with sella turcica. B, posterior aspect. C, sagittal section. *a*, anterior lobe of hypophysis (pituitary body proper); *b*, posterior or nervous lobe; *c*, pineal peduncle; *d*, optic chiasma; *e*, infundibulum; *f*, optic foramen; *g*, quadrilateral plate of sphenoid; *h*, sulcus occipitalis.

epithelial cells disposed in groups or columns, which recall the structure of the parathyroids. Two kinds of cells can be distinguished, the chief cells and the chromaphile (Fig. 8).

The latter have a special affinity for stains, and react like "colloid" substances; they are probably more developed than the chief cells, and serve for the secretion of a hyaline substance, in analogy with the epithelia of the thyro-parathyroid system (Lothringer). The secretion passes into the lymphatic spaces of the surrounding connective tissue, and also in part to the blood-vessels, in which it may for short distances replace the blood entirely (Pisenti and Viola).

Experiment on the functions of the pituitary body has led to

divergent, often indeed contradictory, results. Hypophysectomy, initiated with little success by Horsley, Dastre, Gley, Marinesco, was pursued with a better technique by some of the Italian workers.

Vassale and Sacchi (1892-94), in a considerable number of experiments on cats and dogs, obtained the survival of a few individuals, in which the hypophysis had been totally or partly destroyed by cauterising with chromic acid, a method that is certainly not free from objection.

The first symptoms observed in these animals is that of great depression and complete apathy, making them indifferent alike to caresses or ill-treatment. Motor disturbances, at first slight and afterwards more intense, set in. These consist of fibrillary movements, muscular contractions, rigidity of posterior limbs, curvature of back, unsteady gait, lastly clonic-tonic spasms of varying intensity, in the course of which the animal succumbs without the slightest trace of infective or other complications being discovered at the post mortem. With these symptoms are associated anorexia, tachypnea, polyuria, growing density of highly alkaline urine (without either albuminuria or glycosuria), hypothermia, rapid and progressive emaciation, coma not infrequently preceding death, which occurs in 2-11 days after the operation.

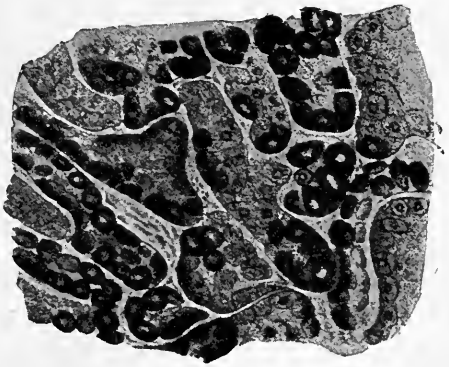

FIG. 8.—Section of pituitary body of horse. Stained with Weigert's method. (Lothringer.) The lighter, principal cells can be distinguished from the darker, chromaphile cells.

Gatta (1896) and Kreidl and Biedl (1897) repeated these experiments, and obtained results which agreed approximately with those of Vassale and Sacchi.

The syndrome obtained by Caselli (1900) in his many experiments on hypophysectomy in both dogs and cats was somewhat different: depression of mental powers, motor disturbances, curvature of back, spastic gait without convulsions, progressive cachexia, rapid loss of weight, coma, death.

This syndrome has undeniable resemblances with that which appears after excision of the thyro-parathyroid organs, justifying the surmise of Rogowitsch (1888) that the pituitary and the thyroid glands are homologous, and are therefore able to function vicariously. In order to discover why rabbits always support thyroidectomy without injury, he made a microscopic examination

of the various organs of these animals in search of possible modifications. The glandular part of the hypophysis proved to be considerably larger in volume, with bigger follicles, and more colloidal substance in the interfollicular spaces. This led him to conclude that in rabbits the hypophysis might supplement thyroid deficiency.

The experiments of Rogowitsch were repeated and confirmed by Stieda (1890), Hofmeister (1882), Gley (1892), and others.

Tizzoni and Centanni (1890) observed the same facts in three dogs that long survived total thyroidectomy as Rogowitsch had noted on rabbits, and came to a similar conclusion. Schönemann (1892) adduced the results of clinical observation in support of the same thesis, and demonstrated a hypertrophy of the pituitary body in cases of goitre, when a great part of the parenchyma of the thyroid gland does not function. These observations, although contradicted by Schwarz, have recently been confirmed by Comte.

This theory of a close relation and functional substitution between the thyroid and the hypophysis was shaken by the work of Vassale and Sacchi, and of Caselli, while the later observations of Gaglio on amphibia (1900), and of Lo Monaco and Van Rynberk in our laboratory (1901) on dogs, proved that the syndromes brought forward to support it are not the necessary and direct consequences of loss of the pituitary body.

Moreover, Luzzatto, working in Coronedi's laboratory on the hypophyses of animals that long survived the total ablation of the thyro-parathyroid apparatus, never succeeded in finding any morphological indication of hypertrophy of the pituitary body from exaggerated function.

The same negative results were obtained by Friedemann and Maass in Germany, and more recently by Dalla Vedova (1903) in the Institute of Surgery in Rome. Thus, whatever may be the function of the pituitary body, we now know that it is not of sufficient importance for its complete ablation necessarily to bring about the death of the animal, provided the technique is satisfactory.

Nor did Cyon's experiments (1898-1902) lead to more positive results. Starting from his work on the thyroid he assumed that the hypophysis co-operated with this organ in maintaining equilibrium of endocranial pressure, founding his theory upon the alterations of pressure consequent on injections of pituitary extract obtained by various methods. It may be remarked that the results of various experimenters as to the rôle of the supposed active principles of the pituitary gland differ widely. According to Szymonowicz (1898) pituitary extract diminishes blood pressure and accelerates the pulse; Schäfer and Swale Vincent (1899) say that it raises blood pressure; Mairet and Bosch (1896), that it excites the nervous system;

Osborne and Vincent, on the contrary, that it has a depressing action; Howell (1897), that it retards and reinforces the pulse; according to Cyon, lastly, it contains two active substances, the one retarding, and the other accelerating, the pulse.

Cyon thought he had demonstrated that the hypophysis regulates endocranial pressure, slowing and strengthening the pulse, and reducing blood pressure, by the fact that its direct stimulation by gentle mechanical compression and weak electrical currents, produced these effects. It is difficult to determine exactly how much of this interpretation can be accepted. The situation of the pituitary body justifies the assumption that its excitatory impulses are transmitted by the lobule of the infundibulum to the cardiac centres of the vagus. If this be so, it plays no part in the production of the phenomena described.

Gaglio, moreover, found that in frogs operated on by hypophysectomy, the bulbar centres of the vagus are as excitable to increased blood pressure, not only days and weeks, but also a few hours, after the operation, as in normal frogs. This does not agree with Cyon's observations on rabbits.

Nor has clinical observation thrown more light on the functions of the hypophysis. Since Marie and Marinesco (1891) suggested that *acromegaly* was the expression of a systematic dystrophy, consequent on functional disturbance of the pituitary body, many new facts have militated against their theory. Collina (1898) diligently collected all cases of this disease in which there had been a post mortem. He found that in a large majority the tumour was represented by adenomata and sarcomata. On the other hand, as was observed by Strümpell (1897), hypophysal tumour is not invariably present in acromegaly, while such a tumour often occurs without acromegaly. As regards organo-therapy, Mendel and Marinesco (1895) noticed improvement with pituitary extract; Schultze, on the contrary (1897), denied that it had any beneficial action.

The function of the hypophysis is therefore wholly undetermined, and it may be stated in conclusion that of the various far-fetched and improbable theories, that proposed by Rogowitsch as above appears least hazardous, although it has not been demonstrated.

Among the more recently acquired experimental data the following should be noted.

Guerrini (1904) found, by a series of microscopic researches on various animals, that the pituitary body, in every alteration of metabolism due to endogenous or exogenous intoxication, exhibits phenomena of functional irritation analogous to those shown in other glandular organs; if protracted, these may lead to hypertrophy and hyperplasia of the parenchyma of the gland.

Fichera (1905) in a first series of experiments (macroscopic

and microscopic) on fowls, buffaloes, oxen, rabbits and guinea-pigs, concluded that there is an intimate relation between the hypophysis and the sexual glands (testicles, ovary), which, as we shall see elsewhere, are also the seat of an important internal secretion.

He found in castrated animals that removal of the testicles or ovaries led rapidly to hypertrophy and hyperplasia of the pituitary body, which showed histological modifications indicative of functional hypertrophy. If the castrated animals are treated by organo-therapy with the sexual glands, the irritative phenomena of the parenchyma of the hypophysis are reduced and eventually disappear.

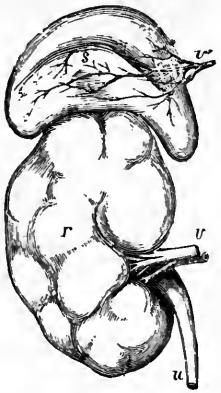

FIG. 9.—Right kidney and suprarenal body of a full-grown foetus. Front view. (Allen Thomson.) *s*, suprarenal capsule; *v'*, vein issuing from it; *r*, foetal kidney; *v*, renal artery and vein emerging from hilium; *u*, ureter.

In a second series of experiments, Fichera (1905) destroyed the hypophysis in fowls by a new method of operating. He found in a number of experiments, confirmed by microscopic examination, that this organ was not indispensable to life. Animals that survived its total destruction merely exhibited an arrest of development, particularly as regards the skeleton.

Gemelli has recently obtained almost identical results.

Cerletti (1906-8), studying in young guinea-pigs, rabbits, dogs, and lambs the effect on somatic growth of continuous injection of extract of lamb's hypophysis, showed that this substance particularly affects the development of the skeletal system, although in an opposite sense to what might be expected from the preceding experiments. He concluded from his observations that persistent dosage with pituitary extract retards the growth of the body in general, as shown most deleteriously for the skeletal system, where the activity of the connecting cartilages (delay in lengthening of long bones) is conspicuously diminished, while the activity of the periosteal ostogenic function (increased development of depth of epiphyses and diaphyses) is, on the contrary, augmented. Control animals treated with extracts of other organs (thyroid, muscle) did not exhibit similar changes.

The results of these new experiments indicate that the hypophysis is a gland of *internal* secretion, serving in some way to excite or regulate the metabolism of the body and the development of its various organs, particularly of the skeletal system. While too indefinite to represent an exact theory of the function of the hypophysis, this view is, on the other hand, supported by clinical observations on acromegaly and gigantism, which are often, if not

always, accompanied by hypertrophy and hyperplasia of the pituitary body.

XII. The Suprarenal Capsules or Adrenals are two epithelial flattened bodies of a yellowish-brown colour, situated above the

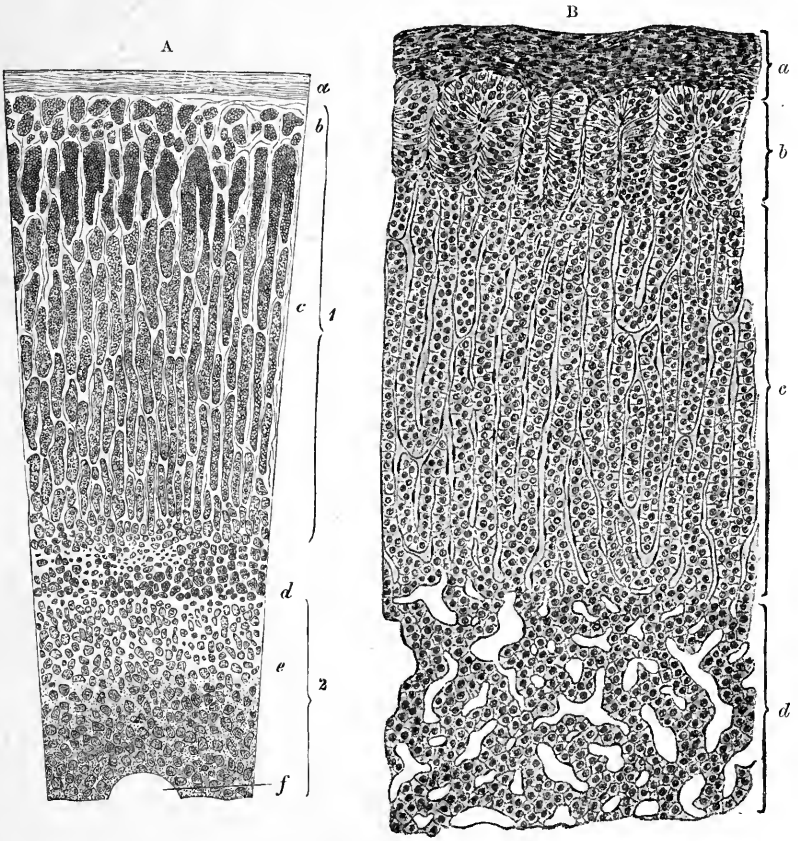

FIG. 10.—A, Human suprarenal body; vertical section. (Eberth). 1, cortical substance; 2, medullary substance; *a*, capsule; *b*, zona glomerulosa; *c*, zona fasciculata; *d*, zona reticularis, *e*, groups of medullary cells; *f*, section of a large vein. B, cortex of dog's suprarenal; vertical section. (Böhm and v. Davidoff.) *a*, fibrous covering; *b*, zona glomerulosa; *c*, zona fasciculata; *d*, zona reticularis.

kidneys, each weighing about four grammes. They reach their maximal development during intra-uterine life. Their size is considerable in proportion to that of the kidneys in the foetus at term (Fig. 9). This fact, discovered by Meckel, was confirmed for man by A. Ecker and H. Frey. It does not, however, signify (as Bischoff maintained) that the functions of the suprarenals are in relation with embryonic life, since they would

in that case atrophy after birth, whereas their growth continues, though very slowly, till the adult age (Brown-Séquard).

In section, the fibrous sheath is succeeded by a broad cortical layer, hard, striated in appearance, and dark yellow, which forms the principal mass of the gland, and an inner, medullary part, soft and brownish in colour: the older anatomists took this to be a dense secretion collected in a cavity, from which they incorrectly designated the whole organ a *capsule* (Fig. 10, A).

From the fibrous sheath, which often contains plain-muscle cells (Fusari), fine septa or trabeculae are given off into the organ, and serve as a framework which supports the columns of polyhedral epithelium cells.

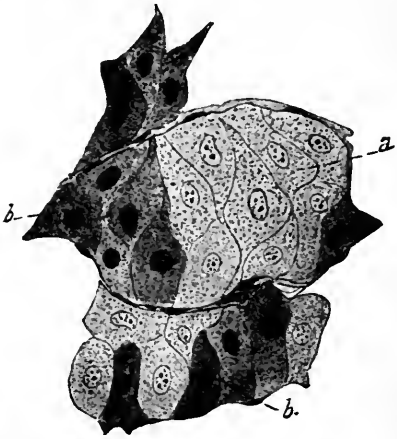

FIG. 11.—Medullary substance of suprarenal body of ox, stained haematoxylin. (Vassale.) *a*, resting cells; *b*, cells in active function, filled with chromaffine substance which is discharged directly into the blood capillaries.

Three zones can be distinguished in the cortex, better in some other animals than in man, which are differentiated by the arrangement of the epithelium cells: these are known as the zona glomerulosa, the zona fasciculata, and the zona reticularis (Fig. 10, B).

The medulla is separated from the cortex by a sheet of loose connective tissue. It is composed of a network, the meshes of which enclose cell-columns, which differ from those of the cortex in being larger, less granular, more irregular in form, and vacuolated, and they stain a brown colour with solutions of chromic acid and its salts, while the cortical cells give hardly any such reaction. Owing to this specific property the medullary cells have been termed *chromaffine* or *chromaphile* (Kohn), a term now frequently used to distinguish the medullary from the cortical substance (Fig. 11).

The difference between the two parts of the adrenal glands is not confined to this histological peculiarity. According to recent work in embryology and comparative anatomy, the medullary and the cortical substance represent two perfectly distinct and independent organs, which in the majority of vertebrates fuse together during foetal development, and apparently form only one single organ. In the Elasmobranchs, on the contrary, the two organs remain separate during the whole of the animal's life. Balfour (1877) showed that these fishes have no

"suprarenal capsules" analogous to those described in mammals, but possess two sets of perfectly distinct organs:—

(*a*) The *inter-renal* body, an unpaired glandular structure, homologous with the cortical substance of the adrenal gland in mammals.

(*b*) The *suprarenal bodies*, arranged in pairs, in close relation to the ganglia of the sympathetic chain, homologous with the medullary or chromaffine substance of the adrenal glands.

These results have been confirmed and amplified by recent workers, among them being Diamare and Giacomini in Italy.

The work of embryologists (of Kohn, in particular) on mammals, including man, has fully confirmed the double nature of the suprarenals. In fact, while the cortical substance is mesoblastic in origin (Wolffian body), the medullary substance is derived from the phaeochromoblast, one of the two groups of embryonic cells into which the primary sympathetic (ectodermic) cells become differentiated. All such chromaffine or chromaphile cells derived from sympathetic ganglion rudiments were classified by Kohn as *paraganglia*. At a later period of development the bulk of the chromaffine or (as Poll termed it) phaeochrome tissue enters into relation with the epithelial substance of the cortex, in which it is englobed, and thus forms the medulla of the gland or "suprarenal paraganglion" (Fig. 12). The whole of the chromaffine tissue derived from the mother-cells of the sympathetic ganglia is not, however, enclosed in the capsule: some of the smaller masses remain in various regions more or less adherent to the sympathetic ganglia or the blood-vessels. These nodules of chromaffine substance constitute the *carotid* and *sacral* glands, Zuckerkandl's *parasympathetic body* or *abdominal aortic paraganglion*, etc., which have long been observed without definite knowledge as to their origin and significance (Fig. 13). They are now shown by recent work in embryology,

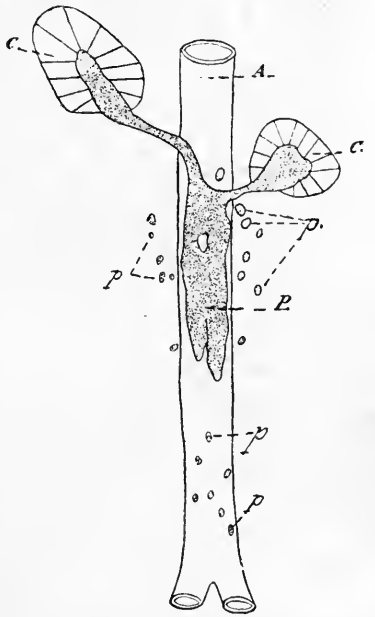

FIG. 12.—Schematic reconstruction of paraganglion in new-born rabbit. (A. Kohn.) *A*, aorta; *C*, suprarenal body; *P*, abdominal paraganglion, which, with its prolongations, joins the medullary substance of the suprarenal capsules; *p*, *p*, *p*, small nodular paraganglia.

histology, and experimental physiology, to be organs entirely similar to the medullary substance of the suprarenal bodies.

Chromaffine or "paraganglíar" tissue is thus closely related to the nerve cells of the sympathetic system, being in fact differentiated from the same embryonic group of cells. In adult animals it is still intimately connected with the sympathetic

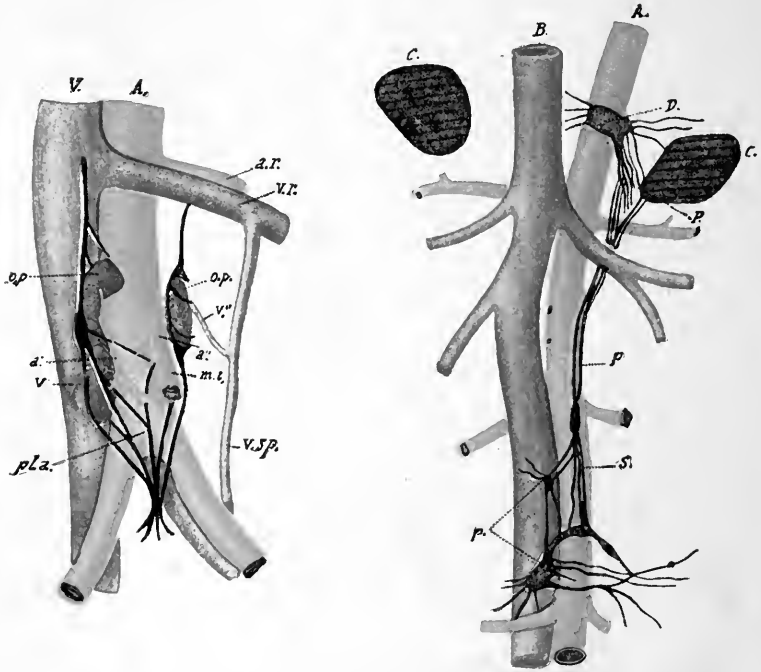

FIG. 13.—(Left.) Parasympathetic bodies of Zuckerkandl (human). From an anatomical preparation of Sperino and Balli. *A*, aorta; *V*, vena cava; *ar*, left renal artery; *vr*, left renal vein; *op*, parasympathetic bodies, or paraganglia; *a' v'*, artery and vein of right paraganglion; *a'' v''*, artery and vein of left paraganglion; *mi*, inferior mesenteric artery; *v.sp*, spermatic or ovarian vein; *pla*, aortic plexus of sympathetic.

FIG. 14.—(Right.) Paraganglion of adult cat. (A. Kohn.) *A*, aorta; *B*, vena cava; *C*, suprarenal capsule; *D*, caeliac ganglion; *S*, sympathetic; *P*, abdominal aortic, filiform paraganglion; *p*, punctiform paraganglia.

system, many ganglion cells being mixed with the cells of the medullary substance of the suprarenal bodies, while nodules of chromaffine tissue adhere to the sympathetic chain in various regions (Fig. 14). Chromaffine tissue has accordingly been defined as "an epithelial tissue of neural origin" (Diamare).

Functionally, too, we shall find an intimate relation between the sympathetic system and the product of the internal secretion of chromaffine tissue.

The arteries that supply the suprarenals penetrate the cap-

sular sheath at various points, after subdividing into small branches. The veins in the medullary substance form a plexus, and usually converge into one large vein for each organ, which leaves by the hilum. That on the right opens directly into the inferior cava; that on the left, after a longer course, into the left renal vein.

According to Pfaundler, the internal vessels of the suprarenals have no proper tunica externa and media, only a thin wall consisting solely of intima.

The lymphatics course through the trabeculae of the cortical substance, and are connected with the lacunae or fissures lying between the trabeculae and the columns of cells, and between the cells themselves (Klein). In the medullary substance the lymphatics, which are provided with valves, form a plexus that interlaces with the venous plexus, and surrounds the central vein.

Both suprarenal bodies and paraganglia contain an enormous number of nerves deriving from the solar and the renal plexuses (Fig. 15). They are mainly medullated fibres of different sizes, interspersed before entering the capsule with a number of small ganglia. They ramify between the cells of the cortex, and are most abundant in the zona glomerulosa. In the medulla there are many ganglion cells united in groups, and nerve fibres, which are distributed to the vessels and also perhaps to the gland-cells.

In rare cases one or both suprarenal bodies are absent. More frequently there are *accessory adrenals,* which vary in size from a pin's head to that of a pea. The smallest have no medullary substance (Rolleston). These accessory capsules are usually found in the neighbourhood of the capsule itself; but they are sometimes partially embedded in the kidney or liver, the broad ligament of the uterus, and along the spermatic vessels.

In 1789 Cassan observed that the suprarenal capsules are larger in the negro than in Europeans, which led him to suspect that these organs are in some relation with the formation of cutaneous pigment. Meckel subsequently confirmed Cassan's observations, but held the greater development of the capsules in negroes to be in relation with that of the genital organs. These anatomical observations of Cassan and Meckel are in line with the work of Addison, published in 1855, which promoted experimental investigation of the suprarenal bodies, and may be said to have initiated the physiological study of these glandular organs.

XIII. Addison was the first to describe a form of disease which is nearly always fatal, and is characterised by a state of progressive anaemia, pronounced weakness of cardiac beat, great irritability of stomach, and general atony of nervous and muscular system, with abnormal brown or bronzed patches on

the skin. From this last very apparent symptom, he named the new form of disease "*bronzed skin.*" Addison believed it to depend on deficiency or functional insufficiency of the suprarenals, of which he recognised the great physiological importance. He further held that there was a relation between the absence or diminished function of the suprarenals, and the amount of pigment deposited in the skin. By diligent research into the

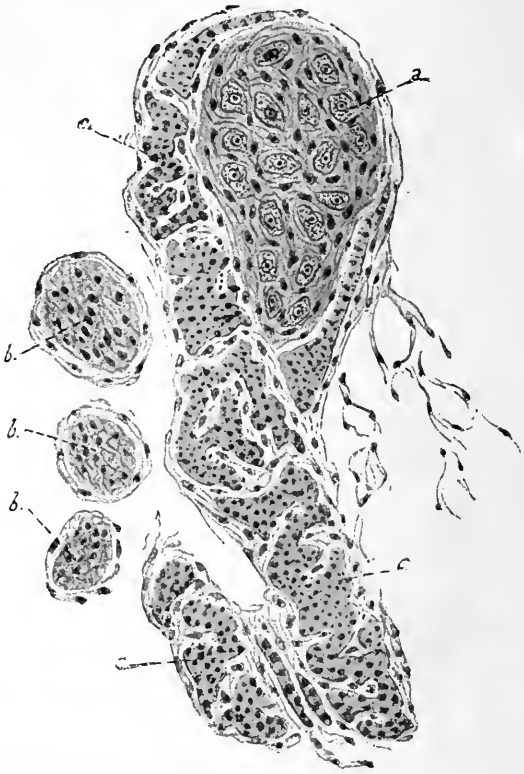

FIG. 15.—Transverse section of abdominal aortic paraganglion of adult cat. (Vassale.) *a*, sympathetic ganglion; *b*, *b*, *b*, nerves; *c*, paragangliar or chromaffine tissue.

pathological anatomy of almost every one who had died of "bronzed skin," he discovered profound alterations in the capsules of various kinds, more particularly of a tuberculous nature.

Starting from Addison's researches, Brown-Séquard (1856) performed a series of experiments on animals, and came to the same conclusion as the English pathologist, viz.: that the suprarenal capsules were organs indispensable to life.

On destroying the capsules, Brown-Séquard found that they

are peculiarly sensitive in rabbits, which give cries of pain when one of these bodies is crushed in the forceps. Those of dogs, cats, and particularly guinea-pigs are less sensitive.

When one capsule only was excised or destroyed by crushing, Brown-Séquard invariably noted the death of the animal (rabbits, guinea-pigs, dogs, cats) in less than three days. But he subsequently found that destruction of the right capsule alone was not fatal. Immediately after the operation the animals rotated upon their own axis, now in one, now in the other direction, and the pupils of the side operated on were found to be more contracted. These are inconstant phenomena of stimulation, due probably to the method of crushing adopted by Brown-Séquard, in which the many ganglion cells contained in the organ are violently excited.

The suppression of both capsules invariably kills the animal, rabbits in 9-10 hours, dogs and cats after 49 hours at most. As a rule young animals survive longer than adults.

In consequence of the suppression of the capsules, the animals fall into a state of profound lassitude, which differs from that consequent on any other severe and painful operation by its sudden onset after 10-15 minutes. The weakness increases, and 15-20 minutes before death assumes the form of regular paralysis, attacking first the hind-limbs, then the fore-limbs, and lastly the respiratory muscles. Sensibility persists to the last hour, and may even be exaggerated. Convulsions are frequent in the hours previous to death. The respiratory and cardiac movements are usually accelerated at first, and then become progressively weaker. Appetite disappears: digestion is suspended: urinary secretion, on the contrary, continues normal. The temperature falls considerably (from 4°-5° C. in winter).

Brown-Séquard, by special experiments, demonstrated that the excision of both capsules usually involves the death of the animal more rapidly than ablation of the kidneys. Hence he regarded them as organs indispensable to life, the death which follows their removal being due to the lapsed function of the suprarenals.

These data at once aroused opposition. Gratiolet and Philippeaux (1856-57-58) in France, Berruti and Perosino (1857-63) in Italy, denied the inevitable death of the animals operated on, and referred it either to operative traumatism, or to peritonitis or other secondary effects. Brown-Séquard did not reply exhaustively to all the criticisms, and the question of the functional importance of the suprarenals remained for a long time a matter of controversy. The subject has been revived of late, with strictly aseptic methods, by a number of workers who have confirmed, developed, and extended to other glandular organs the conclusions of Brown Séquard, to whom therefore belongs the honour of having founded the doctrine of *internal secretion.*

Cases of survival of the animal after the excision of both capsules are rare, and must be explained either by incomplete extirpation or by the existence of accessory suprarenals (Szymonowicz). The most important points in the rich modern literature of the *physiology of the capsules* may be briefly summarised.

The methodical research undertaken by Abelous and Langlois (1891-92) on the frog showed that—

(*a*) Complete destruction of the capsule by the method of cauterisation inevitably causes death (after 12-13 days in winter, after 48 hours in summer) with symptoms of progressive paralysis, which commences in the lower limbs (24-30 hours after the operation) and subsequently becomes general and produces death.

(*b*) General paralysis follows more rapidly if the frog is frequently excited after the operation, so as to provoke muscular movements.

(*c*) Destruction of one capsule alone produces no morbid effects in the frog: complete destruction of one capsule and of the greater part of the other determines death in most cases, but after a longer time. Death is then invariably preceded by convulsions and dyspnoea.

(*d*) On grafting the capsules of a normal frog into the dorsal sac of the decapsulated frog, the survival period of the latter is doubled. On dissection, the graft is found not to have taken, the capsules being reduced in volume and decolorised. Injection of a watery suprarenal extract results in a less marked prolongation of life.

(*e*) Intravenous or subcutaneous injection of the blood of a moribund, decapsulated frog into a frog that has been recently operated on, causes rapid paralysis and death. The same injection into a normal frog produces only slight and transitory disturbances.

(*f*) If immediately after destroying the capsules in a frog the sciatic is exposed, and a thread tied round the leg at a lower point, by Bernard's method, while the blood from a moribund decapsulated frog is injected under the skin, then at a certain stage of intoxication (3 hours after injection) the most powerful induction shocks have no effect on the sciatic of the free limb, while a weak current easily borne by the tongue produces energetic contractions from the sciatic of the ligatured limb. Direct application to the muscles of either leg produces contractions, which are, however, stronger in the tied than in the free limb.

From these facts Abelous and Langlois concluded that death from removal of the capsules is due to the accumulation in the blood of one or more toxic curarising substances, *i.e.* such as act like curare on the end-plates of the motor spinal nerves, and in a

less degree upon the muscles. Albanese, independently of the French investigators, confirmed their results, and brought out still more clearly the influence of muscular fatigue upon duration of life in decapsulated frogs. He held the toxic substances of unknown nature which determined the fatal effects to be produced during work by the muscles and nervous system.

Abelous and Langlois performed a second series of experiments on the guinea-pig, in which the capsules are highly developed in relation to the total weight. Each capsule on an average weighs 12 cgrms. in guinea-pigs of 500 grms., while in rabbits of 2 kilos. they only reach 10-15 cgrms., and 1 grm. in dogs. On the other hand, accessory capsules are very rare in guinea-pigs, while they frequently occur in rabbits and dogs.

The effects of destroying one capsule only, of partial cauterisation, and of total destruction of both capsules in the guinea-pig, tally with the experiments on frogs, and confirm the theory which Brown-Séquard formulated in 1856, *i.e.* that the suprarenal capsules are organs for elaborating substances destined to modify or destroy the toxins of curarising action which accumulate in the body after the destruction of the adrenals.

Much work on rats, rabbits, cats, and dogs was contributed by other observers. The divergence in their conclusions is evidently due to the variations in operative procedure. Schiff (1863), Tizzoni (1884), Russo-Giliberti and Di Mattei (1886), Alezais and Arnaud (1891), Berdach and Pal (1894), Boinet (1895), sustained that the ablation of both capsules in rats, rabbits, and dogs was compatible with survival, but we may now assume that they only partially destroyed these organs, or chanced on animals with accessory suprarenals.

The results which the brothers Marino-Zuco (1892) obtained on rabbits agree perfectly with those of Abelous and Langlois on guinea-pigs. Removal of both capsules was fatal after three to five days, with paralytic phenomena; removal of one capsule only was compatible with survival, and no detrimental changes occurred in the rabbits that were partially decapsulated on both sides. But some time after partial capsular ablation, rabbits that were not albinos frequently exhibited an abnormal distribution of pigment in the skin or the oral or nasal mucosa, viz. formation of bronzed or grey patches in places where they had not occurred previous to the operation (Nothnagel, Tizzoni, Marino-Zuco). This phenomenon recalls the abnormal pigmentation of the skin in Addison's disease.

In conclusion, the long series of experiments carried out in Tigerstedt's laboratory, by his pupils Hultgren and Andersson (1899), generally speaking, confirm the preceding researches; with the addition of some new and interesting details:—

(*a*) The excision of both capsules seems always to be fatal in

dogs or cats, after sixty-eight hours on an average: but if the excision be effected in two or three sittings, life is prolonged by about double the number of hours. Castrated cats survive the longest.

(*b*) Excision of both capsules is fatal to rabbits after five to six days: but if a certain period intervenes between the two operations, the animal may live for months without any pathological disturbance.

(*c*) Partial unilateral or bilateral excisions are compatible with survival. More or less transitory or persistent symptoms of functional insufficiency appear, particularly emaciation.

(*d*) In the final twenty-four to forty-eight hours of survival of decapsulated animals there is a characteristic lowering of temperature.

(*e*) During this hypothermia of collapse, injection of suprarenal extract raises the temperature again, and improves the state of the animal. By such injections life may be prolonged for some twenty-four hours.

(*f*) Suprarenal extract injected into the veins or beneath the skin of normal rabbits in a given variable dose, produces death by oedema and pulmonary haemorrhage.

XIV. Till the opening of the present century the suprarenal bodies (on the strength of the data above discussed) were universally regarded as glands endowed with a single, specific, protective function.

But when further research in comparative anatomy and embryology brought to light the important fact that the cortical and medullary parts of the organ are composed of elements dissimilar in nature and in origin, it became clear that the suprarenals serve a double physiological function.

In Italy Vassale was the first to take up this position. He established the special importance of the medullary substance by a number of experiments (in collaboration with Zanfrognini 1902-3) on the removal of the suprarenal capsules in the cat and rabbit. With complete ablation of the medullary substance, the greater part of the cortical substance being left intact, the animals die with the same acute symptoms as ensue on excision of the entire suprarenals. If the ablation of the medullary substance is partial, and small fragments of it are left, the animals die from serious functional insufficiency after 3-4 weeks, with symptoms of a special cachexia (anorexia, psychical depression, asthenia, fall of temperature, marked emaciation).

Independently of Vassale, H. and A. Christiani (1902) excised the suprarenal glands in rats, with the following results. With bilateral excision death is rapid and invariable, whether the operation be performed in one or in two sittings, even if there be a year's interval between the two operations. Unilateral ablation

produces no ill-effects. If one capsule is wholly, the other partially, excised, it is sometimes found that a minute vestige of the organ suffices to keep the animal alive, while in other cases death supervenes, although a comparatively large portion of the organ may remain. Histological examination shows that in the first case medullary substance has been left, in the second it has perished. The specific function must, therefore, lie in the *medullary substance.*

Another experimental proof of the great importance of the medullary substance appears from the results of *grafting* the suprarenal bodies. Animals subjected to bilateral ablation of both capsules die, even if other suprarenals are grafted in their bodies, and become attached. Now, while the cortical substance is capable of regenerating and becoming rooted in the region into which the organ is transplanted, the medullary substance does not survive and degenerates completely (Poll, H. and A. Christiani). According to Vassale the chromaffine tissue is fundamentally altered, and loses its capacity of increasing in size by hyperplasia of its own cells, when, owing to the partial ablation of tissue, the remainder is forced into functional hyperactivity. The phenomena of compensatory hypertrophia with cellular hyperplasia, observed by Stilling (1889), and Wiesel (1899), in the surviving capsule, or the accessory suprarenal bodies, after the extirpation of one or both suprarenal capsules, involve only the cortical and not the medullary cells. Landau (1898) again found in his experiments on transplantation of the capsule and unilateral capsulectomy that the taking of the graft in the first case, and the hypertrophy in the second, are always limited to the cortical substance, and never involve the medullary.

From these experiments the theory of the heterogeneous nature and double function of the cortical and medullary substance, and of the preponderating importance of the latter, seems well-established. Certain objections, however, may be raised, and have to be met before the question can be regarded as settled. Kohn (1903), makes the following criticisms:—

The rare cases in which the bilateral ablation of the suprarenal bodies was not followed by death, were explained by invoking the vicarious action of accessory suprarenals remaining uninjured in the body of the animal (Stilling, 1887). These accessory organs, however, shew no trace of chromaffine tissue. On the other hand, some mammals, *e.g.* cat and rabbit, in which extirpation of the suprarenal bodies is followed by death, possess in addition to these organs, conspicuous masses of chromaffine tissue, *e.g.* on the ventral surface of the abdominal aorta. Why, he asks, are these masses not capable of saving the animal from death, since a minute vestige of medullary substance is able to do so? The results which Abelous and Langlois obtained from amphibia agree still less with

the modern view, because in these animals the quantity of extra-capsular chromaffine tissue is comparatively large as compared with the intra-capsular bulk of the same tissue.

On the other hand, the experimental results of Pettit (1896) and Swale Vincent (1897), on Teleosteans, give support to the modern theory. They found that eels for months survived the ablation of the suprarenal bodies, which in these animals consist of cortical tissue only. The chromaffine tissue, which, according to Giacomini (1902), lies near the cardinal veins, escaped the operation.

In conclusion, Kohn recommends that more attention should be paid in future to the amount and condition of the whole of the chromaffine tissue, in the individual animals operated on.

Vassale (1905) subsequently attempted by special experiments to decide how great an importance attaches to the extra-capsular chromaffine tissue.

In kittens, extirpation of one capsule and of the abdominal aortic paraganglion may determine death with the same symptoms that are observed after bilateral ablation of the suprarenal bodies, or the bilateral removal of their medullary substance. In the adult cat the same operation does not induce rapid death; the animal succumbs after about ten weeks, during which period, although it eats with great voracity, it becomes more and more emaciated, and perishes of marasmus. Dogs will tolerate the removal in a first operation of one capsule and the abdominal aortic paraganglion, and in a second, of the half of the remaining capsule; on the other hand, they cannot bear this triple removal if performed in a single sitting—the animal then succumbs in twenty-four hours.

Vassale showed that in the dog and cat the extra-capsular chromaffine tissue varied in amount from animal to animal in the same species, and suggested on the strength of his experiments that the survival of some animals after decapsulation in successive sittings was to be explained by the quantity of chromaffine tissue or of extra-capsular paraganglia. The satisfactory state of animals operated on in one or many sittings by maximal capsulectomy, or partial excision, leaving the animals enough capsule to keep them alive, is due, according to Vassale, to adaptation only. Since the remaining chromaffine tissue (he says) is incapable of hyperplasia, although it does exhibit some functional hyperactivity, true compensation of the lost functions cannot take place.

Admitting that the cause of death in animals exposed to bilateral capsulectomy is to be ascribed exclusively to the suppression of the *medullary* or *paragangliar* substance of the suprarenal bodies, we still have to define the specific functions of the *cortical* substance. Vassale and Zanfrognini have proposed the hypothesis that the destruction of this part may be associated with

remote morbid phenomena, similar to or identical with the trophic and cutaneous disturbances of *Addison's disease*. The latter are seldom obtained experimentally because, with total capsulectomy, the animals nearly always die with acute predominating symptoms of severe asthenia and paralysis, due to the suppression of the medullary substances.

XV. We cannot doubt, therefore, that the protective function of the double glandular organ formed by the suprarenal capsule must consist in arresting the action of one or more poisons normally formed in the body, and that the phenomena of deficiency or functional insufficiency of these organs are phenomena of intoxication. Numerous experiments have been made to determine the nature of these toxins, their mode of acting on the body, and the process by which the capsule renders them inactive.

As early as 1857 Vulpian noticed that the liquid extracted from the suprarenal capsules contains a special *chromogenic* substance, which, when exposed to the air, turns gradually carmine-red. The reaction is produced instantaneously with oxidising agents such as chlorine-, bromine-, and iodine-water. Krukenburg, in 1885, returned to the study of this chromogen, and reported that it gave certain reactions characteristic of pyrocatechin. Brunner (1892) confirmed the results of Krukenburg, and Moore (1895-97) succeeded in determining the chemical properties of the chromogen of the capsule more exactly.

Manasse (1893-94) found a substance in the blood of the suprarenal veins which turned brown when treated with potassium bichromate, and which is certainly secreted by the suprarenal capsules.

It is highly probable that these facts are in relation with the theory of Addison's disease, which attributes to the capsule (probably to the cortical part) the function of regulating cutaneous pigmentation. In what exactly this relation consists is unknown.

According to Nabarro (1895) the suprarenal capsules contain globulins and nucleo-proteins that precipitate with magnesium sulphate, and coagulate at 56°, 65°, and 75° C. An albumin is also present which coagulates at 71° C.

It has been shown by F. Marino-Zuco (1888) and F. Marino-Zuco and Dutto (1890-91) that the suprarenal capsules normally contain a considerable amount of *neurine*, and that individuals attacked by Addison's disease eliminate appreciable quantities of this base by the urine. Guarnieri and Marino-Zuco (1888), on injecting solutions of glycerophosphate of neurine in minute doses into rabbits, obtained phenomena of intoxication similar to those observed after excision of the capsules. Albanese (1892) found great sensibility of frogs, as well as of decapsulated rabbits, to neurine. Half a milligramme injected under the skin of the back (an insignificant dose to a normal frog) produces serious symptoms

of intoxication, and even death, if the frog is not very large. The dose of 1 mgrm. is always fatal to the decapsulated frog, while it takes 4 mgrms. to kill one that is normal. On the other hand, the brothers Marino-Zuco state that either the excision of one capsule alone, or the injection of non-toxic doses of neurine will after fourteen to twenty-four days cause slate-grey spots to appear on the skin, the buccal mucosa, and the under surface of the tongue.

These experimental data are the basis of the theory sustained by Marino-Zuco and Albanese, viz. that Addison's disease and the effects of artificial destruction of the capsule are due to neurine intoxication, and that the function of the capsules consists in modifying the neurine produced by the body, so as to render it innocuous.

In order to explain the process by which the capsules neutralise the activity of neurine, Carbone (1894) carried out a series of experiments to determine its effects upon normal and decapsulated dogs, tested by its elimination in the urine. He found that the normal dog bears a hypodermic injection of small doses of neurine without any symptoms; in the decapsulated dog, on the contrary, the same dose immediately produces salivation, and after a few hours, vomiting, diarrhoeal discharges, paralysis of the hind limbs. This led him to suspect that in the normal dog the neurine was rapidly destroyed or fixed by the capsule, while in the decapsulated animal it circulated and was eliminated unchanged in the urine. In order to verify this surmise, Carbone estimated the neurine eliminated by the urine, and found that the amount did not vary perceptibly in the normal dog and in those which had suffered ablation of three-fourths of both capsules. In both cases, only a small part, at most a fourth, of the injected neurine passes into the urine. The remainder is probably transformed or retained in the body.

In regard to the theory that the toxins causing the cachexia of Addison's disease consist in neurine or glycerophosphate of neurine, Neumeister points out that the neurine and glycerophosphoric acid found in the capsules may come from decomposition of their lecithin or choline, owing to manipulation of the chemical extracts. On the other hand, Oliver and Schäfer (1895) showed that the effects of injecting phosphate and glycerophosphate of neurine are totally different from those produced by suprarenal extract *in toto*.

Taken as a whole, these data leave no doubt as to the protective, antitoxic action of the suprarenal capsules, but it is still uncertain if this is effected by the removal from the blood of specific toxic substances, or by the secretion and output into the blood and lymph of one or more active substances, which are directly or indirectly antitoxic.

According to a theory brought forward by Cybulski (1895), the

entire morbid syndrome exhibited acutely after total destruction of the capsules, depends on the depression of tone in the vasomotor, cardiac, and respiratory centres, and also in all probability of the centres of muscular tone.

The active substances produced by the capsules (which reach the blood by the suprarenal veins) thus serve to keep up the normal tone of all these centres.

This view is supported by a series of experiments carried out partly with the collaboration of Szymonowicz, which may be summarised as follows :—

(*a*) After complete extirpation of both capsules (which the dog only survives for eight to fifteen hours) the arterial pressure falls to 20 mm. Hg below the normal; pulse and respiration become considerably slower. Intravenous injection of aqueous suprarenal extract raises pressure conspicuously, slows the pulse, and quickens respiration ; while the injection of other organic extracts has no effect.

(*b*) After section of the cervical cord, injection of suprarenal extract has no effect, showing that the increase of pressure is due to excitation of the bulbar vasomotor centre. On cutting the vagi, the slowing of the pulse caused by injection of the extract ceases, showing it to be due to stimulation of the moderator centres of the heart.

(*c*) The active substance is formed not after death, but during the life of the suprarenal bodies, passing by diffusion into the epithelial cells of the efferent veins. In fact, if the reduced venous blood from the capsule is collected and defibrinated, and then injected into the veins of an animal, the same phenomena are produced as are seen after injection of suprarenal extract, though less acutely. The venous blood from any other vein has no effect in the same doses. These results were confirmed by Salvioli and Pezzolini (1902).

(*d*) A long series of experiments shows that the active substance formed by the suprarenals is not toxic in moderate doses, but merely raises the tone of the vasomotor, respiratory, and cardiac centres, as well as the centres for muscular tone.

(*e*) The transitory nature of the excitation of the above centres by the active substance manufactured by the capsule, is explained on the assumption that it is partly eliminated by the kidneys, partly transformed by oxidation within the tissues. Probably the increase of arterial pressure, the slowing of the pulse, and the dyspnoea that accompanies the asphyxia, depend on the accumulation within the body of the active substances formed by the capsule, which under normal conditions are destroyed as fast as they form.

The exact physiological action of suprarenal extract on various tissues has been recently studied by Velich, Biedl, Wiesel, Gottlieb,

Pick, Langley, Elliott, Gioffredi, Salvioli, Patta, Vassale, Bottazzi, and many others. Contrary to the opinion of Cybulski, most authors now admit in explanation of the enormous vaso-constrictor action of this substance, that it acts peripherally upon the muscular cells of the vascular coats (directly, or indirectly by means of the sympathetic nerve endings), as was stated by the first investigators, Oliver and Schäfer. The experiments of Velich and Biedl, who divided and destroyed the spinal centres, give direct support to this view, together with those of Gottlieb, who eliminated the action of the vasomotor centres by profoundly chloralising the animals; and still more the fact adduced by the last author, that

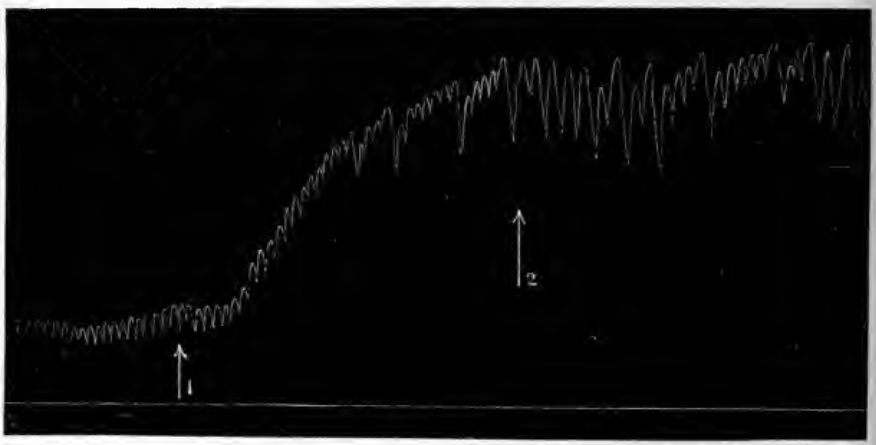

FIG. 16.—Effect of suprarenal extract on blood pressure in curarised rabbit. (Verworn.)
1, injection of extract; 2, section of both vagi.

the vaso-constrictor action also takes effect in the vessels of isolated, surviving organs (kidney, mammalian heart).

The active principle of the suprarenal capsules does not produce the same contractile effect on all the plain muscle of the body as is thus distinctly exerted upon the vascular muscle-cells. On other involuntary fibres it has an exactly opposite effect, causing their active expansion or relaxation, and depression of tone (Lewandowsky, Boruttau, Langley).

Langley (1901) described the effects of suprarenal extract on various organs with plain muscle, in cats and rabbits. Commencing with the results of minimal doses, and going on to those of strong doses of the extract, an enormous increase in blood pressure due to peripheral vaso-constriction first appears (Fig. 16); then relaxation of the cardiac sphincters, intestines (rabbit) and bladder, dilatation of the pupil (cat), retraction of the nictitating membrane (cat), opening of the eyelid (cat). Next follows contraction of the uterus, of the vasa deferentia, spermatic vesicles

(rabbit), salivary and lachrymal secretion, relaxation of the stomach and gall-bladder, increase of biliary secretion, pupillar dilatation, paralysis of the internal sphincters, etc. This shows that suprarenal extract produces sometimes relaxation, sometimes contraction, in different tracts of plain muscle.

Boruttau, Pal, and afterwards Langley and Bottazzi, showed that the peristaltic movements of the intestine are inhibited by suprarenal extract. When the active principle (known as *paragangline*, Vassale, and *adrenaline*, Takamine) is applied to an isolated strip of toad's oesophagus or stomach, Bottazzi (1904)

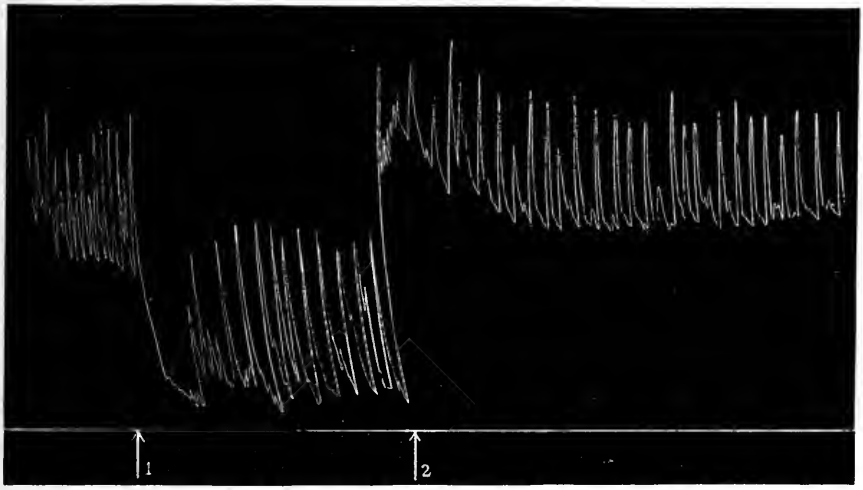

FIG. 17.—Effect of paragangline on plain muscle fibres of toad's oesophagus. (Bottazzi.) 1, injection of extract; 2, its removal by washing. The curves show the very slow contractions of longitudinal fibres of oesophagus. The cylinder revolves about once in twenty-four hours.

observed a marked depression of tone in the plain muscle of these organs (Fig. 17).

To explain the dissimilar action of the same active suprarenal principle on various organs of plain muscle, Langley laid stress on the important fact that the action of this substance almost invariably provoked the same effects as artificial stimulation of the sympathetic, which, as we know, induces sometimes relaxation, sometimes contraction in different organs with plain muscle. His pupil Elliott (1905) confirmed this fact with more ample demonstration by means of adrenaline for all the tissues of the body, whether sympathetically innervated or not. Without entering too fully into details, his conclusions are as follows:—

In all vertebrates the reaction of a given group of plain muscles to *adrenaline* has the same character as that produced by excitation of the visceral sympathetic nerves (lumbar-thoracic) which

innervate the same muscles. The effect may consist in contraction or in relaxation. If the plain muscle has no sympathetic innervation (*e.g.* involuntary bronchial muscles), it is indifferent to the action of adrenaline. Neither the ganglion cells and nerve fibres of the sympathetic, nor the muscular fibre-cells, are directly attacked by adrenaline. Its action is, on the contrary, localised in the end-organs, which unite the nerve fibres with the muscle substance.

These conclusions of Langley and Elliott, based on experimental data, demonstrate clearly that there is a close connection between the active principle of the suprarenal bodies (which are more especially provided with *chromaffine cells*) and the sympathetic nervous system. This tallies with the conclusions of embryology and comparative anatomy, according to which, as we have seen, chromaffine tissue has a common origin with the sympathetic system.

As regards the physiological action of the active suprarenal principle, it must be stated in conclusion that various authors (in addition to its influence on smooth muscular tissues) have ascribed to it a characteristic action on metabolism. Blum (1901) noticed that subcutaneous and intravenous injections of this substance caused elimination of glucose by the urine. This glycosuria, known also as *suprarenal diabetes*, was subsequently confirmed and variously interpreted by other workers (Zülzer, Crofton, Noël Paton, Herter and Wakeman, Aronsohn). According to Landau the substance which on injection produces glycosuria in rabbits exists in the cortical and not in the medullary substance. A causal relation exists between the capsule and the diabetes which is produced by puncture of the fourth ventricle (Cl. Bernard), in the sense that in some very small rabbits that survive bilateral capsulectomy, puncture of the fourth ventricle does not induce this diabetes.

XVI. The discovery of the physiological action of suprarenal extract stimulated the efforts of chemical physiologists to isolate its active principle. Fränkel (1896) first prepared *sphygmogenine*, followed by Abel's *epinephrine* (1898), O. von Fürth's *suprarenine*, Vassale's *paragangline*. In 1901 Takamine announced that both Abel's epinephrine and von Fürth's suprarenine were mixtures, and that he had succeeded in isolating from the suprarenal capsules a stable substance that crystallises, and is of constant chemical composition, to which he gave the name of *adrenaline*. At the same time, but independently, Aldrich also isolated the active suprarenal principle in a crystalline form. F. Battelli discovered a more practical and improved method of preparing the same substance.

Takamine's adrenaline is a white powder, in small crystals, very bitter, slightly soluble in water, faintly alkaline, so that it

forms salts with different acids. It is not an alkaloid. It oxidises readily, and is therefore strongly reducing, and can be used as a developer in photography. Adrenaline has a marked vaso-constrictor action. A cubic centimetre of 0·1 per cent solution injected into the vein produces an increase in arterial pressure of 30 mm. Hg in a dog that weighs 8 kilos. When applied to the conjunctiva it incites marked local ischaemia, of short duration, and on this account is much used in ophthalmology. It has also been resorted to successfully in severe catarrhal hyperaemia of the external mucosae. According to Vassale the active suprarenal principle also has a therapeutic action when introduced into the stomach in gastric and intestinal atony.

In pursuance with the idea expressed above that the suprarenal capsules consist of two distinct organs, and that maximal importance must be ascribed to the medullary substance (*chromaffine tissue, capsular paraganglion*), various attempts have been made to determine which of the two substances, cortical and medullary, is the seat of the active principle.

Salvioli and Pezzolini noted a marked difference in the efficiency of the extract of medullary substance, which they found to be greatly in excess of that of the cortical substance. Oliver and Schäfer (1895) had previously concluded from their experiments that the active vaso-constrictor principle of the suprarenal capsules is contained solely within the medullary substance. The very weak effects which they sometimes observed after injection of cortical extracts were due to post mortem processes of diffusion of the medullary juice and other accidental contamination. Vassale's recent work has fully confirmed these conclusions.

On the other hand, Langlois (1898), Swale Vincent (1896-97), Biedl and Wiesel (1902), have shown that extracts of the extra-capsular chromaffine tissue of the lower vertebrates (*Amphibia, Selachia*) have the same action, while according to Biedl and Wiesel the extracts may be made indifferently from the medullary substance of the capsule, or from other accumulations of chromaffine tissue in these animals. Vassale therefore thinks it more correct to give the name of *paragangline* to the active suprarenal principle, which he prepared exclusively from the medullary substance of the suprarenal capsules.

It must, however, be noted that Vassale's paragangline is not a chemically pure and crystallisable substance like Takamine's adrenaline, but is an extract which contains the vaso-constrictor principle in strong concentration, along with diastatic ferments, and an abundance of lecithin, which has been demonstrated by numerous observers in the medullary substance of the capsules (Crofton, Alexander). Vassale himself admits "that adrenaline is to paragangline as morphine is to opium."

Another series of recent researches was directed to solving the

question of the modifications suffered by the active suprarenal principle when it is introduced into the body of the animal, as also of its remote action when it is given many times in succession. The following are some of the data:—

Langlois (1898) attempted to clear up the mechanism of the destruction of the active principle of the capsule. According to him it is rapidly destroyed *in vitro* by the action of oxidising agents. When introduced into the arterial system, its action on the blood pressure disappears in less than three minutes. The pressure can be maintained at a constant height by successive small injections of extract of the gland, at about three-minute intervals. The disappearance of the effect coincides with the return to normal pressure.

The duration of the effective period is in ratio with the activity of metabolism. In the normal tortoise, in winter, the action on the heart persists for about 3 hours; in the warmed tortoise it disappears after 20 minutes. In cooled mammals the increased pressure persists for 20-30 minutes.

The destruction of the active substance may occur in all the tissues; but the liver takes a preponderating part. In fact, the fluid obtained by maceration of hepatic tissue attenuates the activity of the suprarenal infusion more than the maceration fluids of all other tissues. Infusion of a small quantity of the extract into the mesenteric vein has no effect; while blood pressure always rises if it is injected into a vein of the general circulation. The blood from the hepatic veins of an animal that has received an injection of the extract is less rich in active substances than the blood of another region. Lastly, if the hepatic circulation be cut out, the period of arterial hypertony is prolonged.

Still the problem of the extremely rapid destruction of adrenaline in the body does not seem, according to the most recent work, to be definitely solved in Langlois' sense. Neujean, indeed, held the methods by which Langlois attacked this problem to be inaccurate, and concluded, after more exact research, that it was still doubtful whether adrenaline is destroyed in the body by oxidation.

Later on Patta (1905-7) showed that when adrenaline is injected into the muscles or subcutaneous tissue, it does not produce rise of blood pressure, as it would if injected into a vein, because its absorption is considerably delayed by the vaso-constriction produced at the point of application; it remains unmodified and physiologically active for over two hours.

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Translator's Note.—See also "Internal Secretion and the Ductless Glands," by Swale Vincent (Arnold, 1912), an invaluable *résumé* of the history and literature of this subject.

CHAPTER II

EXTERNAL DIGESTIVE SECRETIONS

CONTENTS.—1. Structure of salivary glands: cranial and sympathetic innervation. 2. Nervous mechanism of secretion in salivary glands. 3. Cytological changes in secretory epithelium during rest and secretion. 4. Selective activity of salivary glands. 5. Chemical analysis of salivary glands and the various kinds of saliva. 6. Structure of pancreas. 7. Innervation and mechanism of its secretion. 8. Pancreatic juice. 9. Internal function of the pancreas. 10. Factors concerned in internal pancreatic secretion. 11. Structure of gastric mucosa and glands. 12. Innervation. 13. Gastric juice and the cells which secrete it. 14. Zymogens which give rise to the gastric enzymes. 15. Intestinal glands. 16. Succus entericus. 17. Mechanism of intestinal secretion. 18. Structure of the liver. 19. Secretion of bile in digestion and fasting. 20. Influence on secretion of changes in hepatic circulation. 21. Chemical constituents of bile. 22. Origin and metabolic activity of hepatic cells. Bibliography.

FROM the group of glands which have no excretory duct, and can only serve for *internal secretion*, we must distinguish the group that are provided with excretory ducts, and are therefore capable of *external secretion*, their products being poured out into the gastro-intestinal canal. The principal function of these secretions is that of chemical and physical transformation of the ingested food, so as to render it fit for absorption and assimilation, and thus to repair the losses perpetually sustained by the tissues during the exercise of their functions.

These organs of external digestive secretion may histologically be divided into three groups: (*a*) acinous glands, forming distinct organs (salivary and pancreatic); (*b*) tubular glands, scattered in the depth of the mucosa of the digestive tube (buccal, gastric, and intestinal); (*c*) glands with branching tubes, grouped into a large organ which forms the liver.

The *external* secretion, which (with the exception of the biliary secretion) is the chief function of these organs, does not exclude them from serving for *internal* secretion also; but this subject will be discussed in a subsequent chapter, the better to appreciate its nature and physiological significance.

I. The excretory ducts of three principal pairs of glands which manufacture and secrete Saliva open into the buccal cavity. From their position these were termed *parotid, sub-maxillary,* and

sublingual. They are glands of the racemose type, *i.e.* they consist of acini, which are more or less saccular or tubular in shape, their cavities or alveoli communicating with one another by one or more branching excretory ducts. The acini are surrounded by a basement membrane consisting of a network of flattened, nucleated, branching cells, the meshes of which are occupied by a delicate homogeneous substance. Inside the basement membrane (Fig. 18) the secreting cells form an epithelial lining which bounds the alveolar cavity. The acini are united into lobules, either by blood-vessels or by loose connective tissue, which contains many lymph spaces and a rich network of blood capillaries.

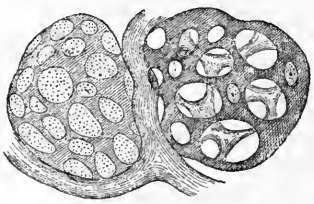

FIG. 18. — Membrana propria of two alveoli isolated. From orbital gland of puppy. (Lavdowsky.)

Two kinds of secreting cells can be distinguished in the alveoli, the *serous* or *albuminous*, and the *mucous* (Heidenhain). The serous cells, which secrete a thin fluid containing serum-albumin, exhibit in the resting state a protoplasm so richly infiltrated with granules that the nucleus is obscured and becomes invisible. The mucous cells, which secrete a fluid that is ropy from the large amount of mucin, are large, clear, and spheroid when the gland is resting. They almost fill the alveolar cavity, their nuclei being invisible because they lie close to the basement membrane, and are pressed against it (Fig. 19). When all the alveoli of a gland are lined with albuminous cells (*e.g.* the parotid in man and almost all mammals, the submaxillary of rabbits, and certain glands that are scattered in the buccal mucosa), the gland, as a whole, is termed *albuminous*; when the alveoli are lined with mucous cells alone (*e.g.* part of the submaxillary in man, and the sublingual in all animals, and many simple buccal glands)

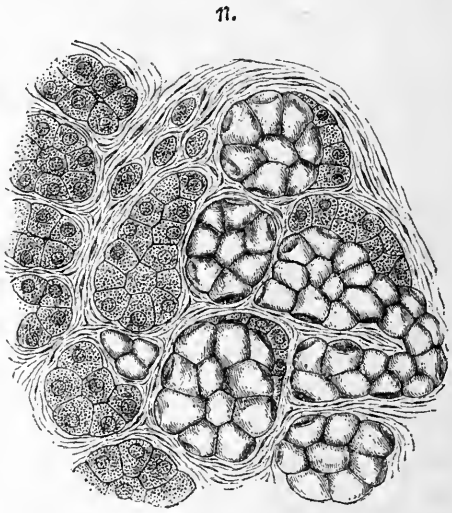

FIG. 19.—Section of part of human submaxillary gland. (Heidenhain.) On the right, a group of mucous alveoli with demilunes of Giannuzzi; on the left, a group of serous alveoli.

the gland is termed *mucous*; when the alveolar walls are constructed partly of mucous, partly of albuminous cells (*e.g.* the submaxillary and suborbital of many mammals, part of the submaxillary in man, and the majority of the scattered buccal glands), the gland, as a whole, is termed *mixed*. In this case the albuminous glands occupy a marginal position, and usually form little crescentic masses known as the *demilunes* or *crescents of Giannuzzi* (Fig. 19).

The epithelial cells which line the intercalary and interlobular excretory ducts are quite different from the secreting cells. The ductules of lesser and medium calibre are lined with flattened, cubical, striated cells; the larger ducts with columnar, epithelial

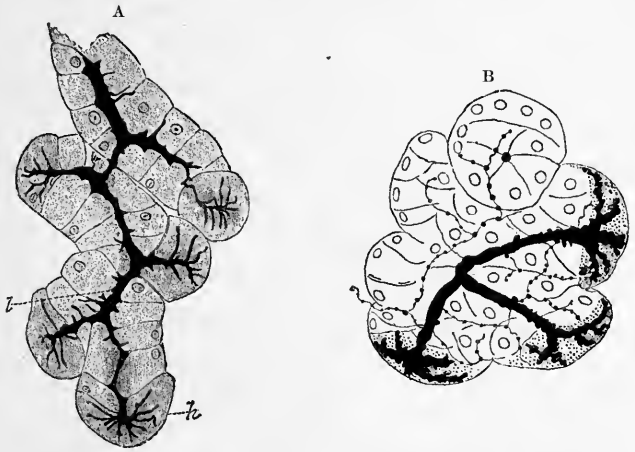

FIG. 20.—A, section of alveoli from human sublingual gland. Silver chromate method. (E. Müller.) *l*, lumen of intra-alveolar excretory ducts, stained black, and terminating in diverticula which penetrate into the cells of the alveoli; *h* diverticula penetrating into crescent cells. B, section of alveolus from dog's submaxillary gland. Silver chromate method. (G. Retzius.) Shows diverticula of excretory ducts extending into crescents of Giannuzzi. Also very fine varicose nerve fibrils which form a network with large meshes between the alveolar cells.

cells. If the ducts are injected before making a microscopical preparation, or treated with Golgi's method, which stains the entire system of excretory channels a uniform black, the lumen can be followed into the alveoli, and is seen to end in terminal diverticuli, which penetrate between the cells, and enter for a short distance into the protoplasm (Fig. 20, A, B).

Both the serous and the mucous salivary glands are supplied by two kinds of nerves, those of cranial and those of sympathetic origin. The former, for the submaxillary and sublingual glands, originate in the roots of the facial nerve as the chorda tympani, unite with the lingual branch of the fifth nerve, and then run through the submaxillary ganglion to the parenchyma of the gland. For the parotid, the cranial fibres from the glosso-pharyngeal nerve run through Jacobson's nerve, the small super-

ficial petrosal, and the otic ganglion, and on reaching the auriculo-temporal branch of the fifth nerve penetrate into the gland. The sympathetic fibres run in the cervical sympathetic to the superior cervical ganglion, accompany the carotid artery, and penetrate with its branches by the hilum to the interior of the three glands.

The nerve fibres are partly medullated, partly non-medullated. Some supply the muscular sheath of the vessels, others the gland cells; the former are vasomotor, the latter secretory fibres. These last, mostly as non-medullated fibres, perforate the basement membrane of the acini, and terminate between the alveolar cells in a free arborescence of the finest varicose fibrils (Fig. 20, B.). Paladino (1872) observed direct terminations of the nerve fibres in the gland cells of the salivary gland of dogs, solipeds, and man. He further described intraglandular gangliated plexuses in the submaxillary of the dog and of man.

II. It is evident that the salivary secretion is directly under the control of the nervous system. The mere mental image of any sapid substance, the sight or smell of a favourite food, is sufficient, in vulgar parlance, "to make the mouth water." Stimulation of the abdominal fibres of the vagus, in nausea, incites a copious flow of saliva, principally during the reflux of food from the stomach to the extremity of the oesophagus, which precedes vomiting.

To these facts of common observation which are within the reach of all, we can add others, arrived at by physiological experiment. The salivary secretion can also be excited by centripetal stimulation of some of the sensory nerves, *e.g.* the central end of the vagus or sciatic in a curarised dog (Owsjannikow). Electrical excitation of a given area of the cerebral cortex (the so-called centre for facial movements) promotes secretion (Landois, Lépine, Bochefontaine), etc. It is interesting in this connection to note that among the forms of partial epilepsy there is one in which the fits are characterised by an enormous secretion of saliva (Emminghaus).

A remarkable contribution to the more exact knowledge of reflex excitation of the salivary secretion was made by Pawlow and his co-workers (1904). The extraordinary aptness of these reflexes is shown by a number of experiments, the most important of which may be briefly summarised:—

If some quartz pebbles are introduced into the mouth of a dog with a salivary fistula, the animal, after turning them over with its tongue, lets them drop out without any flow of saliva, or at most a few drops only, being excited. If, on the contrary, the same stones are introduced into the dog's mouth in the form of powder, so that it cannot push them out with the tongue, saliva at once flows freely and carries away the quartz dust.

Dry, solid food produces an abundant secretion of saliva; fluid aliments, which already contain enough moisture for deglutition,

excite much less. Strongly irritating substances, *e.g.* acids, salts, etc., determine a copious flow of saliva, by which they are diluted and their irritating action reduced. The saliva secreted under these conditions is watery, and contains little mucin.

Excitation of the secretory centres of the salivary glands may occur not only from stimuli in direct contact with the mucous membrane of the buccal cavity, but also from excitation at a distance, by the action of various stimuli on the different sense organs, *e.g.* nose, eye, ear. Since it is impossible to find any other explanation for this kind of stimulation, Pawlow calls it a *psychical excitation*. If, *e.g.*, a hungry animal is shown a bit of bread or other food, a secretion results, while there is absolutely no response on showing it to another that has eaten to repletion. If some food or other substance that provokes nausea is shown the dog several times in succession, the reaction is lessened till it dies out. Yet if a little of the nauseous substance which no longer evokes secretion is placed in the mouth, the first response reappears, and lasts for a certain time.

The smell or other external sign of food is enough to determine secretion. If, *e.g.*, the hand, smelling of meat, is presented to the dog, a flow of saliva is excited. If an acid has once been coloured black, the sight of any black fluid will provoke secretion, assuming of course that the black acid was introduced into the animal's mouth on at least one occasion.

According to Malloizel's observations (1902) on dogs with a permanent fistula, the reflex secretion of saliva is specific for different peripheral stimuli. Thus the saliva excited by the action of salts, sulphate of quinine, or sand, is thin and contains less than 1 cgrm. of mucin in 6 c.c. of saliva: the saliva excited by raw meat, on the contrary, is very viscid, containing 1-2 cgrm. of mucin in 1 c.c. of saliva; that excited by sugar is between the two. Henri and Malloizel further found that the diastatic activity of reflexly excited saliva varies with different stimuli; it is greater for meat than for salts.

The sight or smell of different substances, again, excites a specific secretion of saliva. Section of the chorda tympani abolishes every secretory reflex, while section of the sympathetic has no effect.

All these, like the preceding, are phenomena of *reflex secretion*, in which the excitation travels along the afferent paths to the centres, which then transmit it by the efferent secretory paths. Certain experiments of Cl. Bernard, Eckhard, Loeb, Grützner, and Chlapowski show that the centres of salivary secretion are localised in the bulb, probably at the origin of the facial and glosso-pharyngeal nerves. In fact, when the bulb is separated from the spinal cord by a cross-section, salivary secretion can no longer be excited by the same means. On electrical excitation, or

better on pricking the bulb in the vicinity of these centres, secretion is at once aroused.

Kohnstamm (1902) found that division of the nerve fibres that arise in the chorda tympani and pass by the lingual to the submaxillary gland, was followed by degeneration of a group of cells in the bulb near the facial nucleus, mostly on the opposite side, to a less extent on the same side as the operation. The nerve fibres that come in the submaxillary gland originate in these cells. Hence the latter are termed by the author the *salivatory nucleus.*

The interpretation of the effects of the so-called *scialagogues* is doubtful. These consist in a series of toxic or medicinal substances which, when injected under the skin or into the veins, promote a more or less copious secretion of saliva. The principal are pilocarpine, physostigmine or Calabar beans, curare, etc. Do these substances induce a flow of saliva because they directly or reflexly excite the secretory nerves, or because they act by modifying the metabolism of the secretory cells? It is probable that their action is distributed throughout the system, and that the effect is analogous to the secretion of saliva produced in asphyxia by the accumulation of carbonic acid and the other katabolic products of metabolism in the blood.

As contrasted with the substances which produce *ptyalism*, we have another group, headed by atropine and daturine, which arrest all salivary secretion (Keuchel). These substances act particularly by paralysing the cranial secretory nerves. The flow of saliva excited by pilocarpine can be arrested by atropine, and, *vice versa*, the arrest of secretion by atropine can be antagonised by pilocarpine and also by muscarine.

The process of secretion, more particularly in the submaxillary gland, which is the most accessible to experiment, has from 1851 to the present day been the subject of constant and varied experiments (especially by Carl Ludwig and his school) which have yielded very important results. The most significant of these data and the deductions to which they lead can be summarised as follows:—

(*a*) If after introducing a cannula into Wharton's duct in the dog, the lingual branch of the fifth nerve (or simply the chorda tympani, which runs from the facial to the lingual branch and gives off fibres to the gland) is cut, all salivary secretion ceases, and no saliva flows from the end of the cannula (Ludwig). This proves that secretion of saliva is normally dependent on a reflex nervous act conveyed to the gland by the fibres of the chorda tympani. If the peripheral end of the lingual nerve (or the chorda tympani) be electrically excited an abundant secretion of saliva follows, which will in a few minutes reach, and even exceed, the volume of the gland (Ludwig). This shows that stimulation of

the nerve excites a stream of fluid which passes from the blood capillaries to the lymph spaces, and thence to the glandular spaces, the material contained in the gland not being sufficient for such an abundant flow of saliva.

(*b*) Between the excitation of the nerve and the appearance of the secretion there is an appreciable period of latent stimulation, which may vary between 1·2 seconds (Hering) and 24 seconds (Ludwig).

The secretion persists for a short time after the close of stimulation. This period, known as the *after-effect*, increases in proportion with the excitability of the nerve (Ludwig). In fact, if the stimulation lasts only for a short time, so that the nerve is not excessively fatigued, the after-effect lasts longer. These phenomena confirm the dependence of the secretion upon the activity of the secretory nerve.

(*c*) Excitation of the cervical sympathetic (or of the sympathetic fibres that accompany the carotid and run to the submaxillary gland) also produces a secretion of saliva, although much more slowly and in smaller quantities. Moreover, while the saliva obtained by stimulation of the cranial nerve is watery and slightly viscid, and shows under the microscope very few salivary corpuscles and granulations, the saliva secreted by excitation of the sympathetic is very dense, viscid, ropy from large quantities of mucus, and contains numerous corpuscles and granulations (Eckhard, Cl. Bernard).

(*d*) The blood-supply of the gland is modified in contrary directions by stimulation of the chorda tympani and of the sympathetic. In the former it is enormously increased by active vascular dilatation, in the latter diminished by active constriction (see Vol. I. p. 342 *et seq.*). It cannot be denied that the marked difference in quantity, density, and viscidity of the saliva obtained on exciting the two kinds of nerves depends—at least in part—on the varying blood-supply to the gland in the two cases. The difference is much reduced if the gland be filled with blood by a brief stimulation of the chorda tympani before exciting the sympathetic. In this case excitation of the sympathetic produces a more copious and less viscid saliva.

Burton-Opitz (1904), using Hürthle's haemodrometer, estimated the velocity of circulation in dogs in the branches of the external jugular vein, and found it normally very low. By stimulating the intact chorda tympani it was possible to increase it from two- to six-fold. Stimulation of the sympathetic, on the contrary, determined an almost complete arrest of the circulation. Longer stimulation of the vasomotors fatigues them, and the circulation then returns to the normal rate, even if the stimulation be continued.

(*e*) The saliva secreted after stimulation of the cranial nerve

has a temperature 1·5° C. higher than that of the arterial blood which traverses the origin of the carotid. The difference in the two temperatures is greater in proportion as the flow of saliva from the cannula inserted in Wharton's duct is more rapid (C. Ludwig and A. Spiess). This proves that during secretion the oxidative processes, or the respiration of the secretory cells of the gland, increased — so that much energy is liberated in the form of heat. This is not contradicted by the fact first noticed by Bernard to the effect that during the stimulation of the chorda the blood flowing back from the gland assumes the hue of arterial blood, because the velocity of the blood current in the gland, owing to the vascular dilatation, increases more rapidly than the consumption of oxygen.

(*f*) The presence of oxygenated blood undoubtedly favours secretion. If the principal vein that leaves the submaxillary gland be occluded while the chorda is stimulated, secretion gradually ceases, recommencing after the vein has been freed, with sufficient lapse of time for the black asphyxial blood collected in the vessels of the gland to be replaced by red arterial blood (Ludwig). The rate of flow of saliva thus depends not only upon the amount of nutritive materials that reach the gland, but also upon the quantity of oxygen, *i.e.* the arterial character, of the blood circulating in it.

Barcroft (1901) noted in dogs that during the secretion produced by stimulation of the chorda the amount of oxygen taken up by glandular tissue from the blood is three or four times greater than in the resting gland. After injection of atropine there is no longer any increased assimilation of oxygen on stimulating the chorda, while more CO_2 is still given off, for a time at any rate.

(*g*) If the cranial and the sympathetic nerves of the submaxillary are simultaneously excited, secretion is at first augmented, but soon becomes slower than when one nerve alone is stimulated, until finally it is almost entirely suspended (Czermak). This effect is due to interference of excitation in the two nerves, as well as to functional predominance of the constrictor fibres over the dilators in the nerves of the gland, as shown by von Frey (see Vol. I. p. 351).

(*h*) We have seen that secretion is arrested after section of the chorda, even when the sympathetic is left uninjured. This functional arrest is not permanent. After about 24 hours the gland begins once more to pour out a continuous secretion of very thin saliva, poor in organic substances. This phenomenon was termed by Claude Bernard (who first noticed it) *paralytic secretion.* It increases steadily in the first week: after that it slowly diminishes, owing to the degeneration of the gland. After excision of the submaxillary ganglion (according to Bernard)

paralytic secretion always makes its appearance. It can also be provoked by the injection of small doses of curare into the glandular arteries. It ceases in apnoea, and increases in dyspnoea. After hemisection of the cord, paralytic secretion appears in the gland of the opposite side also (Heidenhain). The interpretation of these facts is very doubtful. Langley believes that the excitability of the central end of the chorda increases after section, so that it reflexly influences the secretion of both glands.

(*i*) A series of striking experimental data prove that the salivary secretion excited by the activity of the nerve depends essentially upon altered metabolism of the secretory cells, and not on alteration of the blood-supply to the gland. Secretory activity excited from the nerve persists for a certain time after all the blood-vessels to the gland have been occluded, and even after decapitation of the animal (Ludwig, Czermak, Giannuzzi). On the other hand, when a mercury manometer is introduced into the excretory duct of the submaxillary gland, and the chorda tympani excited, secretion continues, even when the pressure in the excretory ducts of the gland rises to a height considerably in excess of that in the carotid artery. The pressure in Wharton's duct may rise to 200 mm. Hg, while that of the carotids is not above 122 mm. Hg. This shows that the stream from blood-vessels to lymphatics, and from these to the glandular spaces, is not merely independent of the pressure, but actually occurs against the laws of filtration (Ludwig).

(*k*) We have already seen that the injection of even small doses of atropine and daturine suffices to abolish the secretory activity of the chorda tympani (Keuchel). But if the state of the glandular blood-vessels is watched during stimulation of the nerve, it is found that their active dilatation is in no way hindered by atropinisation (Heidenhain). We must therefore assume that the chorda contains *secretory* fibres as distinct from the *vaso-dilators*. Atropine paralyses the former and leaves the latter unaffected.

(*l*) When a substance that paralyses the activity of the secretory cells, *e.g.* a dilute solution of hydrochloric acid, or of sodium carbonate, is injected into Wharton's duct, and the chorda tympani subjected to prolonged stimulation, all secretion is arrested and there is marked oedema of the gland from congestion of lymph (Giannuzzi). This shows that the dilatation of the arteries is capable of promoting the filtration of the lymph, but not its penetration into the gland spaces.

(*m*) Unilateral excision of the chorda tympani in puppies has as a remote effect a marked diminution in weight of the corresponding submaxillary, which may amount to 50 per cent. There is at the same time a reduction in the volume of the mucous cells and the serous cells, which form the crescents or demilunes of Giannuzzi (G. Bufalini).

All these phenomena relate to the secretory process in the submaxillary gland of the dog, which has been the subject of innumerable researches. But the same facts (with slight differences) may be observed in other animals also. Thus in the rabbit, the saliva that flows on excitation of the chorda and also that from excitation of the sympathetic are limpid and fluid; in the cat, the first kind is more viscid than the second. But in both cases excitation of the chorda produces copious secretion and vascular dilatation, excitation of the sympathetic, scanty secretion, and vascular constriction.

Gerhardt studied the histological changes consequent on section of the secretory nerves on the salivary glands of rabbit, and found substantial differences in the effects of dividing the chorda and the sympathetic. In the former the protoplasm was altered while the nuclei remained intact; in the second, on the contrary, there were marked nuclear alterations with normal protoplasm. The two kinds of histological change were never observed in all the gland cells, but only in foci, without any apparent regularity, partly in big nests, partly isolated. The nuclear alterations from section of the sympathetic were not confined to the side of the section but spread also, although to a minor extent, to the opposite side.

The nervous mechanism of the other salivary glands is similar in its general features to that of the submaxillary gland, on which we have dwelt at length. Division of Jacobson's nerve or of the small superficial petrosal nerve, or excision of the otic ganglion, arrests the secretion of the parotid gland (Bernard, Schiff, Heidenhain). Excitation of these cranial fibres produces in the parotid the same secretory and vascular effects as that of the chorda tympani in the submaxillary. The pressure measured in Stensen's duct rises during stimulation to 106-118 mm. Hg. The flow of blood from the gland is accelerated and assumes the arterial hue (Heidenhain). The effect of stimulating the sympathetic has, on the contrary, been much disputed. Some deny it, others admit a simple constrictor effect on the parotid vessels, others, lastly, assume a *trophic* influence upon the gland cells, as distinct from the secretory influence (Heidenhain).

The sublingual gland is controlled by the same nerves as those which regulate the secretion of the submaxillary. Stimulation of the chorda tympani excites secretion from the sublingual as well, but requires a stronger stimulus (Cl. Bernard, Heidenhain). The stimulation of the sympathetic has no perceptible effect.

III. The most obvious proof that the secretory effect of exciting the nerves is due essentially to their *trophic* influence upon the metabolism of the secretory gland-cells, is shown under the microscope in the marked changes which these cells undergo during secretory activity. We owe to Heidenhain (1868) this

fine discovery, which enables us, up to a certain point, to penetrate to the interior of the cells, and to ascertain what cytological phenomena accompany the process of secretion.

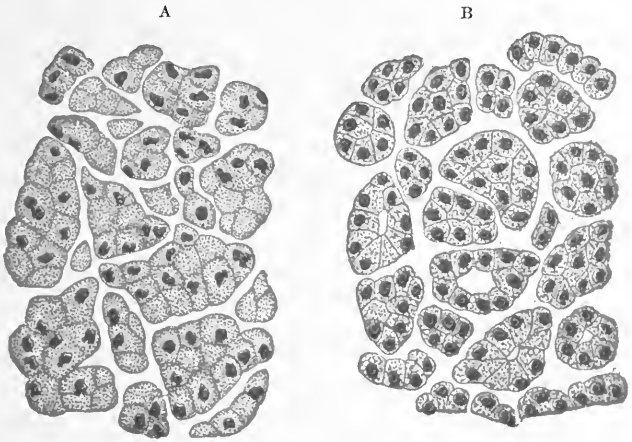

FIG. 21.—Rabbit's parotid. Alcohol-carmine method. (Heidenhain.) A, resting state; B, after stimulation of cervical sympathetic.

Microscopic preparations of serous glands hardened in alcohol and stained with carmine show in the resting state a colourless,

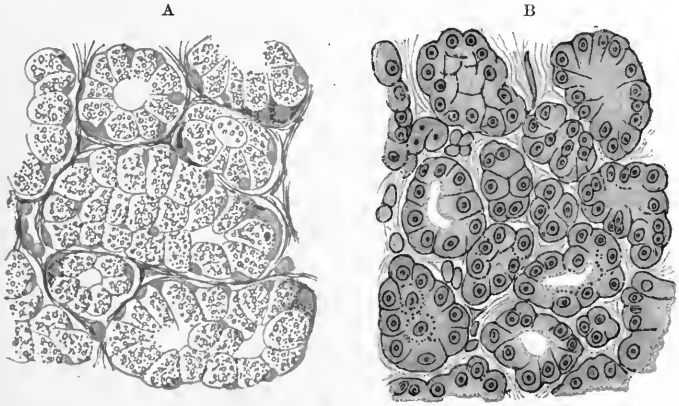

FIG. 22.—Orbital gland of dog. Alcohol-carmine method. (Lavdowsky.) A, resting state; B, maximal degree of change which the gland is capable of exhibiting in secretory activity.

clear, finely granular cytoplasm, and a nucleus that stains red, with wavy outlines and no distinct nucleoli (Fig. 21, A). After excitation of the secretory nerve, and when some cubic centimetres of saliva have been given off, the cells visibly alter in character.

Their total area diminishes from loss of clear cytoplasm; the granular substance on the contrary increases, so that the cell appears more clouded, the nucleus becomes rounded with more regular outlines, and the nucleolus is plainly visible (Fig. 21, B).

Microscopic preparations of mucous glands treated in the same way show in the resting state large clear cells with colourless cytoplasm, which consists of a very fine filamentous network with large meshes, filled with an amorphous, shining, mucinogenous substance, which resembles small granules. The nucleus stains with carmine; it has no visible nucleolus, and is always situated at

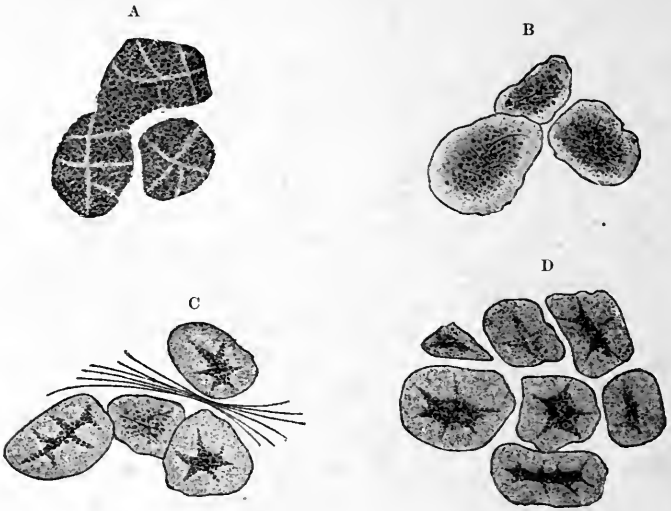

FIG. 23.—Rabbit's parotid in fresh state. (Langley.) A, resting state; B, after injection of weak doses of pilocarpine; C, after stimulation of cervical sympathetic; D, after more prolonged stimulation of this nerve.

the periphery or margin of the cell (Fig. 22, A). After prolonged secretion excited by stimulation of the secretory nerves, the cells appear much reduced from loss of the clear mucinogenous substance, the cytoplasm stains, the nucleus is rounded, with a distinct nucleolus which has moved to the centre of the cell (Fig. 22, B).

The subject of these histological researches is (as Heidenhain points out) not the living cell, but its dead body, altered, moreover, by the technique of hardening and staining. Yet, since the phenomena are so constant, we may safely conclude that the living cells also are differently constituted in the resting and in the active state, owing to the manufacture of secretion. Recent comparative researches on gland cells in fragments of living gland fresh from the body, show that while their microscopic appearance

differs widely from that described by Heidenhain, it lends itself essentially to the same interpretation.

In the serous glands, Langley found that in the resting state the secretory cells exhibit a protoplasm rich in granules, which conceal the outline of the cells and the nuclei. After prolonged secretion, caused either by injection of pilocarpine or by stimulation of the nerve, the alveoli become smaller, and the granules gradually disappear, especially in the outer zone which is covered by the basement membrane; they collect in the inner zone, which surrounds the lumen, and finally vanish, accumulating as secretion in the cavities of the gland (Fig. 23).

Similar phenomena can be observed in fresh preparations of the mucous glands. They are more conspicuous in the simple than in the compound glands, *e.g.* those of the frog's tongue, placed as soon as excised in physiological salt solution (Biedermann). In the resting state the cells are full of dark, highly refracting granules, which often conceal the nucleus; during active secretion, on the contrary, the granulation practically disappears, and what remains is collected at the inner margin (Fig. 24).

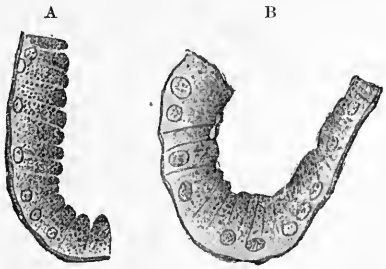

FIG. 24.—Part of lingual gland of *Rana esculenta*, in fresh state. (Biedermann.) A, resting state; B, after stimulation of glosso-pharyngeal nerve for 3 hours.

From these data we learn that a substance is formed during the functional rest of both albuminous and mucous salivary glands which disappears during activity, and passes into the secretion, while the cell becomes swollen. This substance dissolves in alcohol-hardened, carmine-stained preparations; in fresh specimens, on the contrary, it appears in the form of small granules.

These phenomena do not decide the important question whether during the secretory process the living protoplasm of the cells is utilised and converted into the materials of secretion, or whether the secretion is produced by the living protoplasm as a direct elaboration of the lymph absorbed from the perialveolar lymph spaces. Heidenhain adopted the former view, and concluded that the cells liquefy in consequence of their secretory activity. According to him Giannuzzi's demilunes consist of cells intended to replace those which break up. Against this theory is the fact that karyokinesis is rarely seen during secretion, and that if epithelial regeneration be present, it relates not to secretory activity, but to the life cycle of the individual cells. The second theory, which, as we have seen, was held by Johannes Müller, and

adopted by Langley, is more probable, and harmonises with the fact that, generally speaking, living cells in carrying out their functions consume the chemical matters which they have absorbed and elaborated, and only utilise their own protoplasm when all other materials are exhausted.

IV. The important question of the specific property by which the salivary glands select from the substances offered them by the blood the constituents of an effusion that is quite unlike the blood itself, has hitherto been treated only by a few authors, and that incidentally. Novi (1888) estimated the amount of chlorine contained in a sample of blood from the carotid and in one of saliva, before and after injecting a 10 per cent solution of sodium chloride into the jugular. He found that when the concentration of the blood was thus increased, the rate of secretion increased also. Novi further observed that the chloride content of the saliva increased much more rapidly than that of the blood serum. When, *e.g.*, the chloride in the sodium increased from 100 to 155, that in the saliva increased from 100 to 220. Langley and Fletcher confirmed the observations of Novi, showing that dilute solutions of sodium chloride, while they still augment the rate of secretion, lower the concentration of the saliva.

Asher and Cutter (1900) on injecting sugar and urea showed that sugar excites secretion only by causing hydraemic plethora, and does not appear in the saliva; urea, on the contrary, excites it, and partly reappears in the saliva.

According to Aducco these different effects show that the production of the secretion depends not only upon the physical and chemical constitution of the circulating substances, but also upon their effect on metabolism. Thus urea, which is a katabolic product, and is not present in the normal secretion of the gland, is capable of activating it and of stirring up the secretory cells to more work; while sugar does not pass through the gland (provided the physiological limits are not exceeded), and only acts indirectly upon the secretion, *i.e.* by augmenting the mass and the dilution of the blood.

This explanation of the phenomenon appears to us inadequate. If under the said experimental conditions it is a fact that the increased sugar content of the blood increases the flow of saliva, under other conditions, *e.g.* in experimental hyperglycaemia and in diabetes in general, the secretion of saliva is very scanty, much below the normal.

Many salts when introduced into the vascular circulation appear rapidly in the saliva (potassium iodide, lithium citrate, etc.); others, on the contrary (bile salts), which are eliminated by all other glands when present in the blood do not pass through the salivary glands.

In regard to the selective capacity of the salivary glands,

U. Lombroso, on injecting into the dog's jugular a large quantity of pancreatic secretion collected directly from a Pawlow's fistula, noted that the saliva did not (like other digestive secretions) acquire any of the enzymatic properties characteristic of pancreatic juice: bile, *e.g.*, acquires an intense lipolytic activity, which persists for several days after the injection.

V. Chemical analysis shows the presence of a number of proteins in the salivary glands, among them a *nucleo-protein* (Hammarsten), a substance which forms a special enzyme known as *ptyalogen*, or the zymogen of ptyalin (in the albuminous glands), *mucinogen*, the mother-substance of mucin (in the mucous glands), and the mineral salts of blood serum. With prolonged stimulation of the secretory nerves to the albuminous and mucous glands, both the ptyalogen and the mucinogen disappear to form again during the resting period.

The increase of volume and weight in the salivary glands during rest depends largely upon the greater amount of proteins absorbed, since this increases the nitrogen content. Glands subjected to prolonged stimulation contain 7 per cent less solids than the resting gland, but this difference depends partly on the greater amount of water absorbed by the gland during secretion, in analogy with the conditions that prevail during muscular work.

As regards chemical composition we must distinguish the *mixed saliva* or total secretion from the simple and compound salivary glands that open into the buccal cavity, from the *separate salivas* secreted from the albuminous, mucous, and mixed glands respectively.

Mixed saliva is colourless, with no smell, opalescent, viscid, faintly alkaline in reaction (= 0·097 per cent Na_2CO_3) or neutral, its specific gravity being 1002-1006 in man (1007 in dog). It is remarkable that the osmotic pressure of saliva is considerably less than that of the blood. Nolf (1900) showed that the saliva spontaneously secreted from the dog's submaxillary has a freezing-point from − 0·11 to − 0·27, and that secreted during stimulation of the chorda freezes at − 0·19 to − 0·4. The osmotic pressure of dog's blood, on the contrary, corresponds to a lowering of the freezing-point = − 0·549 to − 0·605 (see Vol. I. pp. 142, 148).

If left to itself the mucin of the saliva precipitates, along with the old epithelial cells thrown off by the buccal epithelium. It also becomes turbid from the precipitation of the calcium carbonate dissolved in the saliva in the form of bicarbonate. The microscope shows the so-called *salivary corpuscles*, which resemble small leucocytes with granulations that exhibit lively Brownian movements.

It is not possible to obtain an exact estimation of the total quantity of saliva secreted daily; approximate figures only can be

given. There are marked variations in the different species of animals on which observations have been made. While the horse secretes 14·2 grms. saliva to every gramme of gland per hour, during mastication, the calf only secretes 8 grms. (Tuczek). From this point of view it seems probable that the salivary glands are the most active. In man the secretion of saliva amounts to some 1500 grms. per diem.

The *organic* components of mixed saliva are :—

(*a*) *Mucin*, which precipitates with acetic acid or alcohol, and is derived from the mucinogen of the glandular epithelium.

(*b*) *Ptyalin*, an enzyme discovered by Leuchs in 1831. It is derived from the *ptyalogen* of the gland-cells, and is constant in the saliva of man, horse, rabbit, and of herbivora in general, while it is regularly absent in that of dogs and of carnivora in general (Hoppe-Seyler). It is an amylolytic enzyme, the action of which will be discussed in treating of buccal digestion.

The existence of a pro-enzyme of ptyalin (*ptyalinogen*) corresponding to what exists for the gastric and pancreatic enzymes (*propepsin* and *protrypsin*), was demonstrated by Miss Latimer. On washing the salivary glands repeatedly with water and chloroform, they are freed from the active ptyalin which they contain; on then treating the gland with a dilute solution of acetic acid an extract capable of saccharifying starch is obtained.

(*c*) A *globulin* that precipitates with heat, on addition of mineral acids and also on passing a current of carbonic acid.

(*d*) *Sulphocyanide of potassium* or *sodium*, which is frequent but not constant in human saliva in minute quantities of 0·016-0·084 per thousand (Oehl), according to others in an average quantity of 0·10 per thousand (Jacubowitsch). It may possibly be formed in the mouth by the action of special microbes. According to Krüger it increases in smokers.

Grober's latest investigations (1901) show that the sulphocyanide is not formed by decomposition of saliva; its elimination probably depends on the general protein metabolism, since it is eliminated little or not at all by persons suffering from cachexia.

(*e*) Traces of *urea*, and, in abnormal conditions, of leucine and of lactic acid.

The *inorganic* compounds consist of small quantities of chlorine and phosphoric acid combined with potash, soda, lime, and magnesia; small quantities of sodium carbonate and abundant quantities of sodium chloride.

The amount both of water and of solids in the saliva may fluctuate considerably with food or abstinence, or other changeable factors. We must confine ourselves to citing the results of Hammerbacher's analyses, which are of the mixed saliva (1000 parts) of a young healthy man, and which agree perfectly with those of Frerichs:

Water	994·203
Solid substances	5·797
Epithelia and mucin	2·202
Ptyalin and globulin	1·390
Inorganic salts	2 205
Sulphocyanide of potassium	0·041

The same author found in 1000 parts of ash of human saliva:

Potassium	457·2
Sodium	95·9
Ferric oxide	50·1
Magnesium	1·5
Sulphuric acid	63·8
Phosphoric acid	188·5
Chlorine	183·5

In order to obtain and analyse separately the saliva of the respective glands, the excretory ducts of Stensen and Wharton can be syringed with special metal cannulae (Ordenstein, Oehl, Eckhard) in man, and on dogs artificial fistulae of the same canals can be established.

The *parotid saliva* of man is thin from absence of mucin, but it becomes ropy and viscid if the secretion is scanty; the reaction is alkaline; it is rich in ptyalin even in the newborn; contains but little globulin. Constituents, 99·5 per cent water, 0·5 per cent solids, of which 0·2 per cent are alkaline chlorides, 0·2 per cent carbonate of lime, and 0·15 per cent organic compounds, of which 0·03 are sulphocyanide (Oehl).

The *submaxillary* and *sublingual* saliva in man is more watery, more alkaline, more viscid, because it contains mucin: it has a weaker diastolic action, because it contains less ptyalin; and the amount of sulphocyanide is less (Oehl).

Lastly, the submaxillary and sublingual saliva differs under the microscope from parotid saliva, in containing many more salivary corpuscles and shed mucous cells.

Cohnheim's method is the best for extracting a tolerably pure ptyalin from saliva. (*a*) The saliva is strongly acidified with phosphoric acid (using 2 litres of mixed saliva); (*b*) the filtrate is then made alkaline with milk of lime, which forms a precipitate of tribasic phosphate of lime and brings down the ptyalin; (*c*) the precipitate is collected on a filter and washed with distilled water, which dissolves ptyalin; (*d*) 5-6 volumes of alcohol are added to the filtrate, when a flocculent precipitate is formed; this is dried *in vacuo*; (*e*) this precipitate is redissolved in distilled water, filtered and reprecipitated with absolute alcohol; the precipitate is dried, and consists of purified ptyalin.

To show the presence of sulphocyanide of potassium in the saliva, add a few drops of perchloride of iron, after acidifying with dilute hydrochloric acid. The fluid turns more or less blood-red, according to the amount of sulphocyanide contained in the saliva (Oehl).

Soléra's reaction is based on the fact that the sulphocyanide separates iodine from the iodic acid. On adding starch paste and then iodic acid to the saliva, the iodine is liberated, and gives a blue colour with starch.

VI. The Pancreas is a long gland, of irregular prismatic shape; its external secretion is conveyed to the duodenum by the canal or duct of Wirsung, which runs along the entire length of the gland, buried in its substance. Its size and weight differ considerably in different individuals. It is 12-13 cm. long, with a maximum diameter of 12-25 mm. According to Krause, it weighs 66-102 grms., but Meckel gives a maximum weight of 180 grms., and Sömmering a minimal weight of 45 grms. Its specific gravity is 1·046.

From its structure the pancreas must be regarded as an acino-tubular gland, resembling the salivary glands, but with

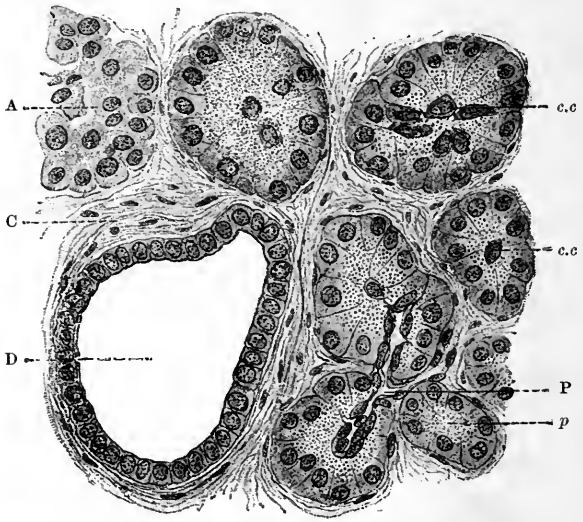

FIG. 25.—Section of human pancreas. (Böhm and V. Davidoff.) D, principal duct; C, connective tissue; A, alveolus or acinus; *c.c*, centro-acinar cells of Langerhans; P, commencement of duct; *p*, small alveolus without central cells.

lobes and lobules more loosely knit together by connective tissue. The secretory alveoli consist of short tubules, which in a section resemble rounded acini. The primary and secondary ducts are lined with simple columnar epithelium, the cells of which become lower in the small ducts, till where these arise in the alveoli they are reduced to narrow, flattened, spindle-shaped cells (Fig. 25).

The number of ducts in the pancreas is not constant even in a series of the same animals. In man they are usually two, the principal, or duct of Wirsung, and the accessory, or duct of Santorini. The latter may be absent (Hess), in any case it is always very minute in the adult, while in the early stages of development it is larger than Wirsung's duct. In the dog there are invariably two ducts, and in a certain number of cases (30 per

cent) a third (Hess). In the rabbit there is a secondary duct besides the duct of Wirsung, but it is of no importance in the adult; U. Lombroso (1907) showed that ligation of the principal duct alone causes diffuse alterations in all the organs, co-extensive with those observed when the secondary duct is also occluded.

When freshly examined, the secreting cells at the end of the alveoli show a clear, homogeneous, outer zone, covered with the basement membrane, and a granular, somewhat clouded, inner zone, which is turned towards the lumen. In very fresh preparations the granules extend over the whole of the cells, but if the preparation is cooled they are packed towards the lumen. In quite fresh preparations, again, the nucleus is invisible, or scarcely seen. In carmine preparations only the outer zone and the nucleus stain (Fig. 26).

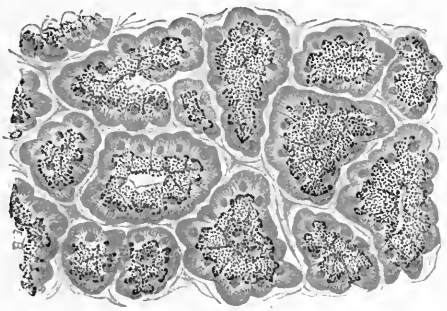

FIG. 26.—Pancreas of fasting dog. Alcohol-carmine method. (Heidenhain.)

In the middle of the alveolus Langerhans (1869) discovered spindle-shaped cells with a homogeneous body, sharp outline, and a large clear nucleus, known from their position as the centro-acinar cells. Saviotti, Boll, Ebner, v. Frey, Giannelli and many others, showed by systematic investigation of various kinds of animals that these cells are constant in all vertebrates. Such centro-acinar cells are more numerous at the neck of the alveolus than at its base, where they may be entirely absent.

The nature of these cells has been the subject of much discussion. Langerhans, Saviotti, Heidenhain, regard them as epithelial cells. Pflüger takes them to be nerve cells. Many authors have supposed them to be connective tissue; but all these surmises have now been abandoned, and after the histogenetic studies of Laguesse and his pupils, their epithelial character is generally admitted.

According to Renaut and Laguesse the centro-acinar cells are the essential factors in all the changes of form that occur within the gland. They also participate in the external secretion.

In addition to the epithelial cells which constitute the alveolar gland proper (acinar cells, centro-acinar, epithelial cells of ducts) the pancreas of all vertebrates presents areas of tissue or compact structures, which are distinct in character from the alveoli. They stain much less freely with ordinary methods; in some cases the individual cells have no sharp outline but resemble a

protoplasmic mass, in which a number of nuclei are arranged irregularly, so that for a long time these cells were thought to be lymphoid. Recent research, has, however, shown them to be epithelial. According to some authors these epithelial bodies are destitute of excretory ducts; but they invariably exhibit a number of tortuous blood-vessels which in certain cases (Kühne and Lea) assume the form of glomeruli. They are generally known as the islets of Langerhans (Fig. 27).

The special significance of these islets has recently been much

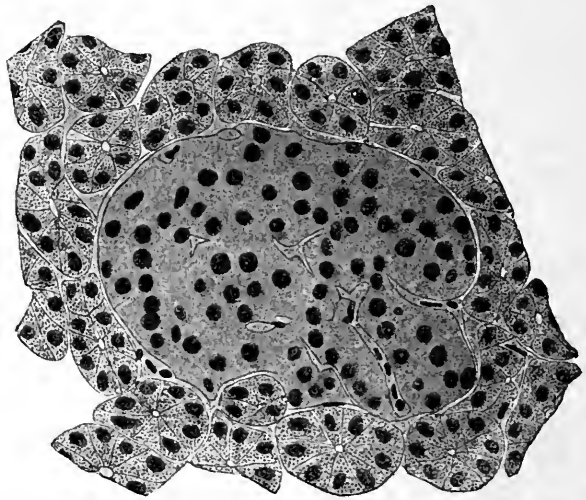

FIG. 27.—Section of rabbit's pancreas. (Marassini.) The periphery shows a number of glandular acini, which are darker in colour; at the centre is a large islet of Langerhans of a lighter colour, composed of cells with indistinct outlines.

discussed. Many observers conclude from their morphological characters (absence of ducts, abundance of blood-vessels) that they are responsible for the internal secretion of the pancreas, while others claim that the alveoli, too, participate in this function.

As regards the relation between the islets and the alveoli, Lewaschew (1886) suggested that the islets represent phases in advancing exhaustion of the secreting alveoli. According as the latter are more or less fatigued, they exhibit cells which approximate to the characters of the islets or the acini. He supported his hypothesis by observations which showed that the islets are more numerous in the pancreas of over-fed animals, and during the action of pilocarpine. Lewaschew's theory was adopted, as regards the possible derivation of islets from alveoli, by Dogiel, Perdisgeat and Tribondeau, Dale, Laguesse, and many others.

Laguesse, however, modified its physiological interpretation,

and regards this process as an alternation between the external and internal secreting conditions of pancreatic tissue, which is necessary to enable the organ to accomplish its double function.

The theory of the development of alveoli into islets, and *vice versa*, was soon contested.

Vassale (1891) first showed that after ligation of Wirsung's duct in rabbit, the islets remain, while the alveoli disappear. Massari (1898) found that in eels the islets were constant and invariable, without any true transitional forms. Immediately after, Giannelli, Renaut, Diamare, Jacotsky, W. Schultze, Opie, and others, on repeating the experiments of Lewaschew's school (hyperalimentation, pilocarpinisation, inanition, etc.), failed to find any constant difference in the number and appearance of the islands, in the various animals experimented on. Since that time the theory of Lewaschew and Laguesse has been unanimously abandoned.

It remained to be seen whether the islands were in communication with the excretory ducts. The results obtained by certain authors who attempted to solve the problem by injecting the ducts with coloured solutions which are readily recognised under the microscope, are directly contradictory. Thus Lewaschew (1886), Mankowski (1901), asserted that the injected substance penetrates to the islets. V. Ebner (1872), G. Rossi (1902), and others affirm that it never reaches the islets. But it must be noted that injection by the ducts does not always reach the whole of the alveoli, as observed by Rossi. These negative results have therefore no decisive value.

Simple histological examination, on the contrary, does tend to support the hypothesis of communication between the islets and the excretory ductules. Laguesse, in a fragment of human pancreas, noted that out of 56 islets followed in serial section, only 4 were entirely independent. Of the other 52, many were either in direct relation with the excretory system, or were joined to it by the alveoli.

A highly important detail, as to which opinions differ, is the existence of a connective capsule, surrounding the islets completely, and separating them sharply from the alveolar tissue. Renaut (1879) pointed out a reticulum enclosing the islets, as did also Opie and Pugnat. On the other hand, Gibbes, Diamare, and Hansemann denied these observations. To solve the problem Marshall Flint (1903) employed tryptic digestion, which spares this capsule; and decided that it existed.

Laguesse also admitted it, but stated that the capsule (*membrana propria*) does not completely surround the islets, which contract relations with the excretory system at the points at which they are not invested.

Golgi's method demonstrates the origin of the excretory

ductules within the pancreatic alveoli: like the salivary glands, they stain a uniform black. As shown in Fig. 28, the excretory duct sends lobular branches to these ductules between the cells, and also to the interior of each cell.

The blood-vessels penetrate into the gland along with the pancreatic duct, ramify in the lobes, and form a capillary network

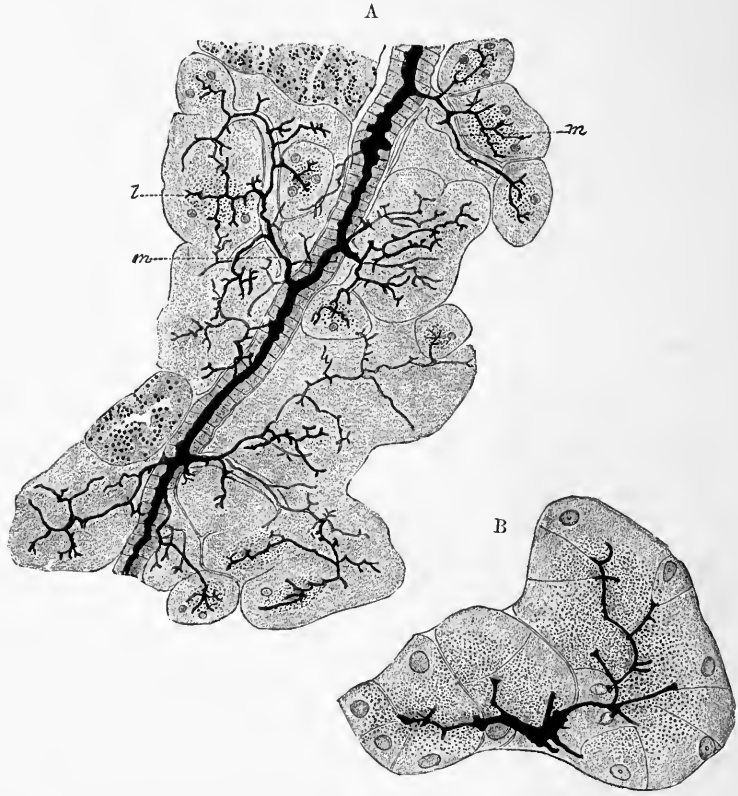

FIG. 28.—Section of two fragments of human pancreas. Silver chromate method. (E. Müller.) A, longitudinal section of excretory duct, lined with columnar epithelium; *m*, lobular ductules, giving off small diverticula between and into the alveolar cells. B, shows commencement of ductules in alveolar cells (higher magnification).

round the lobules and the alveoli with highly uneven meshes, some being so wide that many parts of the alveoli are scantily irrigated with blood.

The pancreas contains nerve fibres, both medullated and non-medullated, which unite with the sympathetic ganglia and the isolated ganglion cells. On staining with Golgi's method the fine nerve-fibrils can be followed into the alveoli. In some

carnivora, *e.g.* cat, numerous corpuscles of Pacini are seen in the pancreas.

VII. The pancreatic, like the salivary, secretion is under the control of the nervous system, for it begins a few minutes after the food has entered the stomach, which must be due to a nervous reflex transmitted from the afferent nerves of the stomach to the efferent secretory nerves of the pancreas. Experiment shows that these afferent nerves are stimulated by the hydrochloric and other acids directly introduced into the stomach, which after a few moments produce a copious pancreatic secretion. If the exciting action of these acids is abolished, by neutralising them with the introduction of alkaline fluids, the secretion is considerably diminished or suspended (Pawlow). The same excitatory effect is obtained when neutral fats are introduced into the stomach; but it is probable that these excite pancreatic secretion by acting on the afferent nerves of the duodenal mucosa; and also because part of the neutral fats that enter the stomach are split into fatty acids by the lipolytic enzyme of the gastric juice (Volhard).

These facts suggest that under normal conditions the secretion of the pancreas is connected with the introduction of acid foods and fluids, particularly the hydrochloric acid of the gastric juice, which reflexly excites the secretory nerves of the pancreas. Direct observations support this theory, and show that when gastric secretion increases, the pancreatic secretion increases also.

Subcutaneous injection of atropine diminishes the secretion of pancreatic juice, but does not suspend it, as in the case of saliva. Injection of pilocarpine and physostigmine produce a contrary effect to atropine (Gottlieb). Pilocarpine, however, does not directly excite pancreatic secretion, but it excites a profuse gastric secretion. The gastric juice, in its turn, on passing into the duodenum, is able, secondarily, to determine the pancreatic secretion. This is proved by Launoy's observation (1904) that, if the stomach be tied at the pylorus, there is no longer any secretion from the pancreas after pilocarpine injection, or, at most, only a few drops of a very dense secretion.

Heidenhain showed that electrical excitation of the medulla oblongata or cervical cord provoked pancreatic secretion if this had been suspended, and accelerated it if the gland were already functioning. Separation of the bulb from the cord by a transverse section did not, however, arrest the secretion, showing that other inferior centres besides that in the bulb affected the functions of the pancreas.

Besides a centre for secretory nerves, the bulb appears also to contain a centre for inhibition of secretion, since, on exciting the central end of the vagus, the pancreatic secretion is arrested (Bernstein). This effect is probably due to a reflex vaso-constrictor action, by which the blood-supply to the gland is much

diminished. The same result is obtained on stimulating other sensory nerves, so as to excite nausea or vomiting.

Pawlow's subsequent work on dogs established beyond a doubt that the secretory nerves of the pancreas run in the vagus. If in a dog one vagus be divided in the cervical region, and the bulb separated from the cord after 3 to 4 days by incision, artificial respiration being given, and a pancreatic fistula established, any stimulation of the peripheral end of the vagus by strong or weak induced currents produces pancreatic secretion. Previous researches carried out without these precautions had always led to a negative result, owing to the great sensibility of the gland to all influences capable of altering its blood-supply.

The vagus is not, however, the only nerve which contains secretory fibres to the pancreas. According to Kudrewetzsky, the splanchnic also supplies some, although their secretory action is much less developed than that of the vagus.

A recent theory of Bayliss and Starling as to the *mechanism of secretion*, whether of the pancreas or of other glands in the digestive tube, has been very generally accepted.

According to these authors there is, besides the nervous control which is able in itself to excite pancreatic secretion, another secretory mechanism, which acts independently of the nervous system. This consists in an internal secretion by the mucous membrane of the duodenum, of a special substance (*secretin*) which, on entering the circulation, travels with the blood to the pancreatic cells, exciting them directly and causing secretion.

Their theory rests particularly upon the fact that, on macerating the mucous membrane of the intestine (especially of the duodenum and adjacent parts) in a solution of hydrochloric acid, a solution is obtained on filtering, which, when injected into the veins, produces a profuse pancreatic secretion.

This fact has been controlled by many, and invariably confirmed; but it does not seem to us to justify the theory that has been based upon it. To say that *secretin* thus artificially prepared is able to excite secretion in the pancreas and many other glands does not mean that it is elaborated and circulated under normal conditions of the duodenum. We know from an observation of U. Lombroso (1903) that such is not really the case. In dogs with a Pawlow's pancreatic fistula the secretion diminishes, and ceases entirely after some days, if the papilla of the duct be destroyed, even if the secretory ducts are still open.

The same occurs if, instead of establishing a pancreatic fistula by Pawlow's method, it is prepared in Cl. Bernard's way, which does not respect the integrity of the duct or the papilla. Why, in all these cases, if the secretory mechanism of the pancreas consisted (as on the *hormone theory* of Bayliss and Starling) in the production of secretin during the passage of the gastric

contents into the duodenum, should the pancreatic secretion decline and cease? Since the duodenum continues to receive uniform quantities of gastric juice, a corresponding amount of secretin should be elaborated to carry on pancreatic secretion.

Popielski (1905-7) and his pupils have recently published a series of experiments and conclusions which completely refute the *secretin theory*. Popielski states that the substance extracted after the maceration of the duodenal mucosa with hydrochloric acid is not specific, but may, on the contrary, be obtained by simple hydrolysis, from any glandular, muscular, or even nervous tissue. Popielski further points out that no appreciable alteration of blood pressure can be observed on introducing hydrochloric acid into the stomach to produce an abundant pancreatic secretion; whereas the so-called secretin has no sooner been injected (even in small doses, with which much less secretion is obtained) than a marked diminution of blood pressure occurs. According to Popielski, this proves that the substance in question acts as a vaso-dilatator.

But the following is the most cogent of Popielski's arguments. On repeating the injections of secretin many times in equal doses, he observed a conspicuous secretion after the first dose, less after the second, less still after the third, till the substance rapidly became ineffective. Now, the introduction of acid into the duodenum, however often repeated, invariably excites pancreatic secretion proportional to the quantity of acid introduced. The body evidently reacts to the introduction of secretin by forming an anti-body capable of fixing it and annulling its action; this suggests that it is not a substance normally developed in the body, but is an artificial extraneous product.

The pancreatic, unlike the salivary, secretion ceases when pressure in the excretory duct reaches the maximum of 21 mm.Hg, which is far below that at which the arterial blood circulates in the gland (Pawlow). During secretion there is, as in the salivary glands, an acceleration of local circulation, which Kühne and Lea observed directly under the microscope, in living rabbits. The capillaries, which are too narrow to permit the passage of more than a single erythrocyte, dilate during activity so as to allow of more corpuscles passing simultaneously. The pulsation or transmission of the blood-wave is visible in both the capillaries and the small veins. These are phenomena of active vaso-dilatation, from physiological excitation of the vaso-dilator nerves by paths which are quite unknown to us.

Pancreatic secretion appears to be *continuous* in herbivora, whose gastro-intestinal tube is never empty of food, and *intermittent* in carnivora, which have a shorter digestive tube and intermittent digestive processes. Colin observed in calves that the secretion is continuous, but that it ebbs and flows in relation

to the degree of digestive gastro-intestinal activity. According to the observations of Heidenhain and his school, the secretion ceases in fasting dogs, and recommences during digestion, continuing with fairly regular fluctuations throughout the process. The rate of secretion reaches its height in the first 3 hours of digestion, then slowly diminishes, to rise again to a second maximum between the third and seventh hours, after which it falls rapidly to the minimum. The interpretation of this will be discussed elsewhere.

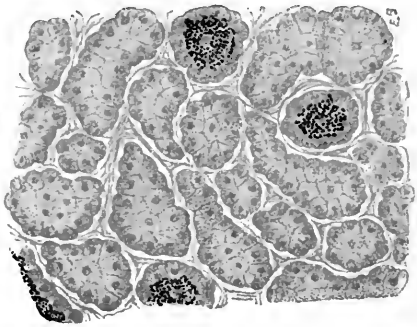

FIG. 29. — Pancreas of dog with permanent fistula, showing changes in the alveolar cells owing to paralytic secretion. Alcohol-carmine method. (Heidenhain.)

In dogs, too, pancreatic secretion may become continuous if the state of the gland is altered. In this case (which recalls the paralytic secretion of the salivary glands) the juice secreted is fluid and highly similar to an ordinary transudate. The alveoli of the gland are reduced; the secretory cells have lost the inner zone and only keep the outer, so that their whole contents stain with carmine (Fig. 29). This change is an exaggeration of what occurs in the gland in normal digestion.

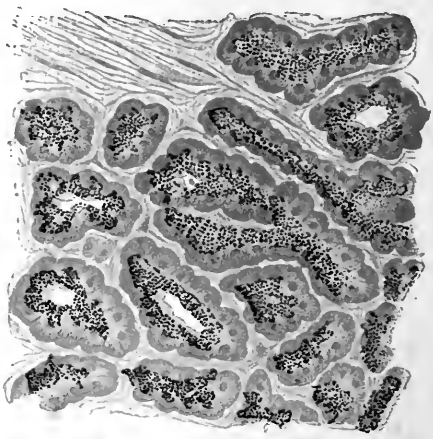

FIG. 30.—Dog's pancreas, excised during first period of digestion. Alcohol-carmine method. (Heidenhain.)

According to Heidenhain's histological studies of the pancreas, by the alcohol-haematoxylin and carmine method, in the first period of digestion (which extends to 6-10 hours after the meal) the outer, staining zone of secretory cells is enlarged in dogs; the inner, granular zone almost entirely disappears, so that the glandular alveoli seem as a whole to be diminished in diameter. The alveoli never show uniform changes, some being more, others less, modified by the secretory process (Fig. 30).

In the second digestive period (which includes the interval between 10 and 20 hours after the meal) the alveoli increase in bulk by a marked enlargement of the secretory cells. Their

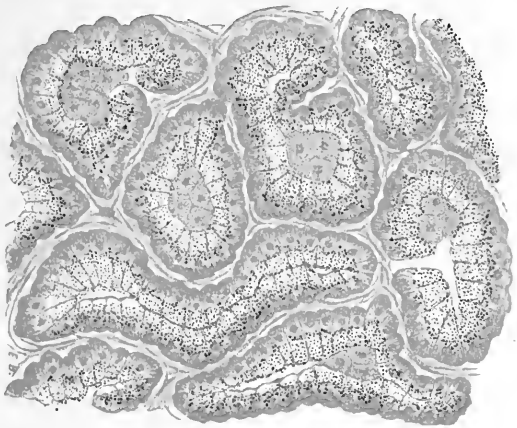

FIG. 31.—Dog's pancreas, excised during second period of digestion. Alcohol-carmine method. (Heidenhain.)

inner zone is much enlarged, while the outer is more reduced than it was during fasting; their nuclei are no longer round, but flat and angular (Fig. 31). From all this Heidenhain concludes that the inner zone of cells is consumed or dissolved during the

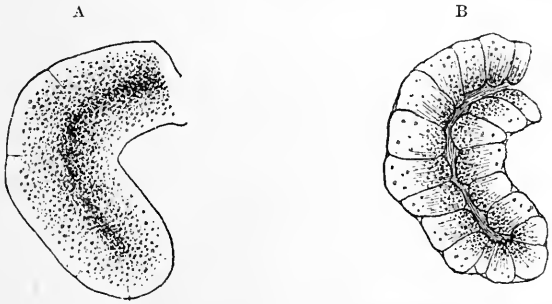

FIG. 32.—Two alveoli from pancreas of living rabbit, in state of rest and of secretory activity. (Kühne and Sheridan Lea.) A, resting state; B, after secretion.

first stage of digestion, and regenerated at the expense of the outer zone in the second, as if the one were transformed into the other.

The later researches of Kühne and Lea, obtained by direct observations on live rabbits, have corrected Heidenhain's observations in accordance with the earlier doctrine of Johannes Müller.

At the commencement of secretion, the cells of the tubular alveoli undergo gradual changes which become very conspicuous. As is partly shown in Fig. 32, the cells shrink in consequence of secretion. The polyhedral cells become rounder; the outlines of the cells, which in the resting state are to a large extent invisible, are well marked after secretion, with a double contour; the granules of the outer zone move towards the lumen of the duct, become smaller, less shining, and gradually disappear altogether. It is therefore the secretory matter elaborated into granules by the metabolic activity of the cells which dissolves and passes into the secretion, and not the protoplasmic substance of the inner zone of cells.

In spite of much research little is known precisely as to the significance of the granules pointed out by Claude Bernard and commonly known as *zymogen granules*, or their relation with the functional phases of the gland. Kölliker, Henle, v. Frey, and others who observed them before Bernard, regarded them simply as fat-granules, owing perhaps to their round and refracting surface.

If fragments of the pancreas are dissociated and pounded up in a drop of serum, the granules are set free, and float for a long while in the fluid before they dissolve. On adding acetic acid they dissolve instantly, while in a solution of potash they first swell and then dissolve slowly. Heidenhain, who (as we have seen) observed variations in the number and arrangement of the granules during the various stages of digestion, suggested that they might consist of masses of *pro-ferment*. This hypothesis was accepted by many authors who gave them the name of *zymogen granules*.

But while the participation of the granules in the pancreatic secretion is beyond doubt, there are certain observations which forbid us to accept without further demonstration that they represent the zymogen, or the whole zymogenic content of the gland.

Liversedge, Laguesse and Debeyre observed that maceration of the pancreas with solutions capable of dissolving the granules (acetic acid or alkali) yields an extract that is completely inactive to protein, even on the addition of kinase which ought to activate it (see Vol. I. p. 30).

On the other hand, U. Lombroso observed that 10 to 12 days after ligation of the ducts, the pancreas of the pigeon, which no longer shows any granules under the microscope, still exhibits well-preserved enzymatic properties (amylolytic activity).

VIII. Alkaline while living, the pancreas after death gives an acid reaction, which is probably due to the development of lactic acid, and of fatty acids.

Chemical analysis of pancreatic tissue shows the presence of an albumin, several globulins, nuclein and nucleo-protein (Spitzer),

various nitrogenous compounds, inosite, lactic acid, neutral fats, volatile fatty acids, uric acid, and mineral substances. The composition of the human pancreas is according to Oidtmann—

Water	74·53 per cent
Organic Substances	24·57 „
Inorganic Substances	0·75 „

The most important substances it contains (the chemical nature of which is still wholly unknown) are the three or four zymogens, which are readily converted into their respective enzymes, on which the digestive properties of the pancreatic juice depend.

The pancreatic secretion differs entirely in its physical characters and composition according as it is collected in a temporary fistula of Wirsung's duct, or from a permanent fistula. In the first case it is stringy and syrupy, forming in the cold at 0° a gelatinous mass, from which a fluid serum separates out. This gelatinous mass readily dissolves in dilute acids. Owing to the amount of protein, the pancreatic juice thus obtained coagulates on heating. The secretion from the permanent fistula is more fluid, and contains a smaller amount of organic matters. Both the one and the other juice have digestive properties, but we must hold with Pawlow that it is only the secretion from a successful permanent fistula that represents the normal secretion, since the pancreas is highly sensitive to all the lesions inevitable in making a temporary fistula.

The quantity of juice that escapes from a fistula in a given time is very variable, and therefore very difficult to estimate. Some hold that the human pancreas secretes 150 c.c. per diem.

This appears to us to be too low an estimate. Since Pawlow obtained 300-350 c.c. of juice from a dog that weighed about 20 kgrm., it is probable that a man would secrete over 500 c.c. per diem.

The *actual* reaction of the pancreatic juice, which is almost neutral (Farkas), must be distinguished from the *potential* reaction, which is, on the contrary, intensely alkaline, and equivalent in the dog to 1/10n NaOH. Pawlow has observed that the alkalinity of the pancreatic juice is equivalent to the acidity of the gastric juice, and therefore suffices to neutralise the acidity.

Normal pancreatic juice contains a large amount of protein. According to Zawadsky that collected from a fistula in a woman operated on for pancreatic tumour contained in 100 parts—

Solids	13·59 per cent
Total Organic Substances	13·25 „
Albumin	9·21 „
Ash	0·34 „

Its most important constituents are the enzymes or soluble ferments. These are usually three; the diastatic enzyme (*amylopsin*), the proteolytic enzyme (*trypsin*), and the lipolytic enzyme (*steapsin*), to which a fourth, on which depends the capacity of the pancreatic juice to coagulate milk (*chymosin*) should perhaps be added. Pancreatic juice further contains a substance which is precipitated by acetic acid (Halliburton); this may be *mucin* or *nucleo-protein*. Besides these, xanthine, leucine, fats, soaps, and salts, more especially alkaline chlorides, alkaline and earthy carbonates and phosphates, have also been found.

Pure *trypsin* is a protein of unknown composition which in the free state is soluble in water and insoluble in alcohol and anhydrous glycerol, in which, however, it dissolves if not quite pure. When dissolved in water, the solution being acidulated and boiled, it splits into albumin and peptone (Kühne). This may, however, be not a true cleavage but a separation, as the albumin may be considered an impurity (Loewi). When dissolved in sodium carbonate and heated to 50° C. its proteolytic activity is destroyed after five minutes: in a neutral solution it is destroyed at 45° C.; it is also destroyed by the hydrochloric acid of the gastric juice. Its digestive activity for proteins is best developed in the presence of a 1 per cent solution of sodium carbonate, at a temperature of 40° C.

The formation of trypsin in the pancreas has been more closely studied than that of any other enzyme. If from a dog that has fasted for 24 hours a glycerol extract of half the pancreas is made immediately after the death of the animal (extract 1), and of the other half when it has been left 24 hours in the air at a temperature of 40° C. (extract 2)—taking in both cases one part by weight of the pancreas (ground up with powdered glass) and ten of glycerol, adding to both extracts a 1·2 per cent soda solution—it is regularly found that the first extract has little or no digestive action upon fibrin, while the second extract has a marked action. This experiment shows that the fresh pancreas contains little or no trypsin, but that it does contain a substance that can be transformed into trypsin, which Heidenhain termed *trypsin-zymogen* (also known as *trypsinogen* or *protrypsin*).

This zymogen is insoluble in water. Its conversion into trypsin is arrested or greatly hindered by the addition of a 1-2 per cent soda solution. But if the glycerol extract containing zymogen is dissolved in sodium carbonate (1-2 per cent), and oxygen passed through it for ten minutes, it becomes strongly active by conversion of the zymogen into the enzyme. Zymogen dissolved in distilled water that has been previously boiled remains inactive; in unboiled distilled water it becomes active owing to the contained oxygen. The same transformation occurs

with platinum black, with dilute acetic acid, and according to Kühne with absolute alcohol also.

According to Heidenhain the amount of trypsinogen in the gland diminishes gradually from the commencement of digestion, reaching its minimum after 6-10 hours. It then begins to increase again, and reaches its maximum 16 hours after the meal, when it remains constant for about 30 hours.

The other enzymes secreted by the pancreas have not been fully worked out.

Amylopsin or *pancreatic diastase* was discovered by Valentin in 1844, and again by Bouchardat and Sandras in 1846. It has an amylolytic or saccharifying action upon starch, similar to that of the ptyalin secreted by the salivary glands, but is more vigorous and rapid, since it is able to act on raw starch. It has been assumed capable of transforming large quantities of maltose into dextrose; other authors (Rohmann) maintain that this effect depends upon another special enzyme, to which the name of *glucase* has been given.

According to Korowin, Zweifel, and Sonsino the diastatic power of the pancreas begins to develop in the second month after birth, and is absent in the new-born.

Little is known in regard to the zymogen of pancreatic diastase, as assumed by Liversedge. According to Grützner the amount of diastase contained in the pancreas fluctuates during digestion like the trypsin; it is minimal in the sixth hour of digestion, and reaches its maximum 14 hours after the meal, after which it decreases slowly, though it is still higher than in the first digestive period.

Steapsin (*lipase*), the enzyme which emulsifies fats, and splits them into glycerol and fatty acid, was discovered by Cl. Bernard in 1846; its hydrolytic power was subsequently confirmed by Nencki, who showed that acetic acid ester and the esters of the aromatic series (salol, benzonaphthol) are decomposed by the same enzyme. It has never been isolated, and is certainly the least known of the pancreatic enzymes. It can be extracted from very fresh glands by a watery solution of sodium carbonate (Paschutin). It does not dissolve in glycerol; is destroyed by alcohol and acids; is not found in glands that are not perfectly fresh. It probably exists in the foetal pancreas because the meconium contains free fatty acids. The optimum of its activity in regard to neutral fats is reached at 38° C. Its action, like that of all other enzymes, is destroyed by boiling. It acts better in a neutral than in an alkaline medium.

Nothing is known of the zymogen from which lipase arises. According to Grützner this enzyme increases slowly in the pancreas from the sixth to the fortieth hour after a meal, reaching its minimum (like the other pancreatic enzymes) at the 6th hour of digestion.

We shall deal in a later chapter with all that concerns the nature of the different digestive processes effected by the pancreatic enzymes, and the conditions which favour, moderate, or inhibit them—the importance, in short, of the pancreatic secretion to the utilisation of food-stuffs in general.

Besides the pancreatic juice obtained by a temporary or permanent fistula of Wirsung's duct, the digestive activity of the pancreas is tested by making an *artificial extract* of the organ. This is prepared by grinding up the pancreas, after dissecting away the fat and connective tissue, and drying it in a desiccator over sulphuric acid. The dried residue is then treated with alcohol and ether to remove the remaining fat, and macerated with a 1 per cent solution of salicylic acid at 40° C. for 12 hours, 500 c.c. of this solution being used for every 100 grms. dried pancreas. The mass is then filtered and squeezed through muslin. The solid material is digested for 12 hours at 40° C. in 500 c.c. of a 2·5 per cent solution of sodium carbonate, containing a few drops of an alcoholic solution of thymol to prevent putrefaction. The filtrate is rendered alkaline with the same solution, and also allowed to digest at 40° C. for 12 hours. Both from the solid material after filtering from any undissolved residue, and from the solution, a very active artificial pancreatic extract is obtained.

From these extracts trypsin can be prepared in a state of comparative purity by Kühne's method. The extracts are allowed to digest for about a week, when all the proteoses will be transformed into peptones. They are filtered, and ammonium sulphate added to the filtrate to saturation. A fine precipitate results, which carries down all the trypsin. This is dissolved in water and dialysed, to remove the greater part of the ammonium sulphate. The remainder of the sulphuric acid is precipitated as barium sulphate by barium carbonate, and the clear filtrate is precipitated with alcohol. The amorphous precipitate thus found is collected on a filter.

IX. That the pancreas exerts an *internal* function in carbohydrate metabolism was suspected long ago by clinicians (Frerichs, Cantani, Seegen, Bouchardat, and others), since post-mortem examination of many cases of human diabetes showed profound and varied alterations of this organ. But as little was known at that time about the internal functions of glands, and there was then no suspicion of the existence of such a function in a gland provided with an excretory duct, they attempted to explain the diabetes as an indirect consequence of the altered *external* function of the pancreas. This gave rise to the hypothesis (to which we must refer, because it is still maintained by certain authors) that the food-stuffs being ill-digested, owing to the absence of the pancreatic enzymes, developed toxic substances which, when reabsorbed, inhibited the normal carbohydrate metabolism.

It was long before any experiments threw light upon this subject. The first attempts at extirpating the pancreas (Conrad Brunner, 1788; Cl. Bernard, 1855; Bérard and Colin, 1857; Senn, 1880; Martinotti, 1880) either resulted in the death of the animal in a short time, making it difficult to analyse the phenomena, or were so incomplete that no disturbance resulted from them, so

that the function of the gland appeared not to be indispensable in the various processes of metabolism.

Nor did glycosuria appear in other experiments (on dogs, cats, and rabbits) in which destruction of the pancreas was attempted *in situ* by ligation and section of the ducts, or their injection with extraneous substances, such as oil, paraffin, acids, etc. (Cl. Bernard, Schiff, Pawlow, Arnozan, and Vaillard).

In 1889 von Mering and Minkowski successfully accomplished the total excision of the pancreas in dogs, and stated that immediately after the operation there appeared regularly, along with grave disturbances of alimentary absorption, an intense glycosuria which lasted until the death of the animal, 2-3 weeks later. The complex of symptoms was very like that of severe cases of human diabetes (*wasting diabetes*), so much so that it was known by the name of *experimental diabetes.*

The results of von Mering and Minkowski were at once confirmed by many authorities (Hédon, Lépine, Capparelli, etc.). Since this glycosuria was evidently not due to impeded flow of pancreatic juice into the intestine (as in the case of the permanent fistula of Wirsung's duct), it was easy to deduce that it depended not on the defective action of the secretion in the intestine, but on the suppression of some other function exerted by the pancreas. This idea, however, was and still is combated by some authors on the strength of the following experiments.

De Dominicis, who excised the pancreas in dogs, simultaneously with von Mering and Minkowski, sustained emphatically that the glycosuria was not a constant phenomenon, and not in any case determined by the suppression of an internal pancreatic secretion. Glycosuria and all the other phenomena by which it is usually accompanied (pollakiuria, polyuria, polyphagia, azoturia, phosphaturia, etc.) depend, according to De Dominicis, upon a reabsorption of toxines formed by the putrefaction of alimentary substances that are not digested owing to lack of pancreatic juice. He observed that injection of faecal extract from depancreatised dogs produces slight glycosuria (1894), while injection of the duodenal contents of depancreatised dogs produces an intense and persistent glycosuria (1908).

Pflüger (1905) long refused to admit that the glycosuria consequent on excision of the pancreas was due to suppression of a true internal function of this gland. In his opinion the operative act excites the nerve plexuses which traverse or have their terminations near the pancreas, and which reflexly affect the centres which he terms *diabetogenic*, leading to increased formation of glucose on the part of the liver. This theory of Pflüger, already brought forward in 1892 by the brothers Cavazzani, was contradicted by the experimental results of Lustig, Kaufmann, Marassini, Zamboni, who, on more or less completely excising the solar plexus, or

dividing the nerves to the pancreatic region, obtained no diabetes, but at most a slight transitory glycosuria. Moreover, Minkowski, Hédon, Thiroloix, Sandmeyer, U. Lombroso, showed that after the extirpation of a large part of the pancreas (leaving only the processus uncinatus freed from all its relations with the duodenum, save the large vessels) there was no glycosuria in the majority of cases, although the lesions involving the nervous system of the region were practically identical with those consequent on complete extirpation, so that it was no longer possible for the external secretion to be poured out into the intestine.

Pflüger denied the value of this experiment, affirming that if one nerve filament were left intact it was able to act vicariously for all the rest, so that the presence of the nerve plexus which accompanies the respective vessels would explain the absence of glycosuria.

Hédon, who had already investigated the neural hypothesis, tried to answer this last objection by dividing the neuro-vascular peduncle of the pancreatic segment left in the body. His results, however, proved little, because glycosuria set in after resection of the peduncle; still he noted that it almost always *increases* when the pancreatic segment is excised.

The subsequent results of U. Lombroso in Minkowski's laboratory may be regarded as an *experimentum crucis* against the neural theory.

In a dog in which the processus uncinatus was grafted under the skin, and which merely showed traces of sugar in the urine (less than 0·3 per cent), the neuro-vascular peduncle was cut a month after the first operation. Slight glycosuria appeared, and vanished after four days, leaving the animal in the initial state. After twelve days, on extirpating the segment of the pancreas so as to separate it completely not only from the duodenum but also from the abdominal cavity, severe diabetes at once set in, and persisted till death.

De Dominicis refused to admit that these experiments, like those which proved that glycosuria does not appear after ligation of the pancreatic ducts, had any conclusive value against his own theory. He pointed out that after ligation of the ducts or excision of that part of the pancreas which contains the ducts, alimentary absorption was far better than after total extirpation of the pancreas. This, according to De Dominicis, showed that the pancreatic secretion was able in some way to reach the intestine, either by ducts that remained open or by a new formation of ducts.

With this is associated another question that has recently come under discussion. Does or does not the pancreas influence food absorption, when it is no longer pouring its secretion directly into the intestine?

De Dominicis, and more recently Visentini and O. Hess, reply in the negative.

According to Hess the dog's pancreas often has more than two ducts, hence the experiment of tying the two ducts is not conclusive. According to Visentini the divided ducts can easily recover their functions. But these authors neglect the fact that alimentary absorption can also be beneficially affected by the presence of a segment of the pancreas completely separated, not only from the duodenum (Abelmann, Pflüger, Hédon, U. Lombroso, Rosenberg), but from the abdominal cavity as well (U. Lombroso).

Abelmann, Minkowski, Pflüger, Rosenberg, supposed that absorption in these last cases still depends upon the external secretion, this being reabsorbed and carried by the circulation to the liver or the intestinal glands, whence it is returned to the intestine.

Lombroso opposes this doctrine. He shows that by infusing a certain quantity of pancreatic secretion into the vein, the enzymatic property of the bile might be profoundly altered for some considerable time, whereas such modification does not occur after occlusion of the orifices into the pancreas. He therefore thinks it probable that in such cases there is no reabsorption of the pancreatic secretion. He has recently demonstrated (1908) in the laboratory of Minkowski (who previously supported the opposite theory) that a segment of pancreas, grafted under the skin, so that its secretion is freely poured out externally, does promote food absorption. Fleckseder, in Vienna, simultaneously arrived at the same results as Lombroso, and therefore supports his theory.

In view of these results it is no longer possible to put forward alimentary absorption as a proof that the pancreas with occluded ducts is capable of pouring the products of its external secretion indirectly into the intestine. The internal function of the pancreas must, therefore, be not solely the arrest of glycosuria, but also, though indirectly, the promotion of food absorption. We shall return to this subject in treating of the absorption of food.

The next question is whether this *internal function* of the pancreas connotes a special secretory process or no. Hédon holds that it should be possible to prove the existence of an internal secretory function of the pancreas, by the modification of experimental diabetes with the introduction of glandular extracts into the circulation, just as the thyreopriva syndrome can be modified by administration of thyroid extracts.

Research in this direction has yielded only doubtful or contradictory conclusions. Capparelli (1891-92) obtained favourable results in depancreatised dogs with injection of very fresh pancreatic pulp. Recent observations of Zülzer, Dohrn, and Maxer (1908), on both human and experimental diabetes, had the same

result. On the other hand, the conclusions of Hédon, Gley, Lépine, and many others were negative. To us it seems too large an order to assert that artificial injections of glandular pulp can replace a physiological function which develops in a continuous and regular manner, or to give a decisive value to negative results in such questions.

A very ingenious experiment, which tells in favour of a *true internal secretion* of the pancreas, is that of Forschbach (1908) with the method of *parabiosis*. This consists in uniting two animals of the same species and litter with a triple suture (cutaneous, muscular, peritoneal). In the animals thus operated on, there is an exchange of blood by the blood-vessels and lymphatics of the two communicating abdominal cavities, and it has been shown that many substances (iodine, sugars, alkali, etc.) injected into one animal pass rapidly into the other.

On extirpating the pancreas from one of the two dogs in parabiosis, pathological disturbances do not set in with the severity described above: in some cases they are very slight, but become aggravated as soon as the depancreatised dog is separated from the other.

Biedl observed permanent glycosuria after ligation of the thoracic duct, or when the whole of the lymph had been drawn off externally, and found (with Offer, 1907) that this experimental diabetes disappeared on injecting lymph, which suggests that the internal secretion of the pancreas may be discharged by the lymphatic system.

These observations render the hypothesis of an *internal secretion* the most probable among the many that have been proposed to explain the internal function of the pancreas.

X. Given the existence of an internal function of the pancreas, and assuming it to be served by a special secretion, Laguesse, Schäfer, Opie, and others formulated a theory that has been widely accepted. The two secretions of the pancreas, external and internal, are held to be distinct functions of different cells, the former being served exclusively by the alveoli, the second by the islets of Langerhans.

The morphological arguments for this theory are, however, inadequate, and too much a matter of controversy to be conclusive. They rest on the well-known fact that the islets are provided with numerous blood-vessels, and on the assertion (supported by very few authors) that they are completely invested by a capsule of connective tissue and contract no relations with the excretory ducts.

If this could be proved, the *insular theory* would obviously have a valid anatomical basis. Even so, however, the possibility that the alveoli also contribute to the internal secretion would not be excluded. Moreover, the fact that the islets contain numerous

blood-vessels is no proof that they serve the internal secretion to the exclusion of the alveoli. It is still conceivable that the internal secretion of the pancreas may be discharged by the lymph capillaries. Biedl's observations as previously quoted support this hypothesis.

Morbid anatomy does, indeed, support the view that the islets are the exclusive organs for the internal secretion of the pancreas. Numerous observations (Hansemann, Opie, Gutemann, Karakascheff, Ssobolew, Herxheimer, Schmidt, Sauerbeck, Visentini, Herzog, Reitmann, etc.) show that the pancreas may exhibit different features in human diabetes. In some cases there is no alteration either of alveolar or of insular tissue. But in the great majority of cases the pancreas is profoundly and diffusely altered, both in the alveoli and in the islets. It is rare for the degeneration to involve alveolar tissue only, still more rare that the changes should be confined to the islets.

The rare cases of diabetes with a healthy pancreas prove that this disease is not necessarily pancreatic in origin; which does not alter the fact that the pancreas normally discharges an internal secretion which affects carbohydrate metabolism.

The rare cases of diabetes in which either the islets alone or the alveoli alone are modified, cannot be taken as a decisive argument in favour of the theory which ascribes the internal secretion of the pancreas exclusively to the islets (Laguesse) or to the alveoli (Hansemann); at most they suggest the hypothesis that both these tissues co-operate actively in the normal internal secretion of the pancreas.

Experiments with the object of localising the external and internal secretions of the pancreas in its two tissues have been numerous.

Schultze and Ssobolew (1900) were the first who maintained the insular theory of internal secretion, starting from the fact that after ligation of the ducts or internal pancreatic lobes in the rabbit, the islets were left unaltered, while the alveoli were modified and disappeared, without causing any true diabetes.

The same fact had been described by Vassale ten years earlier, but not with the intention of localising the internal secretion in the islets: he merely sought to contradict Lewaschew, who affirmed the unitary character of the two pancreatic tissues.

Mankowski and Lombroso failed to confirm the results of Schultze and Ssobolew. They found that ligation of the ducts in the rabbit produced alterations not merely in the alveoli but also in the islets, which diminished in size and number.

Many other authors (Tiberti, Pende, Marassini, etc.) obtained substantially the same results; some (Laguesse, Marassini), however, argued from the greater resistance of islets as compared with alveoli, that the absence of glycosuria must be referred to the

survival of the islets, the internal secretion being served by the islets only.

Lombroso objected that the necessary counterproof was wanting. It is not known whether complete extirpation of the pancreas (as far as possible) would produce glycosuria in the rabbit. It is known, indeed, that complete ablation of the pancreas is not followed by glycosuria in all animals. It is absent in many granivorous birds (pigeons), while it is seen in carnivora (crows, falcons). Moreover, the effects of total excision of an organ, and of the slow and gradual suppression of its function, may differ considerably. Even in the dog, according to Hédon, glycosuria may be absent or very slight when a pancreas previously altered by injection of paraffin into its ducts is excised.

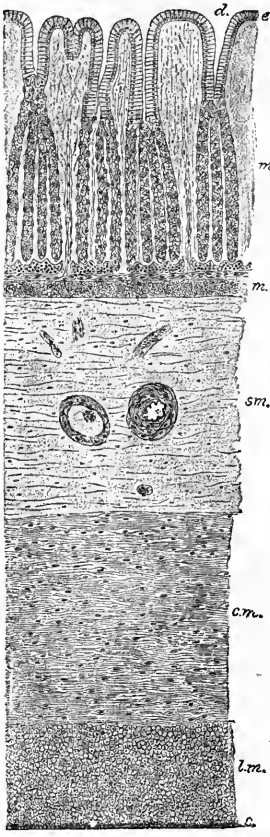

Fig. 33.—Section through the coats of the stomach. Diagrammatic. (Mall.) *m*, mucous membrane; *e*, epithelium; *d*, orifice of gland duct; *mm*, muscularis mucosae; *sm*, submucous coat; *cm*, circular muscular layer; *lm*, longitudinal muscular layer; *s*, serous coat.

After tying or cutting the ducts, and after transplanting a segment of the pancreas in the dog, numerous observers (Hédon, Moruet, Laguesse, Ssobolew, De Dominicis, Hansemann, Lombroso) found that conspicuous groups of alveoli or of islets might survive in perfect preservation, even for a long time after the operation. It was only in grafts upon animals which had rapidly perished, that both alveoli and islets were found to be degenerated. On these data Lombroso founded his theory that islets and alveoli both co-operate in the internal secretion of the pancreas.

Zuntz and Mayer extended the period of observation with dogs thus operated on to 440 days, and obtained the same results as Lombroso. Visentini, on the contrary, out of 24 dogs operated on by tying and cutting the two pancreatic ducts, found in two of them (after 160 and 212 days, respectively, after the operation) that the alveoli were not in the normal state, while the islets, on the contrary, were well preserved. He omitted, however, to notice the effect of excising the pancreas when thus altered, so as to see how far it had been capable of functioning as an organ

of internal secretion. Lombroso's observations indicate a constant relation between the degree of glandular degeneration in cases when a segment is grafted under the skin, and its function before and after excision. The less the segment is altered, the better it accomplishes its internal function, and the more acute are the effects of extirpation.

All this evidence is at present too inconclusive to determine whether the internal secretion of the pancreas is exclusively confined to the islets of Langerhans, or if the alveoli also contribute to it. This question must be left in abeyance for future research.

XI. The walls of the Stomach, in a vertical section, show four coats or layers, known from without inwards as the serous, muscular, submucous (or areolar) and mucous membranes (Fig. 33).

The *mucous membrane* of the stomach, which alone concerns us, is in two parts, the *pyloric end*, which is pale in colour, with fewer longitudinal folds, and the *fundus*, which is reddish, yellow, or brown, with more frequent and irregular folds forming a network. Beside these coarse folds (which are obliterated when the organ is distended with food), a lens shows projections on the internal surface of the stomach, with corresponding depressions of polygonal shape, which become larger and deeper near the pyloric orifice. These are the mouths of the tubular glands with which the gastric mucosa is beset.

FIG. 34.—Epithelium of surface of stomach examined fresh. Highly magnified. (Heidenhain.)

Taken as a whole, the columnar epithelial cells which cover the mucous membrane of the stomach (Fig. 34), may be regarded as a secreting organ which is not, like the glands we have been discussing, gathered into a small space, but is spread out over the surface. The function of this secreting surface does not differ specifically from that of the simple and compound mucous glands found in the buccal cavity and along the mucous membrane of the oesophagus. The columnar epithelial cells of the stomach are, however, richer in albumin than the mucous cells of the submaxillary gland, and behave very differently from them when treated with acetic acid; they do not become clouded, but are clear and swollen. With mineral acids, and on hardening with alcohol, the submaxillary cells scarcely cloud at all, while those of the gastric epithelium become quite turbid (Heidenhain).

The appearance of the columnar epithelium differs to a marked extent in the state of rest and of digestive activity. In the latter, many of the cells become goblet-shaped, open to the outside, and half-empty, owing to escape of the mucin which is elaborated from the mucinogen formed inside the cell.

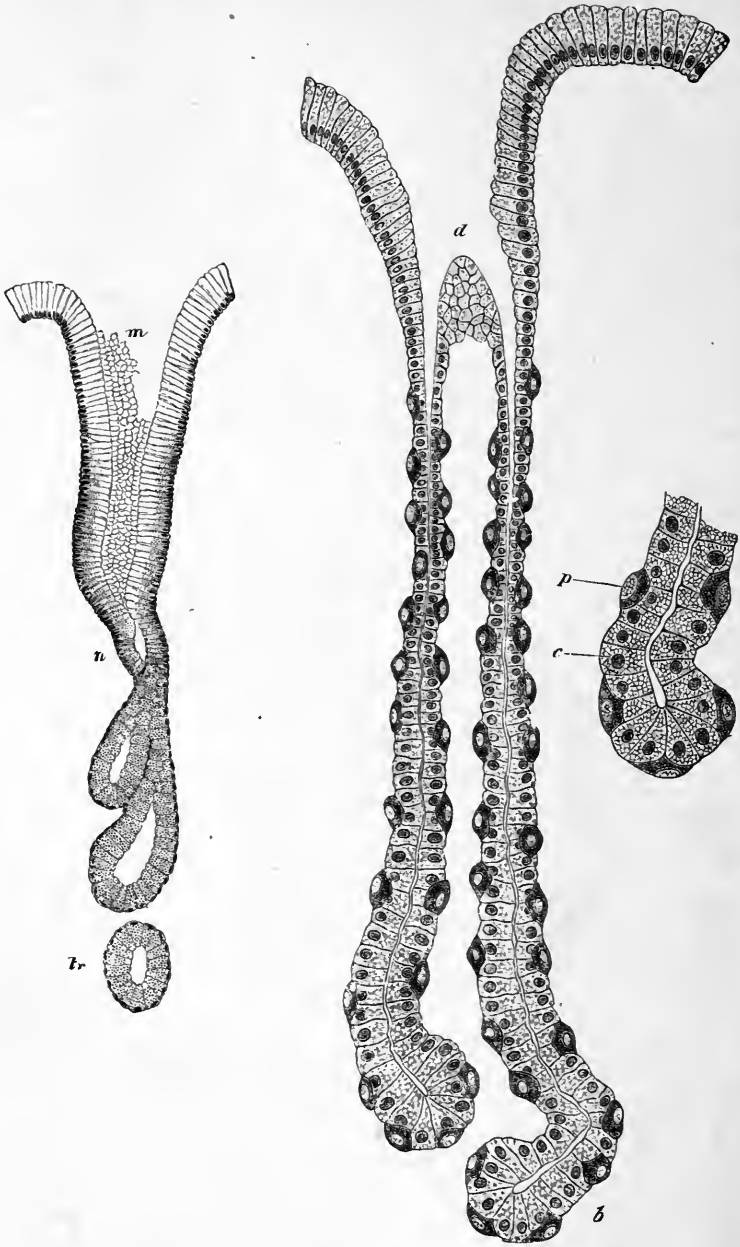

FIG. 35.—(Left.) Pyloric gland, from a section of dog's stomach. (Ebstein.) *m*, mouth; *n*, neck, *tr*, deep portion of a tubule cut transversely.

FIG. 36.—(Right.) Cardiac gland, from dog's stomach. Highly magnified. (Klein and Noble Smith.) *d*, duct and mouth of gland; *b*, base or fundus of a tubule. On the right is the base of a tubule more highly magnified; *c*, central cell; *p*, parietal cell.

The specific secretory organs of the stomach consist of two kinds of glands, which differ both in the character of the cells that line the duct and in the nature of their secretion.

Most of the glands at the *pyloric* end have a long neck, lined with cells identical with those on the surface of the mucosa, and a short body, which is nearly always made up of a number of tubules, lined with an epithelium that is quite different from that of the neck or excretory duct. It consists of finely granulated columnar cells, which are never goblet-shaped, and which react specifically to various stains (Fig. 35). In the glands of the *fundus* the duct is narrower, the neck shorter, and the body longer. But they differ from the pyloric glands mainly in having two kinds of secreting cells: those which Heidenhain termed *chief*—the central or peptic cells, and those he calls *border*—the parietal or oxyntic cells. The first are similar to the cells of the pyloric glands, the second are larger, more irregular in form, darker when hardened in alcohol, more easily stained (Fig. 36). It was formerly supposed, incorrectly, that the first kind of glands were found exclusively in the pyloric region, the second in the curvature and fundus. In reality the former are more abundant in the pyloric and the latter in the fundic region (Stöhr).

FIG. 37.—Secreting duct of gastric gland. Golgi's silver chromate method. (E. Müller.) The cells are not represented, but the lumen extending into the network surrounding the parietal cells is deeply stained.

As we have seen for the salivary glands, so in the gastric, the duct which runs through the tubule is prolonged into canaliculi between the cells, and forms a basket-like capillary network round the parietal cells (Fig. 37).

The stomach is richly supplied with blood by numerous vessels from the caeliac trunk, which form a plexus beneath the submucosa. Each tubule is lined with a capillary network, from which the veins form again. They are few in number, but are larger than the arteries, with a stronger muscular coat than is usual in veins, and many valves (Hochstetter).

The lymphatics of the stomach arise in a rete of lacunar spaces that lie between the tubules of the gland and form a more ample plexus in the submucosa, whence the efferent lymphatics emerge to traverse the muscular coats and the lymph nodules situated along the two gastric curvatures.

The nerves to the stomach consist of the terminal gastric branches of the vagus, and the sympathetic fibres of the solar plexus. Both are almost invariably composed of non-medullated fibres. Numerous small ganglia (according to Remak) form plexuses with these nerve fibres, either between the layers of the muscular coat or in the submucosa. From these plexuses, nerve fibres run through the muscular tissue, or the glandular tissue of the mucous membrane.

XII. Until recently the direct influence of the nervous system on gastric secretion was regarded as doubtful. The results of experiments were either negative or less obvious than for the salivary secretion. Recent experiments have fully elucidated this point.

The flushing of the gastric mucosa owing to active vascular dilatation during digestion, the increased rate of circulation which causes bright red blood to flow through the veins that differs little from that in the arteries (Claude Bernard), are phenomena perfectly analogous to those observed during salivary secretion. They show the existence of vasomotor nerves to the stomach, and justify the conjecture that *special secretory nerves* control the gastric, like the salivary, secretion.

A stronger argument for the direct nervous control of gastric secretion lies in the fact that in fasting animals with a gastric fistula, the mere sight or smell of some favourite food causes a flow of gastric juice through the fistula (Bidder and Schmidt, 1842; Schiff, 1865). This is not due to deglutition of saliva, which might excite the gastric mucous membrane, because the same thing is seen when the ducts of the salivary glands or the oesophagus are occluded in the dog. The secretion "psychically excited" by sight or smell does not begin immediately, but only after some (5-15) minutes, and persists for a long time after cessation of the stimulus (Sanotzky, 1892).

Greater interest attaches to Richet's observations (1878) on a girl who had stricture of the oesophagus and was fed through a gastric fistula. Each time she was made to chew or taste a highly sapid substance (sugar, lemon juice, etc.) while fasting, a considerable quantity of juice flowed from the fistula. This was undoubtedly a reflex secretion, but it was uncertain whether the reflex *directly* promoted the secretion, or if, by dilating the vessels of the stomach, and contracting its muscular coat, it determined the secretory phenomenon *indirectly*.

Pawlow and Mme. Schumowa-Simanowskaia (1889) made a series of striking experiments in order to decide this question and clear up these phenomena of the innervation of the gastric glands. They established the usual gastric fistula on dogs, and in a subsequent operation divided the oesophagus half-way up the neck, and sutured the two ends to the lips of the cutaneous wound, so

that when the animal fed the alimentary bolus dropped out through the oesophageal fistula. For food to reach the stomach it was necessary to introduce it either through the lower orifice of the oesophageal fistula or through the gastric fistula.

When an animal thus prepared was made to masticate and swallow food that dropped out again through the oesophageal fistula (*sham* or *imaginary* feeding), a marked secretion of gastric juice (*psychical secretion*) was invariably noted 5-6 minutes later. On section of the vagi (the right below the point at which the cardiac branches and the inferior laryngeal are given off, and the left at the neck) this reflex secretion ceased entirely. On exciting the peripheral trunk of the left vagus with two induction shocks per sec. the flow through the fistula reappeared.

These results, which were constant under the given conditions, contradicted the previous negative results of vagus excitation obtained under other experimental conditions by many physiologists, Heidenhain included. They prove beyond doubt that the centrifugal nerves that regulate the gastric secretion are contained in the trunk of the vagus.

Von Mering (1899) showed that atropine and pilocarpine produce similar effects on gastric secretion to those which Heidenhain obtained on salivary secretion: the former diminishes or suspends secretion of gastric juice, the latter increases it even fourfold. These effects can only be explained by admitting that atropine has a paralysing, and pilocarpine an exciting, action on the secretory fibres contained in the vagus.

Other facts, however, show that the gastric secretion does not depend exclusively upon the secretory fibres of the vagus, since the stomach is capable of sufficiently digesting the alimentary substances introduced into it, even when the vagi have been divided. This suggests that other secretory fibres, spinal or sympathetic in origin, influence the gastric glands: but there are at present no experimental proofs of this conjecture. Experiments made with this object (section of splanchnic, excision of caeliac plexus) have given negative results. Heidenhain assumed that the digestive capacity of the stomach persists after division of the centres of all cranial and spinal nerves to the stomach. It is probable (although it has not been experimentally demonstrated) that the gangliar plexuses in the walls of the stomach represent a system capable of special reflex activation of secretion.

The stimuli that normally determine gastric secretion by reflex paths are the food-stuffs, which excite the nerves of taste and other centripetal nerves to the mucous membrane of the mouth, pharynx, oesophagus and stomach. The fine experiments of Pawlow and his collaborators (1889-97) have established as an indispensable condition of the production of a flow of gastric juice by the aliments introduced through the mouth, that the animal

shall have *appetite* for the food offered it. Mechanical or non-sapid stimuli applied to these sensory surfaces are not effective in promoting gastric secretion to any appreciable extent (contrary to what was formerly held). When, on the other hand, sham feeding has been carried on for only five minutes with the oesophageal and gastric fistulae, the secretion of gastric juice lasts 23 hours or even longer. This can only be explained by assuming that the excitation of the taste centre persists for the whole of this time. Section of the vagi, by which the psychical influence is transmitted to the gastric glands, in fact suffices at once to arrest the secretion.

Cohnheim and Soetbeer (1903) showed that in new-born puppies, which had a gastric fistula with divided oesophagus (Pawlow's method), the act of sucking produced an abundant psychical secretion of gastric juice. Psychical secretion, therefore, appears to be a congenital reflex as hereditary in these animals as that of sucking, and not acquired by individual education and force of habit.

It is very probable that the mechanical acts of mastication and suction may not in themselves have any influence upon the secretory work of the stomach. This agrees with Hornborg's observations (1904), showing that when a bit of gutta-percha, *i.e.* an indifferent substance, was masticated there was no gastric secretion, while mastication of sapid substances is always followed by secretion, or by an obvious increase of the flow.

According to Schüle (1901) pure psychical secretion in Pawlow's sense is seldom manifested in man. The acid secretion of the gastric glands is excited by the action of a purely chemical reflex, due to the alimentary substances which come into contact with the gastric mucosa. He further remarks that in man the act of mastication in and by itself, independent of psychical associations (taste, smell), must come into play in determining the secretion of gastric juice, as well as the direct contact of the food stuffs.

In order to study the process by which gastric secretion occurs when food is present in the stomach, Heidenhain, in a bold surgical operation, separated a portion of the fundus of the dog's stomach, and reduced it to a closed sac or pouch communicating with a fistulous opening to the outside, after which he restored continuity to the remainder of the viscus by stitches. In this operation the branches of the vagus, by which the taste centre transmitted the secretory stimulus to the gastric glands, were divided. There was no secretion in the isolated sac of the fundus during the mastication and deglutition of meat. It only begins 15-30 minutes after ingestion, and lasts a longer or shorter time, according to the nature and amount of the food ingested, *i.e.* 13 to 14 hours after a moderate meal, 16 to 20 hours after a heavy one. If instead of meat the animal is given some very indigestible food,

e.g. *ligamentum nuchae* coarsely cut up, there is no secretion in the sac. This only appears when, after such a meal, the animal is given drink, but in this case it lasts a very short time, from 1½ to 4 hours at most.

This fact was confirmed by Sanotzsky (1892), who held, like Heidenhain, that it depended on a reflex excitation (other than that of the secretory fibres of the vagus), or on a direct excitation of the secretory gland cells, due to the action of the digestive products absorbed by the walls of the stomach.

Khizhin (1895) held, on the contrary, that the secretion was due to chemical excitation of the centripetal nerve-endings of the gastric mucosa by certain special foods, previous to their absorption. Direct mechanical stimulation of the mucous membrane also produces secretion, but to a negligible extent.

There can be no question as to the gastric secretion being, at least in the first instance, determined by nervous stimuli. On the other hand, the influence on which the continuation of the secretion depends is still debateable. According to Pawlow, it is a chemical action on the peripheral nerve-endings, of the digestive products of the proteins. He observed a profuse secretion when peptones, extract of meat, etc., were introduced into the stomach, without the animal being aware of the same.

But after Bayliss and Starling published their *hormone* theory (mentioned above in treating of pancreatic secretion), which obtained a large following, experiments were set going to see whether the same might not hold good for gastric secretion also.

Edkins (1905) demonstrated that it was possible to extract a substance from the pyloric mucosa which produced a secretion of gastric juice when injected into the circulation, while extract of the mucosa of the fundus had, on the contrary, no effect.

This substance pre-exists in an inactive state, and becomes active on adding acids, or on boiling (which proves it not to be an enzyme).

Frouin (1905) noted that the subcutaneous injection of 40 c.c. of gastric juice considerably increased the gastric secretion in dogs with isolated stomachs, from which he deduced the existence in the gastric juice of substances that have the property of increasing the secretory activity of the gastric mucous membrane.

Without questioning the data cited by these authors, it seems a little premature to use them (with the followers of Bayliss and Starling) as arguments in favour of the *hormone* theory, which has been shown, in speaking of *secretin* and the pancreatic secretion, to be ill-founded.

The amount of juice secreted by the small stomach always bears the same ratio (taking into account the extent of the secreting surface) to the amount secreted by the large stomach, in sham feeding. The degree of acidity, too, is much the same, but the

digestive power is decidedly weaker. This digestive power decreases from the first to second, or first to seventh hours, then rises again and reaches its maximum at the fifth, or according to other experiments, the eighth hour.

Pawlow and his co-workers have recently succeeded in isolating a closed pouch or *cul de sac* from the stomach, without injuring the vagus fibres that control secretion (*infra*, page 114). From the animals thus operated on, they have collected important data relative to the influence upon the secretion of the blind sac of certain alimentary substances introduced into the stomach. In order to exclude reflexes by the secretory fibres of the vagus excited from the surface of the mouth, pharynx, and oesophagus, the food is introduced into the stomach by the sound. The results may be summarised as follows:—

(*a*) Water, 0·1-0·5 per cent solutions of hydrochloric acid, 0·01-1 per cent salt solutions, introduced into the stomach in amounts of 100-150 c.c., produce only a very weak secretion of juice in the blind sac.

(*b*) Water, 0·5 per cent salt solution, 10 per cent solutions of cane-sugar or starch, in quantities of 500 c.c., produce a stronger secretion, which commences 13 to 29 minutes later, and lasts some 60 to 135 minutes.

(*c*) These substances do not affect the secretion of the blind sac in themselves, but in virtue of the water in which they are dissolved. In fact, if plain distilled water is injected into the stomach, a secretion of equal quantity and duration is evoked.

(*d*) When, on the contrary, peptone is introduced into the stomach by the sound (this being, as we shall see, the principal product of the digestion of proteins by the gastric juice), there is, after about 13 minutes on an average, an abundant secretion in the pouch which lasts for some 3 hours.

(*e*) Neither ov-albumin nor proteoses produce a similar effect. They only cause a weak secretion for a short time, which may be due to the amount of water in which they are dissolved. We may conclude that peptone is a specific stimulus for the secretory elements of the stomach, probably because it is capable of exciting the centripetal nerve-endings of the mucous membrane, which determine the secretion reflexly by the centrifugal paths of the vagus, and possibly also by way of the sympathetic.

(*f*) Other observations show that after the secretion from the sac has been started by the stimulus of peptone, it increases considerably when egg-albumin is introduced into the stomach, though this by itself is ineffective.

(*g*) The gastric secretion excited by the presence of food in the stomach reaches its maximum in the first and second hours (after ingestion of milk only in the third hour). After that it gradually diminishes, and then ceases entirely. For any given kind of

food the absolute amount of juice secreted increases with the amount ingested. For different kinds in equal quantities, the absolute amount of secretion varies; it is greater for meat than for bread, for bread than for milk (Khizhin and Lobassoff, 1897).

(*h*) The introduction of carbohydrates excites no secretion of gastric juice (Barbèra, 1898); that of fats may cause its diminution or arrest if it is already present (Khizhin, 1895; Lobassoff, 1897).

This inhibitory action of gastric secretion by fats has been carefully studied by Pawlow's pupils. Their observations show that not only is the total quantity of gastric juice diminished, but the enzymic activity of the secretion is also depressed. Thus, *e.g.*, on administering 400 grms. of flesh to a dog provided with Pawlow's miniature stomach, about 40 c.c. of secretion was obtained in the first four hours, with a peptic digestive power (measured by Mett's method in mm.) equal to 5·00. On adding 75 c.c. olive oil to the 400 grms. flesh, a secretion of only 18 c.c. was obtained, with a digestive power lower by 3 mm.

The inhibitory action of fats is shown particularly in the first period of digestion (in which the influence of psychical factors is specially felt). Sham feeding in a dog operated on by Pawlow's method, when the large stomach contains oil, or has been subjected for some time to the action of oil, produces a secretion much less in quantity and activity than the same sham feeding when the stomach has not been acted on by fat.

These observations have an important practical significance, since they justify the long-established use of fats in therapeutics, for the cure of gastric ulcers, or of gastric hyper-secretion which predisposes to ulcers.

(*i*) Alcohol in moderate doses excites, in excessive doses arrests gastric secretion (Bernard, Lussana, Albertoni). Many observations have been made upon the use of alcoholic beverages (wine, beer, liqueurs) in relation to the gastric secretion. Many authors admit that these excite gastric secretion. But it is still unknown whether this is by simple psychical reflexes (sight, smell, agreeable taste) or by direct excitation of the mucous membrane.

Frouin and Pekelharing showed that on administering alcoholic solutions per rectum the increase in secretion was to be attributed to the absorption of alcohol in the blood, by which the cells of the gastric glands are excited immediately, or mediately by the nerves, to an extent corresponding with the amount of alcohol absorbed.

(*k*) With an empty stomach there is normally no gastric secretion, provided there are no central taste stimuli to provoke it reflexly. On opening the tap of the cannula of a gastric fistula in a dog that has fasted for over twenty-four hours, only mucus as a rule flows out, which usually gives an acid, more rarely a neutral or alkaline reaction. In a woman with oesophageal occlusion due to cancer of the cardia, operated on by gastric fistula by Postempski,

Bocci constantly observed an acid reaction from the gastric mucosa, twelve hours after the last meal. We must not assume from this that gastric secretion is continuous. When gastric juice, with all its chemical and physiological characters, flows from gastric fistulae in animals or man, with a perfectly empty stomach, under perfect physiological conditions, it can easily be shown that this apparently spontaneous secretion is aroused by psychical taste-suggestions (Pawlow).

In order to study the course of gastric secretion, *i.e.* its quantitative and qualitative modifications during digestion, it is convenient to employ

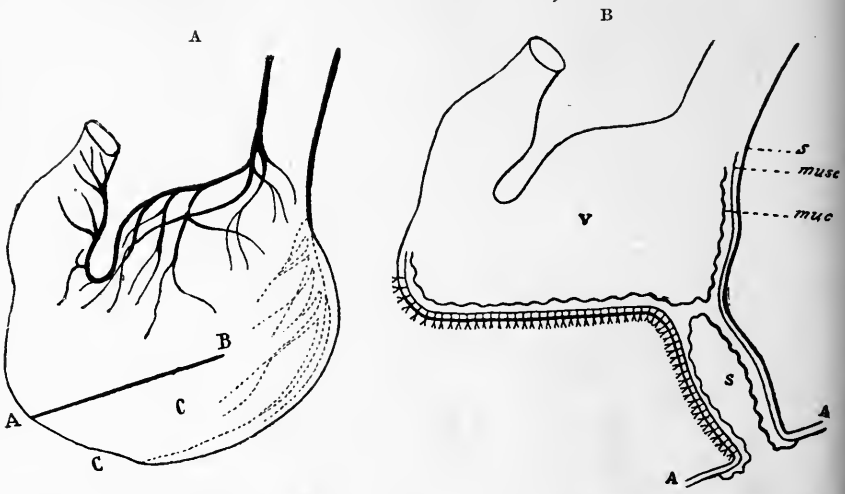

FIG. 38. — A, stomach of dog previous to Pawlow's operation, showing direction of principal nerves. B, stomach after the operation, which has divided it into two, the large (*V*), and the miniature stomach or blind sac (*S*), which is sutured to the abdominal walls (*AA*), and communicates with the exterior by means of a fistula. *S*, serous coat; *musc.*, muscular coat; *muc.*, mucous membrane of wall of stomach operated on.

Pawlow's "miniature stomach" or pouch, which served for most of the experiments we have been discussing. It is prepared as follows:—

The first incision A, B (Fig. 38, A), which begins in the fundus of the stomach, 2 cm. from its junction with the pyloric portion, is carried in the longitudinal direction through all the coats of the anterior and the posterior wall for 10-12 cm. along the great curvature. A triangular flap C, C is thus formed. A second incision is made exactly at the base of this flap, but only through the mucous membrane. The serous and muscular coats are left intact, and pass from the main stomach into the flap, while the mucosa is completely separated from it. The edges of the mucous membrane of both stomach and flap are detached from the submucous tissue for 1-1½ cm. from the wall of the stomach, and 2-2½ cm. from the wall of the flap. The posterior and anterior margins of the mucous membrane of the stomach are then brought together and sutured in a straight line from cardia to pylorus. The flap is converted into a cup. Lastly, the margins of the incision in the walls of stomach and flap are stitched together. The cavity of the stomach is thus restored, and the flap remains as a pouch, or small appendicular stomach

(Fig. 38, B), which is united to the main stomach by the two outer walls. The two cavities lined with mucous membrane are completely separated by a double septum consisting of the sutured mucous coat of the stomach and that of the cup-shaped flap. The opening of the pouch is stitched to the abdominal wall (A, A).

XIII. The *chemical composition* of the gastric juice must be studied before discussing the process by which it is formed.

The gastric juice obtained by C. Schmidt from a healthy woman with a gastric fistula, after the ingestion of peas and a little water, was found to be a clear thin fluid, much less acid than that of the dog, with specific gravity of 1·0022-1·0024. It became slightly cloudy on boiling, and left a solid residue of about 2 per cent.

The gastric juice obtained by Pawlow and his co-workers and pupils from the dog by the above method of sham feeding is certainly purer, as well as that obtained from the fundus sac by Pawlow's method, which preserves the integrity of the vagus fibres.

This pure secretion, which is free of all alimentary residues, is as clear as water, acid, with no extraneous taste, specific gravity 1·0030-1·0059. It turns the plane of polarisation to the left (from 0·70° to 0·73° in a layer of 20 cm.). On evaporation it leaves a solid residue of 0·29-0·60 per cent; 0·10-0·17 per cent ash on combustion. It constantly contains a little protein, but no peptone, leucine, nor tyrosine. On lowering the temperature it becomes cloudy, and forms three layers: the top one clear, the middle turbid, the lower consisting of a deposit of homogeneous, highly-refracting granules.

According to the chemical analysis made by Mme. Schumowa-Simanowskaia of the secretion obtained from the dog by sham feeding, its composition is as follows:—

Acid	0·46-0·56 per cent.
Chlorine	0·49-0·62 „
Dry residues	0·43-0·60 „
Ash	0·09-0·16 „
Substances coagulated by alcohol	0·14-0·19 „
Substances coagulated by boiling	0·13-0·18 „
Substances precipitated at 0° C.	0·011-0·003 „
Phosphoric acid	0·004 „

As we shall see elsewhere, the digestive activity of the gastric juice is due to the *hydrochloric acid* and the *enzymes* which it contains, these being the specific secretory products of the gland cells. The quantitative variations of these products, and the process and seat of their formation are as follows:—

(*a*) The acidity of the gastric juice, owing to the constant presence of a *free acid*, is well established for all vertebrates. Prout (1824) was the first who suggested that this free acid was

hydrochloric acid; but C. Schmidt (1852) first proved it, and showed that the gastric juice of the dog and pig contained chlorine in excess of what was required to combine all the inorganic bases obtained by calcination of the solid residues of the gastric juice. This fact shows that a considerable part of the chlorine is combined with hydrogen in the form of free hydrochloric acid.

Other acids can be detected in the gastric juice, *lactic acid* in particular, which is also thought by many to be a secretory product of the gastric glands. Everything, however, points to the probability that lactic acid is a decomposition product of carbohydrates produced by special bacteria, that are able to live inside the stomach. The same applies to the *butyric acid* that has occasionally been found in the gastric juice.

The amount of hydrochloric acid in the gastric juice varies considerably in different animals. It is much more abundant in dogs (= 0·46-0·58 per cent) than in man (= 0·17 per cent on an average). But the exact determination of the amount of hydrochloric acid and its variations during digestion presents serious difficulties, because the acid enters into chemical combination with the proteins introduced into the stomach, the pepsin and the digestive products, and also replaces the phosphoric acid of the phosphates contained in the food. Yet at all phases of digestion the contents of the stomach are acid, because a much larger quantity of hydrochloric acid is always present than is required for combination with the proteins and the bases of the alimentary phosphates. According to Kretschy, Richet, Uffelmann, the amount of free acid increases constantly during digestion in man. Heidenhain, on the contrary, found no marked differences in the dog in this respect.

The experiments made with the object of determining the seat of formation of the acid of the gastric juice all point to the conclusion that it is secreted by the glands of the mucosa of the fundus. In fact, in the fasting animal these often exhibit an acid reaction, while the mucous coat of the pyloric portion is alkaline. The value of these observations is, however, impaired by the fact that the pyloric portion always contains a denser stratum of alkaline mucus which may neutralise the acidity of the secretion. That the acid is not formed on the surface as Cl. Bernard supposed, but comes from the secretory cells of the glands, was demonstrated by Brücke on the compound glands of the fowl's stomach. These have a central cylindrical duct into which all the tubules of the gland open, and in which a considerable quantity of secretion collects. He found that under these conditions the secretion collected within the gland has an acid reaction.

Heidenhain by indirect arguments arrived at the conclusion that the cells which secrete the acid are the external or border

cells of the fundus glands. The pyloric glands, which are destitute of these cells, yield a persistently alkaline secretion. Miss Greenwood provided direct evidence in favour of this theory, by showing that when the gastric mucosa is treated with silver nitrate the border cells alone stain black, while all the other cells, which do not secrete acid, are unstained.

(*b*) The dissolving (*protcolytic*) action of the gastric juice upon proteins, which we shall examine in discussing digestion, is due to a special enzyme, guessed at or noticed by Spallanzani, Eberle, Beaumont, and Joh. Müller, and to which Schwann in 1836 gave the name of *pepsin*.

Wassman first isolated it in the impure state. Brücke, Wittich, Pettit, and others, perfected the methods of extraction and purification in various ways, but little is even yet known as to its chemical constitution, or if it contains nitrogen, and it is doubtful whether it belongs to the protein group.

Pepsin is an amorphous substance, greyish-yellow, odourless, soluble in water and in glycerol, particularly if acidulated, insoluble in alcohol, which precipitates it from its solutions. It is not dialysable, and can thus be easily separated from the acids, salts, and peptones, which dialyse readily (Hammarsten).

An acid medium is an indispensable condition to the exhibition of the digestive activity of pepsin. In neutral solution it is inert; it is destroyed in an alkaline medium. It neither increases nor diminishes in quantity during the process of digestion, but according to Grützner it loses some of its activity.

In consequence of Wassmann's experiments, which showed that the artificial juice prepared from the mucous membrane of the fundus digests a given quantity of fibrin in an hour and a half, while with that made from the mucous membrane of the pyloric portion the same digestion requires 6 to 8 hours, it was supposed that only the fundus glands secrete pepsin, and that the pyloric glands secreted mucin only, the small amount of pepsin they contain being due to infiltration of that secretion from the fundus.

The ingenious experiments of Heidenhain and his disciples Ebstein and Grützner, however, showed that the pyloric glands also secrete pepsin, although to a minor extent, because the glandular substance is less abundant there. Langendorff, again, found pepsin in the pyloric part of the calf's embryo. But the most decisive proof of the digestive activity of the juice secreted by the pyloric end was given by Klemensiewicz and Heidenhain, who showed that this part of the stomach when isolated and converted into a *cul de sac*, secretes an alkaline juice containing pepsin, so that it is capable of digesting protein on the simple addition of acid. According to Klemensiewicz, this pyloric juice in acid solution usually digests better than the secretion of the

fundus, thus excluding the objection that the digestive action of the pyloric juice is due to the presence in the pyloric mucosa of some of the glands which predominate in the mucous coat of the fundus.

(*c*) It was formerly held that milk coagulates, on coming into contact with gastric mucous membrane or its extract, owing to the gastric juice, because on merely acidifying fresh milk its casein comes down in a flocky precipitate. But after the experiments of Selmi and Heinz, and the exhaustive work published by Hammarsten in 1872, and confirmed by A. Schmidt, it was recognised that the extract of gastric mucous membrane is able to clot milk even in a neutral or alkaline medium. This phenomenon is therefore independent of acid and is due to a special enzyme, distinct from the pepsin, which is called *chymosin* (or *rennin*).

Hammarsten succeeded in separating the chymosin from the pepsin by neutral lead acetate, which precipitates pepsin but not chymosin. Of unknown chemical constitution, chymosin has all the properties common to other digestive enzymes. In neutral solutions it is destroyed at 70° C., in acid solutions at 65° C. It is not diffusible; its maximal activity is reached at 38-40° C. Its action is exerted exclusively on the caseinogen of milk, and differs from that of acids, as we shall see in the chapter on Digestion. According to Hammarsten, one part of chymosin is able to clot 400,000-800,000 parts of casein.

Chymosin is present in large quantities in the stomach of sucking animals, especially calves, lambs, and kids. Schumberg found it in 15 out of 34 stomachs of adult men, and in 4 out of 6 of new-born infants. It is probably decomposed by the alkalinity of the intestinal juice, or absorbed like other ferments, since it does not occur in the faeces. It seems to originate like pepsin from the pyloric glands and the chief cells of the glands of the fundus.

(*d*) The existence of a lipolytic enzyme in the stomach had long been suspected (Cash, 1880; Ogata, 1881, etc.). Others, however (Contejean, 1894; Boldireff, 1904), denied the value of previous researches, carried out for the most part *in vitro* and with artificial extracts of mucous membrane, or with gastric juice extracted by the sound, and attributed the results described either to the adulteration of the substances or to the presence of pancreatic juice that had flowed back into the stomach. Finally, Volhard (1900-1902) demonstrated in a series of experiments that a very active lipolytic enzyme is produced in the stomach, which acts particularly on emulsified fats. This enzyme is contained chiefly in the mucosa of the fundus (in man) or of the pyloric region (dog, cat, pig). Its action is reduced in the presence of acids, and may be altogether inhibited; this does not, however, occur during the physiological digestion of fat, since the secretion

of gastric juice, and still more its acidity, is much diminished when fat is present.

Among the many proofs of the presence of a lipolytic ferment in the gastric mucosa, those adduced by Laqueur (1904) are of special importance, because he makes use of Pawlow's miniature stomach, in which there can be no question of any possible reflux of pancreatic juice.

Laqueur points out one essential difference between the gastric and the pancreatic lipolytic enzymes, viz. that the former is not aided by bile, which multiplies the activity of the pancreatic juice twenty or more times. With this reservation, the lipolytic

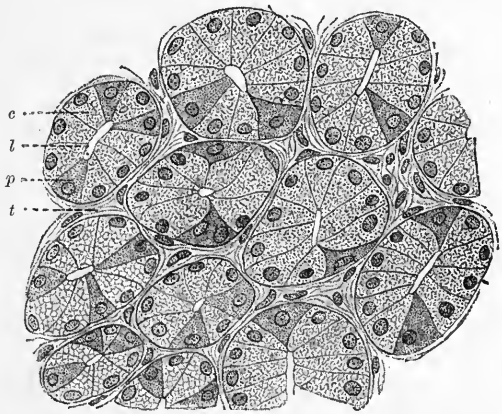

FIG. 39. — Cross-section of cardiac glands from human stomach during fasting. (Böhm and v. Davidoff.) $\frac{500}{1}$. *c*, central cell; *l*, lumen of gland; *p*, parietal cell; *t*, connective tissue between glands.

enzyme of gastric juice behaves like the lipolytic enzyme of succus entericus.

XIV. Heidenhain and Ebstein, in their alcohol-hardened preparations of gastric mucosa, studied the cytological changes that occur in the secretory cells in hunger and in the digestive process. These changes are quite similar to those suffered by the cells of the serous salivary glands and the pancreas. In the fasting state, and during the intervals of digestion, the chief cells of the fundus glands enlarge and look clear; while the parietal cells are small, and triangular in section. During the first hours of digestion, the former continue large, but become clouded; the latter, on the contrary, increase in size and grow round, bulging forward to the outer surface of the tube. From the sixth to the ninth hour of digestion, the chief cells are reduced and grow more turbid, while the lining cells remain large or become still more swollen. At the fifteenth hour the cells begin gradually to resume the appearance and characters which they exhibited during hunger.

These phenomena noted on the dog were confirmed for man, as shown in Figs. 39 and 40.

Langley repeated these observations on fresh preparations of the gastric mucous membrane, and noted changes which, although different, lead to the same interpretation as that of Heidenhain. In abstinence the chief cells are strongly and uniformly granular; during digestion they become clearer, and are differentiated into two zones, the outer of which ($\frac{2}{3}$ or $\frac{1}{2}$ the cytoplasm) does not exhibit granules, which only appear in the inner zone. Since, as we shall see, the extracts of gastric mucosa contain more pepsin

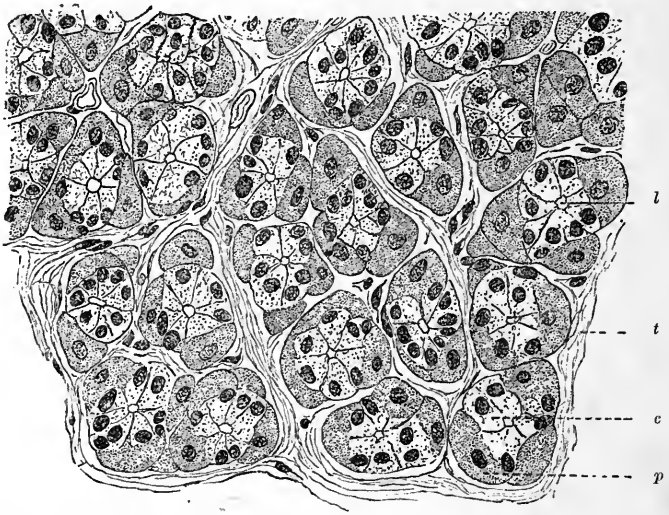

FIG. 40.—Cross-section of cardiac glands during digestion. (Böhm and v. Davidoff.) $\frac{500}{1}$. References as in Fig. 39.

and chymosin, according as the number of granules in the chief cells of the fundus and pyloric glands is greater, this confirms the theory which attributes the formation of the enzymes of the gastric juice to these cells.

The granules seen in the cells of the gastric gland in the fresh state do not, however, represent the enzymes of the gastric juice, but contain the *zymogens, i.e.* the proteins from which pepsin and chymosin are formed during the process of secretion.

Schiff first recognised that active pepsin comes from the transformation of an inactive substance found in the gland cells, which he called *propepsin.* The experiments of Ebstein and Grützner confirmed this theory. They gave the name of *peptic zymogen* or *pepsinogen* to the inert substance which is converted into pepsin. They found that in a watery, non-acidulated, or glycerol extract of gastric mucosa, a certain amount of pepsinogen

was extracted with the pepsin, and yielded a further quantity of pepsin when hydrochloric acid or even sodium chloride were added. Langley afterwards found that on extracting the gastric mucous membrane with a 1 per cent solution of sodium carbonate, and acidulating with hydrochloric acid, the extract contained pepsin, as shown by its digestion of proteins. As sodium carbonate abolishes the activity of pepsin, the gastric glands must contain a substance other than pepsin, which is not destroyed by the soda solution, and is readily transformed by acids into pepsin. This substance is pepsinogen.

Grützner performed a series of experiments to determine the maximal quantity of pepsin which can be extracted by excess of acid, with long digestion at 40° C., from the fundus and pyloric mucous membrane of dogs killed at various hours after a meal. He found that the pepsin is maximal in the fundus glands during hunger, and minimal nine hours after a meal: in the pylorus glands it increases in the first hours after a meal, reaches its maximum at the ninth hour, and then decreases slowly. This fact agrees well with the modifications observed in the cells of the pyloric glands, which (unlike the changes in the fundus) increase in the first hours after a meal, and then decrease slowly,—signifying that in the first hours after a meal more pepsinogen is formed than is simultaneously excreted as pepsin.

The process by which pepsinogen is normally transformed into pepsin during the digestive period is still imperfectly known. It was suspected, on the analogy of the transformation by the pancreas of trypsinogen into trypsin, that the formation of pepsin from pepsinogen might also be due to the action of an internal secretion of the spleen, which becomes *actively turgid* during digestion. This hypothesis, which Baccelli advanced in 1868, has not been fully worked out, possibly because excessive value has been put upon the fact that animals deprived of their spleen are able to live and digest perfectly. This objection might be met by the further and well-established fact that it is also possible to live without a stomach. At all events the assumption that the spleen takes part in the formation of pepsin does not exclude the possibility of the formation and secretion of pepsin without a spleen.

The congested spleen of a dog in full digestion is excised, and divided into small fragments, which are rubbed up in a mortar with powdered glass. This paste is placed in a retort, with five times its volume of 4 per cent boracic acid. This is digested in a stove at 37° C. for six hours, and on filtering a transparent dark-red fluid is obtained.

Two equal parts of this extract, 15 c.c. each, are poured into two small flasks, with 15 c.c. solution of 0·4 per cent hydrochloric acid, and $\frac{1}{2}$ gramme of raw fibrin, ready swollen by the action of

0·2 per cent HCl, in which it has been standing in the cold for 30 minutes.

In order to compare the effect of the acidified splenic extract with that of the plain hydrochloric acid on the raw fibrin, the same amount of swollen fibrin is placed in two other flasks, with 15 c.c. of 4 per cent boracic acid, *plus* 15 c.c. of 0·4 per cent HCl.

On placing the four flasks to digest in the oven at 39° C., the fibrin with splenic extract is seen after two hours to be about half digested, while that with hydrochloric acid alone shows no trace of digestion. After $3\frac{1}{2}$ hours the other flasks are examined, and the splenic extract is found to have digested almost all the fibrin, while there is no trace of digestion in the fibrin left in the plain acid solution.

This fact, many times repeated in our laboratory by Lo Monaco and Tarulli, proves that extract of congested spleen contains pepsin, or at any rate an enzyme with an identical capacity for digesting fibrin in an acid medium. The living spleen probably contains not pepsin proper but some zymogen capable of transformation into pepsin during the manipulations necessary for the preparation of the extract.

Hedin and Rowland (1901) further showed that the spleen contains a proteolytic enyzme, which exhibits its maximal activity in an acid solution. They also found it in many other organs (lymph glands, kidneys, liver, and to a less extent the muscles also; *infra*, also Vol. I. p. 34).

XV. Two kinds of glands are found in the mucous membrane of the Intestine—those of Brunner, which are confined to the first portion of the duodenum, and those of Lieberkühn, which extend throughout the canal.

The duodenal mucosa of certain rodents also presents groups of cells which are structurally exactly like the acini of the pancreas (particularly the duodenal pancreas described in rabbit). Accessory pancreases in the duodenum are not uncommon in man.

The mucous coat of the small intestine differs from that of the stomach in having not only small ridges or folds that are obliterated by distension, but also large permanent folds in the form of crescentic projections of the mucous membrane, placed transversely to the axis of the bowel, at a short distance from one another (*valvulae conniventes* or valves of Kerkring). The whole surface, including the valvular folds, is closely beset with villi, of varying length, cylindrical in the jejunum, filiform in the ileum (Fig. 41), which enormously increase the intestinal surface. The mucous coat of the large intestine is smooth, and destitute of villi (Fig. 42).

Between the villi of the small intestine, in every part, are the simple tubular glands, Lieberkühn's crypts, which resemble the fingers of a glove, the orifices being somewhat dilated at the

extremity. These crypts are more numerous in the large intestine, owing to the absence of villi (Fig. 42).

The epithelium by which the crypts are lined is exactly similar to that which clothes the surface of the villi. It consists of irregular columnar cells, with a large nucleus, and striated

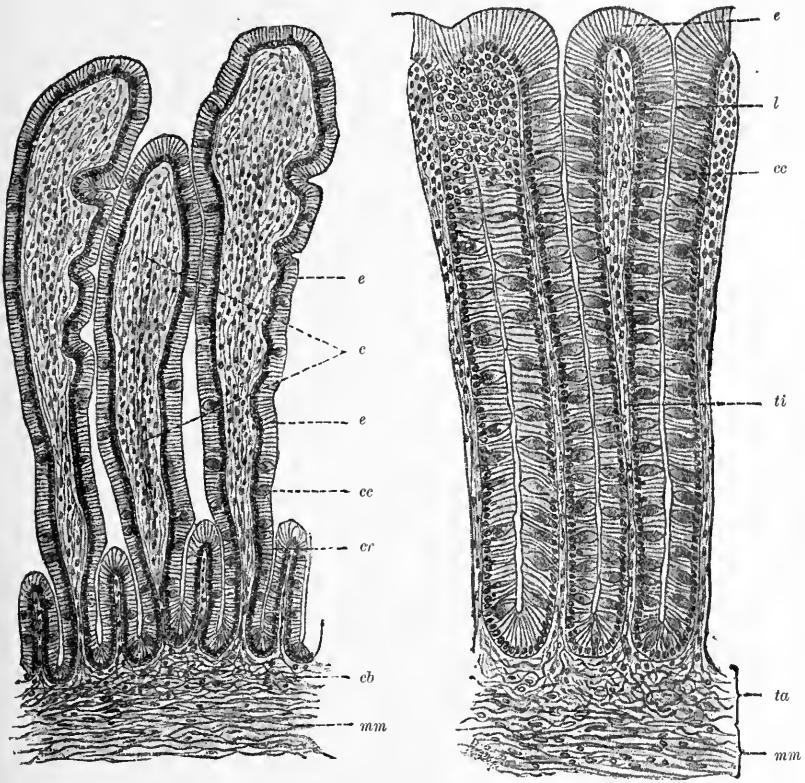

FIG. 41 (Left).—Section of intestinal mucous membrane (infant), shows three villi, with crypts of Lieberkühn. (Böhm and v. Davidoff.) $\frac{8}{1}$. *e*, *e*, epithelium of villus; *c*, connective tissue of villus; *cc*, goblet cells; *cr*, Lieberkühn's crypts; *cb*, connective tissue at base of gland; *mm*, muscularis mucosae.

FIG. 42 (Right).—Section of mucous membrane of human colon, showing three crypts of Lieberkühn. (Böhm and v. Davidoff.) $\frac{2}{1}$. *e*, epithelium; *l*, lumen of gland; *cc*, goblet cells; *ti*, interglandular tissue; *ta*, areolar tissue of mucous membrane; *mm*, muscularis mucosae.

cuticular layer, and a somewhat flattened end which is attached to the surface of the basement membrane, without extending (as was formerly supposed) into the reticulated tissue of the villi. Leucocytes are seen here and there between the epithelial cells (Fig. 43).

Goblet cells produced by mucoid degeneration of the ordinary columnar cells are seen between the latter, the outer half of these

swelling and filling with mucus, which bursts through the free end, and is discharged externally. The number of goblet cells varies with the animal and the state of abstinence or digestion. They are specially abundant in the mucous coat of the large intestine, while in the small intestine they are wanting altogether.

Brunner's glands are situated in the upper part of the duodenal mucosa; they also extend beyond the pyloric antrum of the stomach, and may be found in the mucous membrane between the crypts of Lieberkühn. They are small acino-tubular glands, which consist of branching and twisted tubules, ending in prolonged dilatations or alveoli, which unite into a secretory duct lined with epithelial cells similar to those of the alveoli. These cells resemble those of the pyloric glands of the stomach (Fig. 44).

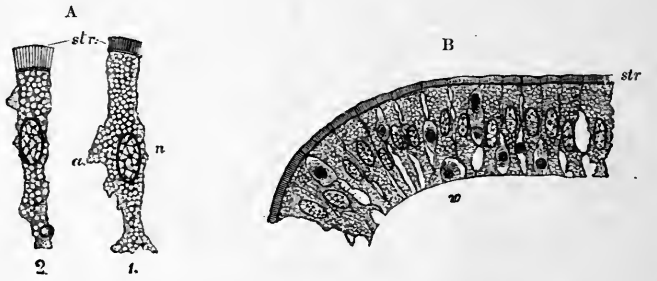

FIG. 43. — Columnar epithelium from rabbit's intestine. (Schäfer.) A, two isolated cells after maceration in very weak chromic acid, showing striated border, and the bright disc which separates them from the cell protoplasm; *n*, nucleus with internuclear network; *a*, thin projection of cell, which probably fitted between two adjacent cells. B, row of columnar cells from intestinal villus of rabbit; *str*, striated border; *w*, smaller cells of the nature of lymph corpuscles, between the epithelial cells.

Little is known about the secretion of Brunner's glands. According to Hirt, they undergo the same modifications during digestion as the pyloric glands; in the fasting state their cells are comparatively large and clear, in digestion they are small and clouded. Grützner found that at different distances from the pylorus the glands are in a different functional state. A watery extract of Brunner's glands, freed as far as possible from the duodenal mucosa, contains (according to Krolow) a ferment which digests fibrin, but not boiled egg-albumin, in an acid medium. They must therefore secrete pepsin like the pyloric glands. According to Grützner, the enzyme (or zymogen) accumulates during hunger, and discharges during digestion, when the secretory cells become smaller. Mendeldorp also finds a diastatic enzyme in the extract of gland substance. From the little we know as to the nature of the secretion of Brunner's glands their product appears to mix with the acid chyme which passes rhythmically from the stomach to the duodenum, through the pyloric valves, after the first hours of digestion.

XVI. To study pure *succus entericus* (which is the product of all the secretory cells of the small intestine, both in the external epithelium of the villi, and in the epithelium which lines the crypts of Lieberkühn internally) it is necessary to isolate a loop of intestine, closing one end by stitches while the other is sutured to the wall of the bowel, after bringing together the two ends of cut intestine, so as to re-establish the continuity of the gut (Thiry's method). It is more convenient to stitch both ends of the intestinal loop, separately, to the abdominal walls, so as to

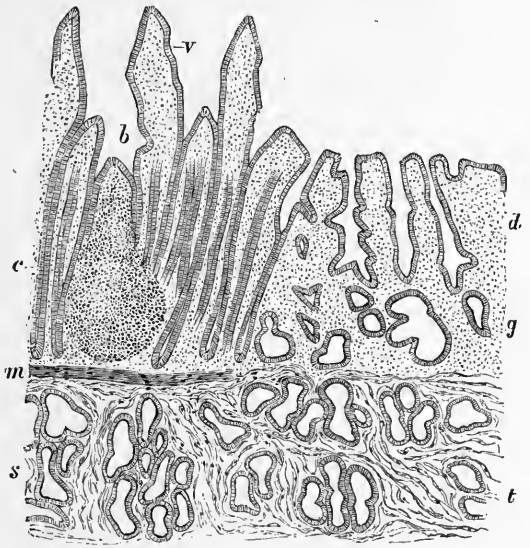

FIG. 44.—Section of mucous membrane through commencement of duodenum at pylorus. (Klein.) *v*, villi; *b*, apex of a lymphoid nodule; *c*, crypts of Lieberkühn; *m*, muscularis mucosae; *s*, Brunner's glands cut more or less obliquely; *d*, ducts of pyloric glands of stomach; *g*, oblique section of same; *t*, deeper tubes in submucous tissue, corresponding with Brunner's glands of intestine.

make two fistulous apertures communicating with each other by the loop (Vella's method).

During inanition, according to Boldireff (1905), the secretion from Vella's loop is scanty, with a rhythmical maximum and minimum cycle of about 2 hours—5-6 c.c. of succus entericus can be collected altogether in 8 to 10 hours.

Some authors say that mechanical stimuli (sounds, sponges, etc.) introduced into the loop are able to excite a true secretion there, even during hunger. But according to U. Lombroso, these stimuli only excite a small increase in the flow of secretion, which is probably due to increased peristalsis.

Electrical stimuli are more effective than mechanical. The effects of chemical stimuli are better known (Frouin, Lombroso,

Delezenne). When acetic, hydrochloric, lactic, or weak carbonic acid is injected, a certain amount of secretion is observed. The secretion obtained with these acids is serous, fluid, colourless if the solution is weak, lemon-yellow or pinkish if more concentrated. It has a very slight lipolytic action. Acids combined with pepsin or with the alimentary proteins also excite enteric secretion. The higher fatty acids dissolved by bile, and soap solutions (which at once set free the fatty acids when introduced into the loop of Vella) are more powerful than any other substance in exciting enteric secretion.

Besides being more copious, the secretion excited by the higher fatty acids (oleic acid) has quite different physical characters; it is dense, ropy, and contains a number of enzymes. Bile and alkalies produce no noticeable secretion.

Masloff obtained rich secretions from the intestinal fistula (preternatural anus) in dogs, with subcutaneous injections of pilocarpine. Vella confirmed the same on his isolated loop of intestine.

The physiological conditions for the secretion of succus entericus during digestion are as follows. In the isolated loop, where no food can penetrate, a secretion of juice (more or less abundant according to the nature of the food) is seen some time after the meal. This tends to increase for a certain time, and only ceases at the seventh to eighth hour of digestion. The time at which the secretion reaches its maximum varies greatly, and seems to depend on the varying nature of the food. The total quantity of secretion that can be collected after 8 to 10 hours does not exceed 8 to 12 c.c.

Data in regard to the chemical composition of the succus entericus differ with the animal used and the method by which it is collected. The fluid that issues from the isolated loop of the lower tract of the small intestine (ileum), is, according to Thiry, thin, opaline, yellowish, strongly alkaline, of specific gravity 1·010. It contains—

Water	97·2-97·9 per cent.
Solids	2·2- 2·8 „
Protein	0·7- 0·12 „
Ash	0·7- 0·8 „

In addition to sodium chloride the ash contains large quantities of sodium carbonate, as on adding acids the succus entericus effervesces. It always exhibits a few enzymes, to which its weak digestive powers are due. Its action is *diastatic* on starch and glycogen, *invertive* of saccharose into dextrose, *curdling* on milk, *emulsifying* on fats, similar to that possessed by all alkaline fluids. Succus entericus is further credited with the property of *splitting up fibrin*, which cannot be very important, but Schiff,

and afterwards Vella, stated that it had the property of digesting all proteins, which (if true) would raise the physiological value of succus entericus to that of pancreatic secretion. The best work with artificial digestions of succus entericus and boiled egg-white, flesh, and proteins in general (putrefaction being avoided), has, however, given entirely negative effects (Thiry, Wenz, Boccardi, Malerba and Jappelli, Bastianelli, Klug, Pregl, and others).

But if succus entericus is incapable of digesting coagulated albumin and natural proteins, it does contain a special enzyme, Cohnheim's *erepsin* (1902), which acts on peptones, and splits them into their final crystallisable products. All authors do not agree in giving erepsin the importance which Cohnheim attributes to it. Kutscher maintains that tryptic digestion alone is capable of completely splitting the proteins until the biuret reaction disappears. Bottazzi—experimenting with intestinal extract—denies, on the strength of his results, that this particular proteolytic enzyme is secreted by the intestinal mucosa. He refers it to the activity of the trypsin secreted by the pancreas, and left to a greater or less extent adherent to the intestinal mucosa. We shall return to this in discussing intestinal digestion.

The existence of a lipolytic enzyme (or *lipase*) in succus entericus was long a subject of discussion. Early experimenters (Vella, Schiff) were inclined to admit its presence; but later work with the natural secretion, given necessary precautions for preventing putrefaction (Malerba, Jappelli, Bastianelli, Pregl, and others), proved that there was no true lipolytic action, or that it could only be minimal. Thus Lombroso, on investigating the succus entericus secreted naturally by a loop of Vella during digestion, or after injections of pilocarpine, observed that it had a very slight lipolytic activity. He found, however, that the intestinal secretion poured out in large quantities when a higher fatty acid is introduced into the loop, is actively lipolytic to an extent approximating to that of the pancreatic secretion.

But the lipolytic enzyme of intestinal, unlike that of pancreatic, juice is not aided in its action by bile. Lombroso's observation cannot be met by the objection made to earlier workers, viz. that the positive result is due to the presence of pancreatic enzymes in the mucous membrane of the intestine, for the succus entericus exhibiting this lipolytic activity is excited only by definite stimuli (fatty acids), and does not diminish even when, by repeated experiment, many hundred c.c. of juice have been secreted by the Vella's loop.

Besides these enzymes, which are normally contained in the mucous coat of the intestine, there is in mammals during the secreting period an enzyme (*lactase*) capable of transforming lactose (which is not directly utilisable by the body) into glucose and galactose (Beyerick, Fischer and Niebel, Portier, Orban).

Sisto showed that the mucous membrane of adult mammals, which does not normally contain lactase, can produce this enzyme after a diet containing a large quantity of lactose, extending over several weeks. Birds, too, can be induced to secrete lactase by a still longer period of alimentation.

The glandular crypts of the large, unlike those of the small, intestine do not secrete any digestive juice. The food-stuffs introduced into the large intestine, after making an *anus preternaturalis*, undergo no digestive modification. It is impossible, by any means, to obtain any considerable quantity of secretion from this part of the gut. The small amount that can be obtained by little sponges enclosed in wire capsules introduced by the fistula is clear, gelatinous, neutral in reaction, laden with flocculi of mucus (Klug and Koreck). Injections of pilocarpine, which exaggerate all secretions of the gastro-intestinal tube, change the appearance of the mucinogenous epithelial cells of the large intestine, so that they exactly resemble those which line the crypts of the small bowel (Fig. 45). This fact, noted by Heidenhain's pupils, shows that the glandular epithelium of the large intestine is more subject than that of the small bowel to mucosal changes during rest, and that during secretory activity the mucus formed is excreted, and the primitive cells which predominate in the small intestine are regenerated, by a new formation of the cytoplasm which surrounds the nucleus. Secretion of mucus (which is very useful in facilitating the expulsion of the faecal matters, which harden in the last part of the intestine by absorption of water) thus seems to be the only well-ascertained function of the secretory cells of the mucous coat of the large intestine.

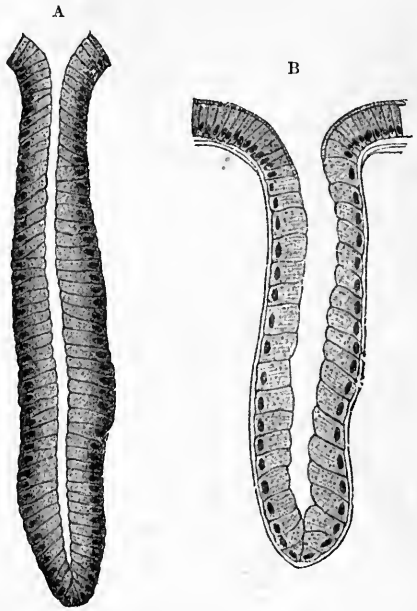

FIG. 45.—Glands of large intestine of rabbit. (Heidenhain.) A, after copious secretion of mucus; B, after long rest.

XVII. Little definite is known as to the dependence of the intestinal secretion on the nervous system. According to Thiry and others, stimulation of the vagus produces no effect. According

to Budge, extirpation of the caeliac plexus causes increase of intestinal peristalsis, with increased secretion of succus entericus. Moreau's results are more important (1868). After making an intestinal loop, he cut the mesenteric nerves which accompany the vessels of the loop, and at once, or shortly after, saw an extraordinary amount of juice secreted in the loop, but not in the contiguous parts of the intestine in which the nerves were intact. This excessive secretion may amount to $\frac{1}{11}$ of the body-weight; it lasts for several hours, becomes less after 4 to 5 hours, and only ceases after 24 hours. The secretion is at first a clear liquid, which presently becomes clouded with flocculi of mucus. Sometimes it looks milky, and it contains large quantities of detached epithelial cells.

This enormous formation of intestinal juice (which has the same properties as the normal secretion collected in the loop of Vella) is not explained by simple paralytic dilatation of the vessels. We must assume that the phenomenon depends on lapse of control by special nerves, of the secretory processes of the epithelia. Since the secretion is in this case the effect, not of excitation, but of severance of the nerves, we are forced to assume that the latter *inhibit* the intestinal secretion, *i.e.* normally serve to keep it in bounds by their tonic action. Nothing similar has, however, been produced on stimulating the nerves to these glands. Moreau's phenomenon plainly recalls Cl. Bernard's discovery of paralytic secretion for the submaxillary gland, and presents the same difficulties of interpretation.

According to the supporters of Bayliss and Starling's theory (see p. 90 *et seq.*), the intestinal secretion, also, is due to the production by the duodenum of *secretin*, which, on absorption and circulation in the blood, comes into contact with the intestinal epithelia of the gut, and excites them to secrete. This theory rests on certain observations on secretion in a Vella's loop after the injection of secretin. We have already pointed out the inadequacy of these observations, and it is unnecessary to recapitulate the objections in reference to intestinal secretion also.

According to Delezenne and Frouin, the succus entericus, after undergoing the action of acids in the intestinal cavity, is reabsorbed and excites secretion in other parts of the intestine. They observed that succus entericus, acidified with hydrochloric acid and subsequently neutralised and injected into the vein, excites an abundant secretion. Moreover, in a dog provided with two Thiry's intestinal fistulae, the introduction into one of the fistulae of substances that excite secretion (hydrochloric acid, ether, water) produced secretion in the other fistula also. This secretory action at a distance is determined, according to Frouin and Delezenne, not by the propagation of secretory stimuli by nervous paths, but by the action of the reabsorbed succus entericus.

U. Lombroso opposes this theory by a number of data worked out in our laboratory. He observed the secretion in a Vella's loop, made at a certain distance from the duodenum, on many occasions, and for many hours. He has proved that there is always a very scanty secretion (4-6 c.c. of juice) in 6 to 8 hours, even after meals that are rich in flesh and fat, or consist of fat alone. But if a solution of oleic acid or of soap is introduced directly into the loop, an abundant secretion is at once called out. With 25 c.c. oleic acid dissolved in bile, it is possible in a few minutes to obtain 30-40 c.c. or more of succus entericus.

It is a familiar fact that soap and fatty acid dissolved in bile are found throughout the intestine after giving fats. If no secretion occurs in Vella's loop, even after the digestion of large quantities of fats, this must mean that the hormones which activate secretion in the isolated tract of the loop are either not produced or not absorbed during digestion.

But if it be proved that enteric secretion is not excited by hormone stimuli; if, on the other hand, Lombroso's observations tell against the hypothesis that the mesenteric nerves convey the secretory stimuli to the intestinal mucosa (as we said above, they appear rather to have the task of inhibiting the intestinal secretion), the question still remains open as to whether the said secretion results solely from the *direct* action of chemical stimuli, or if these may determine it by *reflex* paths from other regions that are not directly excited, *e.g.* the stomach.

Lombroso's observations on the ordinary Vella's loop have not solved the problem, because the operative act completely destroys the relations of continuity of the nerves that run throughout the extent of the intestinal walls, so that they can no longer propagate the secretory stimuli.

Lombroso has accordingly modified his method of operation. He separates a fairly long segment of intestine (50-80 cm.) as if making a Vella's loop. After suturing the two extreme ends of the divided portion to the abdominal walls, he attaches 3-4 cm. of the middle part of the loop to the same wall. When adhesion takes place, *i.e.* in 3 to 4 days, he slits up the middle of the loop so as to bring it into relation with the exterior. This produces twin loops of Vella, which preserve connection with the nerve plexuses that run along the coats of the intestine.

On introducing a substance that excites secretion into the first loop, the second loop does not secrete unless the same substance is made to pass into it by bringing the two lips together. This indicates that direct action of the proper chemical stimuli on the mucous membrane is necessary to excite the intestinal secretion.

XVIII. The Liver in its structure and functions is a gland, which in adult man weighs about 1579 grms. (1526 grms. in

woman), with an average volume of 1720 c.c. (Vierordt). This gigantic development, and the intimate relations by means of the portal system with the gastro-intestinal system, point to the true physiological function of the liver as a laboratory for complex and mysterious chemical operations, in which the preparation of the bile that is formed and poured out into the gall-bladder and duodenum is probably only a secondary process. The amount of bile secreted daily by man rarely, in fact, exceeds 800 grms., while the little parotid gland (which only weighs 24-30 grms.) daily discharges as much as 1000 grms. of secretion. In this chapter, however, we shall only consider the liver as the organ of *bile*

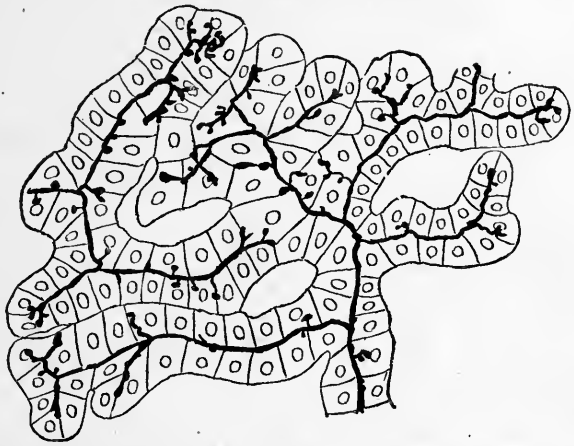

FIG. 46.—Diagram of fragment of liver from a six-months' foetus. Silver chromate method. (G. Retzius.) The bile canaliculi are stained black. They have not yet anastomosed, and give off minute twigs between the hepatic cells, with a terminal dilatation.

secretion. Its complex metabolism and internal secretions will be discussed elsewhere.

Morphologists regard the liver as a tubular retiform gland, consisting of cells arranged round glandular spaces which form a very fine capillary network, the bile canaliculi. These appear to have no membrane propria, and to be merely grooved out between adjacent liver-cells, running on into the bile ducts, which have walls and unite in larger and larger branches, till they converge into the excretory, hepatic duct.

In the lower vertebrates, and the embryos of birds and mammals, the liver is a tubular gland. The tubules do not anastomose to form a network, but end in small branches, the ends of which are often enlarged and penetrate into the hepatic cells (Fig. 46). In adult vertebrates, on the contrary, the ramifications of the canaliculi do anastomose to form an intercellular network, which communicates with special vacuoles in the cell protoplasm

(Fig. 47). Whether these vacuoles leading into the network of the bile canaliculi, and first observed by Pflüger and by Kupffer, and confirmed by others, are permanent structures, or whether they are only formed at the moment of secretion, or produced artificially by the staining fluids injected through the bile ducts (which may fairly be excluded seeing that nothing of the sort has been met with in other injected tissues), is unknown.

The peculiar structure of the hepatic parenchyma is determined by the arrangement of its blood-vessels, which (with the lymphoid connective tissue connected with Glisson's Capsule) constitutes the scaffolding or framework of the hepatic cells. Unlike all other organs, the *afferent* vessels of the liver consist not only of an

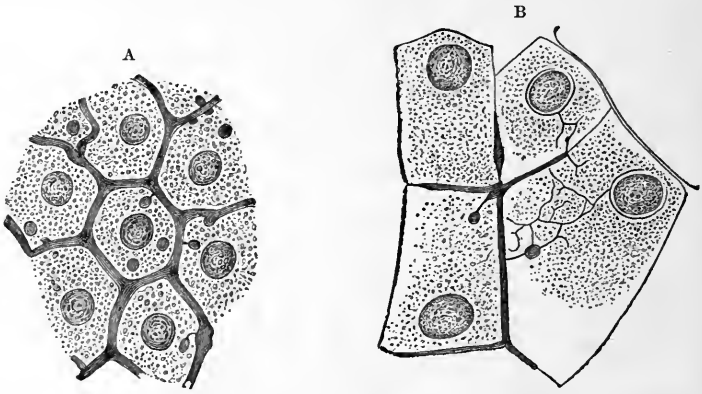

FIG. 47.—Section of liver from adult animals, with injected bile capillaries. (Kupffer.) A, bile canaliculi of rabbit's liver, artificially injected from hepatic ducts with Berlin blue solution. They give off minute projections like a pin's head, which penetrate into the protoplasm of the liver cells. B, the same from frog's liver, after natural injection with sulphindigotate of soda. Here the projections form a network of fine fibrils inside the hepatic cells, with terminal dilatations.

artery—the hepatic artery, but also of a vein—the portal vein, which is formed by the union of the efferent veins from the stomach, intestine, pancreas, and spleen; these form a venous trunk with exceptionally robust and muscular walls, and a much larger calibre than the hepatic artery. The *efferent* vessels are: the hepatic veins, with thin walls, which arise in the portal capillaries, run towards the posterior surface of the liver, and open into the inferior vena cava; and the lymphatics, which are large and numerous in the liver, originating in the lymph sinuses round the portal capillaries, and which accompany and to a large extent enclose the branches of the blood-vessels, and leave by the portal fissure with the portal vein, the hepatic artery, and the bile or hepatic duct. This last leads by the cystic duct to the gall-bladder, and the junction of the two ducts (hepatic and cystic) form the common bile duct or *ductus choledochus*, which pours

the bile into the duodenum during digestion, 7-10 cm. from the pylorus.

By a special system of distribution, capillary formation, and reconstitution of these vessels, the hepatic parenchyma is divided into a number of lobules or acini varying in diameter from 1 to 2 mm.—polyhedral or spheroid in shape,—which profoundly modify the original tubular form of the gland. The branches of the

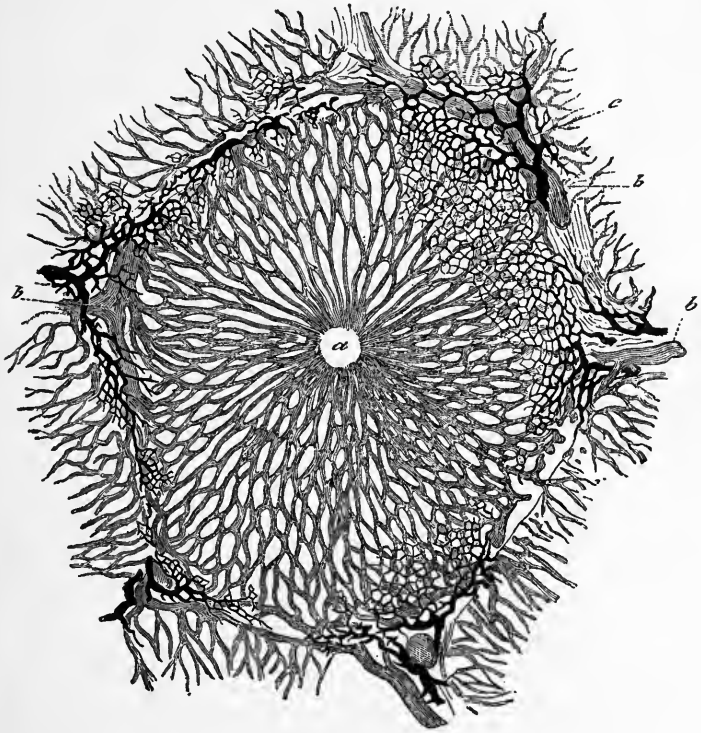

FIG. 48.—Section of liver lobule, with blood-vessels and bile-ducts injected. (Cadiat.) *b*, *b*, interlobular veins; *a*, intralobular vein; *c*, interlobular bile-ducts, with which the bile canaliculi of the lobule are connected. The latter are only injected in the peripheral parts of the lobule.

portal vein and hepatic artery penetrate as the interlobular veins and arteries between the lobules, sending twigs to the interior of the lobule which soon form a dense capillary network, from which the intralobular veins re-form, and lead into a central vein (Fig. 48). The intralobular and central veins are the beginning of the efferent hepatic veins, which traverse the lobule in a radial direction, and unite in the sublobular veins; these form into larger and larger branches, converging towards the posterior surface of the liver, where they open, as we said, into the inferior vena cava.

The interlobular course of the hepatic duct is similar to that of the portal vein and the hepatic artery, but its interlobular branches form a much finer network of canaliculi than that formed by the blood-vessels, as shown in Fig. 48.

The hepatic cells lie in the interstices of the network of blood capillaries, and round the closer meshes of the bile canaliculi. They are polyhedral, 17-22 μ in diameter, destitute of cell membrane, and have a clear nucleus, with intranuclear network, and one or two nucleoli.

The finely reticulated cytoplasm, the deutoplasmic content, and the aspect as a whole of the liver-cells change considerably (as we shall see below) according to whether they are examined in the fasting state or after food. Fig. 49 shows the relations and respective size and position of the hepatic cells, the network of blood capillaries, and the finer network of bile canaliculi.

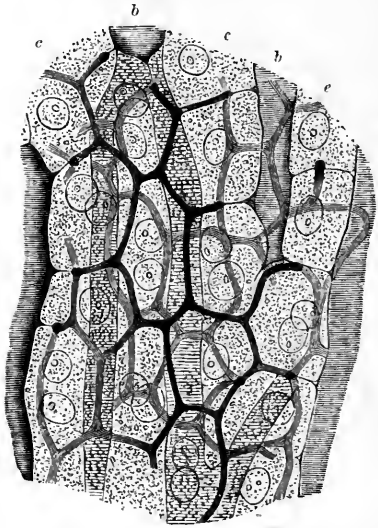

FIG. 49.—Section of rabbit's liver after injection of intracellular network of bile capillaries. (Hering.) Thick section, showing two or three layers of cells and relative size and position of blood capillaries, *b*, *b*; bile canaliculi, *c*, *c*; and hepatic cells, *e*, *e*.

The nerves to the liver are branches of the vagus and of the solar plexus of the sympathetic. They enter by the portal fissure, accompanying the hepatic artery and the portal vein. They consist partly of medullated, partly of non-medullated fibres. The latter are distributed almost exclusively to the arteries and the veins; the former enter the lobules, where they lose their medullary sheaths and ramify between and over the cells, in a network of fine filaments (Fig. 50).

XIX. The external secretion of Bile produced by the liver is distinguished from the four secretions above described, by being continuous—although it presents considerable fluctuations, particularly in relation to the state of digestion or fasting; by having no specific enzymes; and by being apparently regulated merely by the hydraulic conditions of the hepatic circulation and absorbed digestive products, independent of any direct influence of secretory nerves, to which the other digestive secretions proper are subordinated. For all these reasons the biliary secretion presents more analogy with the secretion of urine as performed by the kidneys than with the secretions of digestive juice which we

have been considering. But there is one fundamental difference between the biliary and the urinary secretions, *i.e.* the specific components of bile are, as we shall see, formed exclusively by the metabolism of the hepatic cells, while the constituents of the urine eliminated by the kidneys are mainly pre-formed in the blood, and represent the products of the metabolism of other tissues.

The bile secretion is studied in animals by making a fistula of the gall-bladder (Schwann, 1844), either leaving the bile-duct free or tying it. In

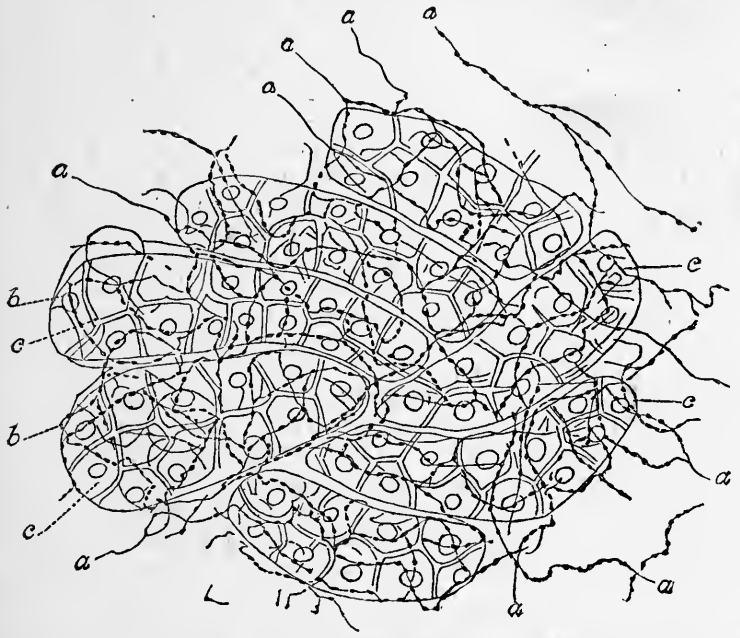

FIG. 50.—Plexus of nerve fibrils within hepatic lobe of pigeon. Methylene blue method. (Korolkow.) *a*, *a*, axis-cylinders of nerve-fibres passing between cell-trabeculae of the lobule; *b*, *b*, fibrils ramifying over the cells; *c*, *c*, hepatic lobules.

the first case (incomplete fistula), if the fistula of the gall-bladder is properly closed, the bile can flow, as normally, into the duodenum; in the second (complete fistula), it is compelled to flow out to the exterior. In order to study the process of bile secretion, it is necessary to make the fistula complete and permanent, so as to be sure that *the whole of the bile secreted* escapes by the orifice of the fistula. In cases of fistula of the gall-bladder observed on man (Ranke, 1871, down to Noël Paton and J. M. Balfour, 1891), the fistula is always incomplete, and in these cases it is seen by the colour of the faeces that some of the bile secreted by the liver does not pass through the opening of the fistula, but escapes by the bile duct and discharges into the duodenum.

The innumerable experiments on bile secretion by complete or incomplete fistulae of the gall-bladder in man and animals have

yielded very divergent results, especially as regards the influence of the various foods ingested. Heidenhain recognised these discrepancies, but held to the opinion that the secretion of bile not only increases during digestion, but exhibits two rises during this period, one 3-5 hours, the other 13-15 hours after a meal. Not being satisfied with these results, which differed from those obtained by Spiro with Ludwig, we advised Baldi in 1881 to repeat the same experiments in our laboratory, on dogs with a complete biliary fistula, when they had quite recovered from the operation and were in good physiological condition. He found a surprising irregularity in the flow of the bile secretion, and was unable to show any constant influence of digestion in general, or of the nature of the foods administered to the animals.

On comparing the quantity of bile secreted in the space of a few hours before and after a meal, he obtained a certain increase during the period of digestion; but the difference was not very conspicuous, and may be interpreted as the effect rather of increased blood-supply during digestion than of secretory excitation of the hepatic cells. The entirely negative results obtained with the so-called *cholagogues* (podophyllin, rhubarb, jalap, pilocarpine, aloe, etc.), in comparison with the immediate and conspicuous increase of the biliary secretion observed after injecting ox bile, caused Baldi to revive the ancient doctrine of Aristotle, Galen, and Morgagni, according to which the bile is a complex of the products excreted by other tissues, the hepatic cells being only the instruments of their selective elimination, as the cells of the renal canaliculi are for the urinary products.

Later work has shown this position to be untenable; but it was certainly owing to Baldi's experiments that attention was once more directed to this important problem.

With regard to the process of bile secretion and the influence exerted on it by various foods, Barbèra's results (in a series of publications, 1894-98, which sum up the methodical researches he made in Albertoni's laboratory) are particularly interesting.

Barbèra carried out a number of comparative experiments under identical conditions on dogs with a complete biliary fistula, healed some time previously (at least four months) from the operation, when they had regained their initial body-weight, and were accustomed to remain quietly in a Cyon's holder. The day before each experiment, the dogs received a scanty meal of mixed food, which was always identical in quality and quantity. Twenty-four hours after, the animal was fixed to Cyon's holder, and about three hours after fixation received the test meal, which varied in its nature in different experiments on the same animal. By this mode of procedure, it was possible to avoid any influence of the preceding meal on the flow of secretion, while the effect of the test meal was fully brought out.

Barbèra's results are plain from the accompanying diagram (Fig. 51). As it shows, during an absolute fast the quantity of bile secreted in each hour oscillates slightly round a minimum (4-5 grms. in a dog of about 20 kilos.). This amount of bile, secreted during hunger, is not perceptibly affected by the ingestion of water, even in considerable quantities, provided the animals had

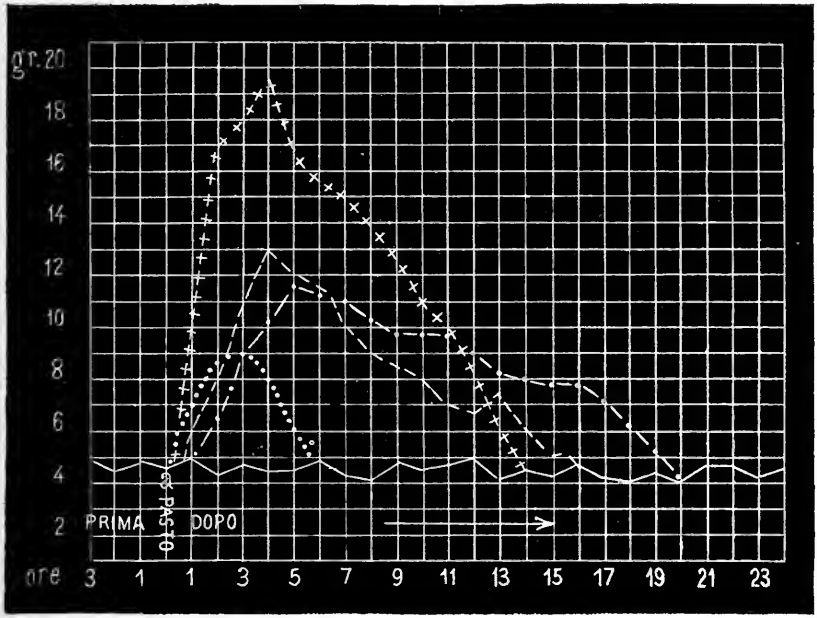

FIG. 51.—Diagram to show course of bile secretion in fasting and with different kinds of diet, in a healthy dog of 20 kilos., operated on four months previously by complete and permanent fistula of gall-bladder. (Barbèra.) Continuous line shows course of bile secretions during abstinence or injections of water only; the line of crosses, after injection of 500 grms. horse-flesh; the dotted line, after ingestion of 100 grms. cane-sugar; the broken and dotted line, after ingestion of 100 grms. fresh butter; the broken line, after mixed diet of 300 grms. flesh, 30 grms. butter, and 300 grms. bread.

not previously been deprived of water for any length of time, in which case the bile is denser than usual.

A meal of protein is followed by a *very marked* increase in bile elimination, which commences after about 30 minutes, reaches its maximum after four hours, and then declines till it ceases entirely in about fourteen hours.

A meal of fats is followed by *marked* increase in bile secretion, which commences after about one hour, reaches its maximum after about five hours, and drags on with a slow decline till it stops after about twenty hours.

A meal of carbohydrates is followed by a *slight* increase in

secretion, which commences suddenly, reaches its maximum at the third hour, and ceases entirely during the sixth hour.

After a mixed meal the increase may be *marked*, when proteins and fats predominate (see diagram), or *slight*, as when the carbohydrates predominate.

These striking results, along with what is known of the metabolism of the hepatic cells, suggest interesting considerations, which we shall discuss in a future chapter, in studying the liver as an organ of internal secretion. Here we must confine ourselves to stating that the formation of bile is not activated by the presence of food-stuffs in the gastro-intestinal tube, as a reflex along nerve paths, but only when the alimentary substances reach the liver by way of the portal vein, after digestion and absorption. In fact, the experiments of Barbèra show that the influence of the food on bile secretion is conditioned by digestion and absorption. When injected per rectum, those food-stuffs only increase the secretion of bile which are absorbed (carbohydrates and proteins), not such as are non-absorbable by this method (fats).

The production of bile continues to a less extent, even when the products of food digestion no longer reach the liver. During a fast protracted till death occurs from inanition (Chossat, Luciani, Albertoni), the amount of bile secreted gradually diminishes, but is not arrested, up to the end. Albertoni, who studied this phenomenon methodically (1893), saw that in fasting the quantity of bile secreted diminished daily, while its specific gravity, *i.e.* the relative amount of solid residues, nitrogen, and sulphur, increased.

Bile is also formed from the third month of intra-uterine life, and during the lethargic period of hibernating animals, though only in small quantities (as in the fasting state).

According to Brand (1902), who studied the secretion and composition of human bile in nine cases of fistula of the gall-bladder, the amount of bile that flows out in man (from a complete fistula) varies considerably from hour to hour. The daily amount oscillates between 500 and 1100 c.c. The biliary secretion diminishes in the night, and falls to its minimum in the early hours of the morning; it then increases rapidly, reaches its maximum about noon, and is usually succeeded by another maximum in the evening. G. Galli (1906) obtained similar results in an analogous case of fistula of the gall-bladder in a woman.

This proves that the secretion of bile, unlike the other secretions which we have previously studied, is not co-ordinated with the digestion of foods, since it is effected under conditions in which no digestion takes place in the intestine, and increases when digestion and absorption have already occurred. Biligenic and cholagogic materials, such, *i.e.*, as are capable of being transformed in the liver

into bile, or of exciting the secretory metabolism of the hepatic cells, are continuously circulating in the blood that courses through the liver, independent of the digestive products absorbed.

Evidently these bile-forming and eliminating substances must be katabolic products, both of the cells circulating in the blood and of the fixed tissue-cells. This is proved by the fact that transfusion of blood (particularly when heterogeneous) conspicuously increases the production of bile (Landois). The so-called *cholagogues* of the pharmacologists are ineffective, save in so far as they destroy the cells of the blood and tissues,—the waste products being then elaborated by the liver (Noël Paton, 1886). If dogs with fistula of the gall-bladder are made to ingest the products of nitrogenous consumption, *e.g.* extractives of meat and uric acid (provided this be rendered soluble and absorbable in the form of potassic urate), there will be a constant augmentation of the bile secretion, with increase of urea in the urine. Ingestion of urea, on the contrary, even in very large doses, does not excite biliary secretion. When it reaches the liver, the urea is entirely taken up by the central veins of the lobules, and excreted by the kidneys. This fact, established by Barbèra (1898), proves the continuity of the bile secretion, showing that the extractives and the uric acid which are never absent from the blood of animals, either under ordinary conditions or in fasting, excite metabolism in the hepatic cells, by which they are transformed into urea. Urea, on the contrary, has no action on the liver-cells, because it is the end-product of the oxidation of nitrogenous substances, and is excreted unchanged by the kidneys.

Barbèra's later work (1902) also confirms this theory. Instead of administering the various substances by the mouth or rectum, he injected them subcutaneously in dogs, and studied their action on the bile secretion. Injections of distilled water, of solutions of glucose (up to 10 per cent), of medium doses of sterilised olive oil, and of 5 to 7 per cent solutions of somatose had no effect on the elimination of bile. On the other hand, he observed increase of the secretion on injection of more concentrated solutions (glucose 20 per cent and more, somatose 10 per cent and more), or of large doses of non-sterilised olive oil. But since these last injections simultaneously induce local phenomena of irritation at the point of injection, accompanied by increased elimination of urea and slight rises of temperature, Barbèra came to the conclusion that the increase of bile secretion depends not on any direct action of these substances on the hepatic cells, but, indirectly, upon the increased destruction of proteins, the cleavage products of which excite augmentation in the biliary secretion of the liver.

Another fact worth noting is that the secretion normally poured by the liver into the gall-bladder is not all newly-formed bile: a considerable part of it is only bile reabsorbed from the

intestine, conducted back to the liver by way of the portal vein, and eliminated once more from the liver by the bile ducts. This kind of entero-hepatic circulation of the bile was worked out particularly by Schiff, Lussana, Baldi, Tarchanoff, and Wertheimer. It is only necessary to give bile by the mouth, or to inject it directly into the duodenum, of a dog with a fistula of the gall-bladder, in order shortly after to see a flow from the fistula, proportionate to the amount of bile administered. Again, on injection by the veins, the bile is not excreted by the ureters but entirely by the hepatic duct, if a moderate amount be injected. On injecting ox-bile, which is green (owing to the large preponderance of biliverdin), the secretion flowing from the biliary fistula of the dog loses its orange colour (due to preponderance of bilirubin), and assumes the hue of ox-bile (Baldi). This fact demonstrates the specific excretory function of the hepatic cells for the constituents of bile, which is of great importance, since it extends not only to these but also to many other toxic and medicinal substances introduced into the gastro-intestinal tube, which on reaching the liver are carried back to the intestine with the bile (Lussana, Moroni and Dyall, Acqua, Schiff, and others). Barbèra (1898) rightly insisted on a phenomenon which is not easy to explain by known laws of physics and chemistry. If fasting dogs with a fistula of the gall-bladder are made to ingest large quantities of bile and urea together, then although both substances are taken up by the portal vein, and carried to the liver, the whole of the bile is constantly eliminated by the bile-ducts, while the whole of the urea passes into the capillaries which lead to the central veins of the lobule, and is excreted by the kidneys. To account for this fact, he assumes a differentiation into two parts of the hepatic cells; the one in contact with the bile canaliculi, the other in relation with the blood capillaries which lead to the central veins of the hepatic lobules. These two parts must have different excretory functions, due possibly to a difference in cytological structure, which we are unable by our present methods to detect. But without invoking any unfounded hypothesis, the fact may be explained as depending on the selective attraction of the hepatic cells for biligenic substances (*positive chemotaxis*), while they repel urea (*negative chemotaxis*).

XX. The biliary secretion can be modified not only by the composition of the blood that circulates round the hepatic cells, but also by the amount of blood that flows to the liver, and the vascular tonicity of the portal vein and hepatic artery. The augmented secretion that occurs during digestion is partly due, no doubt, to the active vascular dilatation which accompanies the secretory work of all organs that function during the digestive processes.

Just as the bile secretion is promoted by a rapid and abundant

flow of blood through the liver, so the interruption of the blood-stream by ligation of the hepatic artery and portal vein arrests it (Röhrig). After tying the hepatic artery alone, bile may still be copiously secreted, fed from the portal blood alone (Simon, Schiff, Schmulewitsch, Asp). The hepatic artery supplies the nutrient vessels of the gall-bladder, bile-ducts, and interlobular branches of the portal system, while it takes no direct part in the formation of the intralobular network of blood capillaries. For this reason, ligation of the hepatic artery gives rise after some time to the formation of multiple necrotic foci in the liver, the larger of which are converted into cysts, while the smaller are replaced by connective tissue, so that hepatic cirrhosis develops (Cohnheim and Litten).

The rapid and complete occlusion of the portal vein speedily produces the death of the animal, owing to stasis and excessive congestion of blood throughout the portal system. But if one branch alone be tied, leading to one lobe of the liver, the biliary secretion may continue in that lobe, fed solely by the artery (Schmulewitsch, Asp). The same is also seen when ligation is gradually applied to the entire portal trunk (Oré, Osler); also when the blood of the hepatic artery is led directly into the opened portal vein (Schiff).

When arterial pressure is lowered, either by haemorrhage, or from vascular paralysis consequent on section of the cervical medulla, there is diminution or arrest of the bile secretion. It increases, on the contrary, after section of the splanchnic, because in this case, although arterial pressure is diminished, the flow of blood to the liver is increased, owing to paralytic dilatation of the vessels at the roots of the portal system. By a diametrically opposite effect, the bile secretion diminishes with electrical excitation of the cord, of the splanchnics, or on strychinisation of the animal (Heidenhain, I. Munk).

Circulation in the blood-vessels of the liver can be modified, not only by the effects of constriction or dilatation of the roots of the portal, or by increase or decrease of aortic pressure, but also by the constrictor or dilator action of the nerve fibres which regulate the tone of the branches of the hepatic artery and the portal vein in the liver. According to certain experiments of E. Cavazzani and G. Manca (1894-95), the vaso-constrictor fibres of the branches of the portal come directly from the splanchnics and the caeliac plexus, and the vaso-dilators mainly from the vagi. The branches of the hepatic artery, on the contrary, receive their vaso-constrictors mainly from the vagi, their vaso-dilators mainly from the caeliac plexus. During asphyxia, phenomena of dilatation are mainly obtained in the branches of the hepatic artery, and phenomena of constriction in those of the portal vein. Electrical stimulation of the vagi and branches of the caeliac

plexus produces opposite phenomena in the region of the portal vein and in that of the hepatic artery; while the former contracts with excitation of the plexus, and expands with stimulation of the vagus, the latter contracts on exciting the vagus, and enlarges with excitation of the caeliac plexus. While section of the vagus abolishes the effect of asphyxia on the artery, it does not affect its action on the branches of the portal vein.

Although the influence of these changes in the tone of the venous and arterial hepatic vessels upon the process of biliary secretion was not studied by the above workers, it may on analogy be taken as highly probable that vascular constriction (particularly of the portal branches) determines a slowing, and dilatation an acceleration, of the flow of bile.

While there can be no doubt that the secretory activity of the liver, like that of the other glandular organs, is *indirectly* affected by the nerves which regulate vascular tonicity, there are at present no data to demonstrate the existence of secretory nerves to the liver, exerting a *direct* control upon the secretion of bile. All the nerves to the liver can be divided without causing arrest of the biliary secretion; all branches of the nerves to the liver can be excited one after the other, without causing a flow of bile, if the secretion was suspended, or accelerating it if already taking place (Heidenhain).

Falloise (1903) found on dogs that application of hydrochloric acid to the mucous membrane of the duodenum, or upper part of the small intestine, provoked increase of the biliary secretion. At the same time it may be questioned whether this is a true reflex, as asserted by Fleig. Falloise interprets the phenomenon by admitting the transformation of pro-secretin into secretin, which on reaching the liver increases the formation of bile by local stimulation. In reality this pretended cholagogic action is abolished neither by narcotics, nor by strong doses of atropine. On the other hand, Henri and Portier (1902) observed that the injection of secretin caused an acceleration of biliary secretion. The same objections apply here in regard to the "secretin hypothesis" as were raised for the pancreatic and intestinal secretions.

Friedländer and Barisch (1860) connected the hepatic duct of the guinea-pig with a vertical glass tube, so as to determine the point to which pressure can be raised in the bile ducts. They saw that the bile ascends in the glass tube with a gradually decreasing velocity, which ceases when it has reached a certain height, varying from 184-212 mm. Since the pressure in the portal vein, according to the determinations made by von Basch on dogs, varies from 7-16 mm. Hg, corresponding to a column of bile about 191-208 mm., the pressure under which bile is secreted is always *more or less higher* than the pressure at which the blood circulates in the portal system. This was confirmed by comparison

of the two pressures, measured simultaneously by Heidenhain on dogs. This phenomenon, perfectly analogous with that which Ludwig found for the salivary secretion, shows that the bile secretion cannot, even if it fluctuates with the variations in the circulatory conditions of the liver, be regarded as an effect of simple filtration through the vessel walls, but must depend on the activity of the hepatic secretory cells.

In proportion as the elimination of bile by the excretory duct is obstructed, it is reabsorbed, and the phenomena of *jaundice* appear. The skin and conjunctiva of the eye become yellow, which is the external sign of *cholaemia*, or admixture of bile with blood. The bile is not absorbed directly by the blood-vessels of the liver, but by the lymphatics, which convey it to the thoracic duct, whence it is poured out into the blood torrent. This fact, already surmised by Sanders in 1795, was demonstrated experimentally by von Fleischl in 1872. Harley has recently shown that if after ligation of the choledochus the thoracic duct is also tied in a dog, there will for 17 days be no constituents of bile, either in the blood or the urine, and no external sign of jaundice. In this case, all the bile collects in the gall-bladder, and along the thoracic duct and its roots in the liver.

XXI. The bile collected from the gall-bladder of dead bodies, or obtained by fistula from man and other animals, is a mixture of the secretion from the hepatic cells, and that of the epithelia which line the bile ducts and gall-bladder. Along the excretory ducts, the products of the hepatic cells are mingled with mucus and cells in process of disintegration, which make it more dense, more viscid, and less limpid and transparent. The reaction is alkaline from the carbonate and phosphate of sodium, the colour varies in different animals (golden-yellow in carnivora, grass-green in herbivora, greenish-yellow in man), the taste is bitter. That of man, exclusive of mucus, contains 0·5-1 per cent solids, of which 0·7-0·8 per cent are mineral. Within the gall-bladder it condenses from absorption of water till the solids amount to 16-17 per cent with specific gravity 1·010-1·040.

The specific constituents of bile are the *bile acids* and *pigments*.

The *bile acids* are never found in the free state, but always in the form of sodium salts (potassium salts in sea fishes). They are acids containing nitrogen, and are composed of cholalic acid (or related acids), glycine and taurine. It is remarkable that the quantity of cholalic acid never varies sensibly in animals of the same species. On the other hand, in different biles the relative amount of glycocholic and taurocholic acid may vary, although the former always exceeds the latter in quantity. Besides cholalic acid, according to Schotten and Lassar Cohn, human bile contains two other related acids—fellinic and choleïnic acid, which

last is constantly present, and according to Lutschinoff forms the fundamental acid of ox-bile.

Chemists distinguish a numerous series of *bile pigments*, which represent various degrees of oxidation in the same molecular aggregate. Under physiological conditions only two of these pigments appear in the bile, the red or *bilirubin*, and the green or *biliverdin*. The first is less oxidised, and represents the mother substance of all the other pigments, and it is readily transformed into the second by simple exposure to air (Maly). Biliverdin is, vice versa, converted into bilirubin by a process of reduction. By action of hydrogen in the nascent state these pigments are converted into *hydrobilirubin*, which, as we shall see, occurs continually in the intestine; a certain amount of hydrobilirubin can, however, be found even in human bile. Bilirubin and biliverdin usually co-exist in the bile, but the first largely predominates in the bile of carnivora, the second in that of herbivora, while the one or the other predominates in that of man (omnivora) according as the food is mainly animal or vegetable.

Hammarsten's analysis of the chemical composition of human bile, taken from the gall-bladder of persons operated on for cholelithiasis, and from patients with a fistula of the gall-bladder, give the following results:—

	In 100 Parts.	
	Bile from the Fistula.	Bile from the Gall-Bladder.
Water	96·5 –98·3	82·96–83·98
Solid substances	3·5 – 1·7	17·03–16·02
Mucin and pigments	0·27 – 0·9	4·19– 4·43
Alkaline bile salts	1·8 – 0·26	9·69– 8·72
Glychocholic acid	1·6 – 0·2	6·95– 6·78
Taurocholic acid	0·05 – 0·3	2·74– 1·93
Fatty acids (from soaps)	0·024– 0·14	1·11– 1·05
Cholesterin	0·04 – 0·16	0·98– 0·87
Lecithin	0·06 – 0·17	0·22– 0·14
Fat	0·06 – 0·10	0·19– 0·15
Soluble salts	0·7 – 0·8	0·28– 0·3
Insoluble salts	0·02 – 0·05	0·22– 0·23

As shown by this table, besides the bile salts and pigments (which are the specific substances of bile), fats, soaps, cholesterol, and lecithin are never absent; these substances are compounds present in other tissues and secretions. In the bile of certain animals there is also a *diastatic enzyme*; this is probably not hepatic in origin, but is absorbed from the pancreas, and eliminated by the liver in the bile. *Choline* and *glycero-phosphoric acid* are also found, which are probably decomposition products of lecithin.

Normally the bile also contains *urea*, particularly that of the cartilaginous fishes. As regards mineral substances, sulphates are almost entirely absent from the bile, which shows traces of *copper*, *zinc*, and particularly of *iron*, in an amount that varies with the nature of the food. According to Novi, the quantity of iron is less in dogs fed with bread, greatest in a flesh diet; according to Dastre, the iron content of the bile varies even with a uniform diet, according as the haematopoietic or the haematolytic processes predominate. The iron introduced in a medicinal form is also, according to some authors, retained by the liver and eliminated in the bile (Novi, Kunkel), this being disputed by others (Hamburger, Gottlieb, and Anselm).

According to Craciunu (1901), the composition of bile varies with age. The bile of young animals up to three years old contains less water and more solids than that of adults (9·8-10·5 per cent against 8-8·1 per cent solids). In young animals there are also more mucin, more mineral salts, cholesterol, and bile salts; in adult animals more fats and lecithin.

Pettenkofer's Reaction is used to detect the presence of bile acids. The acids or fluids containing them are treated with a little 25 per cent solution of cane sugar, and sulphuric acid is carefully added, so that it forms a layer under the solution. A reddish-purple colour appears at the junction of the liquids, and also where it comes into contact with any froth at the surface. The presence of nitrates may disturb the reaction.

In testing for bile acids in the blood and urine, the following is the best method:—

Dilute the blood with two volumes of water, and coagulate the proteins by heating with a few drops of acetic acid. Filter off the coagulum and evaporate the solution on a water-bath. Extract the residue with absolute alcohol which dissolves the bile salts, while the proteins remain undissolved, and evaporate off the alcohol. Dissolve the residue in water containing a little sugar, and add sulphuric acid diluted with an equal volume of water and cooled. On gently warming, the originally cloudy solution clears up, and turns successively orange, yellow, red, and purple. To detect bile acids in urine, it is only necessary to evaporate it to dryness, then extract with alcohol, and proceed as described for blood.

A more convenient method has recently been introduced, based on the fact that the presence of bile acids enormously increases the surface tension of urine. We shall give this method in detail when discussing the katabolic products of urine.

Gmelin's test for bile pigments. Pour 5 c.c. nitric, with a drop of nitrous acid, into a watch-glass, then carefully introduce the fluid to be examined by a pipette, without allowing it to mix with the reagent. At the point of contact of the two fluids, rings of different colours are formed, which are green, blue, violet, red, and yellow, as they spread from the centre to the periphery. Each colour represents a successive stage in the oxidation of the bile pigment.

The tests for cholesterol are also interesting. *Cholesterol* is the chief constituent of the calculi formed in the bile-ducts and gall-bladder, which give rise to hepatic colic.

1. On adding a few drops of sulphuric acid diluted with one-fifth its volume of water to some cholesterol in a porcelain capsule, a carmine-red colour results (Moleschott).

2. On adding a few drops of a mixture of 2-3 volumes concentrated HCL, and 1 volume of dilute perchloride of iron to some cholesterol, and evaporating, a residue is obtained, which is at first red-violet in colour, afterwards blue-violet (U. Schiff).

XXII. Far more is known of the *origin of bile salts and pigments* (though the data are still incomplete) than of the formation of the other secretory products which are poured into the intestinal tube.

The fundamental question is whether these specific constituents of the bile are pre-formed in the blood, the liver only having the task of eliminating them, as the kidneys eliminate the constituents of urine, or whether they are exclusively formed in the liver, *i.e.* are they specific products by external secretion of the hepatic cells, and not the products by internal secretion of many or all the tissues of the body. The first theory (already adumbrated by Aristotle and Galen) was upheld in more recent times by Morgagni, van Swieten, and Glisson; the second by Sanders, Joh. Müller, Kunde, Moleschott. In accordance with their opposite points of view, the former admit the possibilities of a *haematogenous* as distinct from a *hepatogenous jaundice*; the latter regard *cholaemia* and *jaundice* as invariably due to the reabsorption of the bile formed in the liver, *i.e.* as being essentially *hepatic* in origin.

Till quite lately, the arguments in favour of this last theory were not adequate to solve the question:—

(*a*) The blood that supplies the liver contains (it was said) neither acids nor bile pigments; these must therefore be formed in the liver. But (as Baldi pointed out) this argument loses all value if we reflect that many kilos. of blood pass through the liver in the 24 hours, and that the amount of biliary products the blood must contain as the equivalent of what the liver secretes during the same period is excessively small, certainly less than 3 grms. per cent, and therefore not to be detected by the chemical means at our disposal.

(*b*) After extirpation of the liver in the frog (J. Müller, Kunde, Moleschott), the bile constituents do not accumulate in the blood, as they do after tying the bile-duct. The frogs in which Moleschott excised the liver lived 15 to 21 days, without any appearance of cholaemia or jaundice. To this Baldi replies that the metabolism of frogs is so sluggish that enough bile would not collect in a few days in the blood or urine, to be detected chemically. In fact, when Leyden tied the bile-duct in frogs there was no sign of jaundice after 14 days. Köbner, in Heidenhain's laboratory, did detect bile acids in the frog's urine, after ligation of the bile-duct. But even if this argument proves that the liver forms bile, it does not exclude the possibility of its formation by other tissues also.

(*c*) Secretion of bile ceases in cases of fatty degeneration of the liver, yet there is no jaundice. Frerichs cites a clinical case in which no bile salts were found in the urine. But Baldi, on poisoning dogs with a fistula of the gall-bladder by small doses of phosphorus which produced fatty degeneration of the liver, observed that bile still flowed from the liver up to a few days before the death of the animal. When, owing to catarrh of the bile-ducts, the flow from the fistula ceased, bile salts were found to be present in the urine. He noted, moreover, that after long abstinence the hepatic cells of frogs became atrophied, while the gall-bladder swelled, owing to the enormous accumulation of bile, till it equalled or exceeded the volume of the liver. He further observed that transfusion of ox-blood into dogs with fistula of the gall-bladder not only increased the flow of bile freely given off by the fistula, but caused the passage into the urine of bile acids and pigments. From this it is legitimate to conclude that bile is not an *exclusively hepatic* formation, and that the heterogeneous blood transfused gives rise by decomposition of haemoglobin (as held by Landois) to the bile pigments, and may possibly, by decomposition of protein, account for the formation of bile acids.

(*d*) It is impossible, either during abstinence or in digestion, to demonstrate the presence of bile constituents in normal hepatic tissue by micro-chemical means. The varying aspect of the hepatic cells in these two periods (which we shall study elsewhere) seems to be exclusively connected with the formation of *glycogen* (Cl. Bernard), and not with the formation of *bile*. This fact seems to favour the ancient doctrine of the diffuse formation of bile, rather than the theory which regards it as the exclusive secretion of the liver cells.

None of these data, as can be seen, gives a decisive answer in regard to the exclusively hepatic origin of the specific products of bile. Other more recent work, however, leaves no doubt as to this point. We may summarise the most cogent and conclusive arguments:—

(*a*) If bile, like urine, were the excretory product of different tissues, its nitrogen and sulphur content would vary in proportion to the total protein consumption of the body. Kunkel (1870) and Spiro (1880), on the contrary, show on dogs with fistula of the gall-bladder that only a small part of the nitrogen and sulphur from the proteins of the food are eliminated with the bile, and that this quantity does not increase proportionately with the amount of protein ingested. When the amount of protein introduced as food is increased eight times, the amount of nitrogen and sulphur in the bile is only doubled. Barbèra (1896) showed that this increase of nitrogen in the bile is also seen after the ingestion of fats. It does not therefore depend on the greater quantity of nitrogen circulating in the blood, but solely on the

fact that both proteins and fats excite the hepatic cells and accelerate the secretory function.

(β) Stern's experiment on pigeons (1885) is more decisive. After total occlusion of the liver in these birds, by ligation of all the vessels that enter or leave it, including the bile-duct, urinary secretion is arrested, and bile pigments do not appear either in the blood serum or in extracts of the tissues, even with Gmelin's highly sensitive test. When, on the other hand, Stern confined himself to occluding the bile-duct only, the pigments appeared in the urine after an hour and a half, and after five hours they could be detected in the blood serum. This shows plainly that the bile pigments in circulating blood are formed exclusively in the liver.

(γ) The experiments of Minkowski and Naunyn (1888) on geese are no less important. They destroyed a considerable proportion of the erythrocytes of two geese, in one of which the liver had been excised by inhalations of arseniuretted hydrogen, and observed that after half an hour the goose with a liver gave off urine containing biliverdin and bile acids, while the goose with no liver gave urine which contained abundance of haemoglobin with no trace of pigments or bile acids. On then removing the liver of the first goose, and occluding all the vessels, including the bile-ducts, they noted after some time that the serum of the blood contained neither bile pigments nor bile acids. These experiments are complementary to those of Stern, showing that not only the bile pigments but also the bile acids have an *exclusively hepatic* origin.

(δ) The same interpretation holds for the experiments performed by v. Fleischl with Ludwig on dogs. Having tied the bile-duct and inserted a fistula in the thoracic duct, he showed that the lymph that escaped from the fistula contained the constituents of bile, which are absent when the bile-ducts are not occluded. On tying both the bile-duct and the thoracic duct on the other dog at the same moment, he saw that the latter swelled from the accumulation of lymph, while no trace of bile salts could be detected in the blood. This result, which was subsequently confirmed by Harley, shows not only that bile is exclusively produced by the liver, but also that after occlusion of the bile-ducts it is reabsorbed exclusively by the lymphatic paths to the thoracic duct. Both these experiments of Fleischl and those of Minkowski and Naunyn with inhalations of arseniuretted hydrogen show that the *haematic* or *extra-hepatic* origin of jaundice can, under no circumstances, be admitted, even where the latter is confined to the accumulation of the bile pigments in the blood. The presence of bile pigments in the urine of a patient invariably denotes reabsorption—in part at least—of the bile by the lymphatics of the liver. Occlusion of the larger bile-passages is

not essential to this absorption. A slight obstruction to the outflow of bile in any of the primary bile-ducts suffices to cause overflow of the secretion stagnating in these passages into the lymphatics, and thence into the blood.

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CHAPTER III

MECHANICS AND CHEMISTRY OF DIGESTION IN THE MOUTH AND STOMACH

CONTENTS.—1. Historical. 2. Mastication, insalivation, formation of alimentary bolus, and saccharification of starch. 3. Mechanism of deglutition. 4. Innervation. 5. Artificial digestion *in vitro* to determine action of gastric juice on different food-stuffs. 6. Influence of spleen on gastric digestion. 7. Natural digestion in the stomach. 8. Effects of total gastrotomy. 9. Active movements of stomach in gastric digestion. 10. Mechanism of vomiting. 11. Peripheral and central innervation of stomach. Bibliography.

THE term "Digestion" usually denotes the complex of mechanical and chemical changes effected in the food-stuffs by the muscular tissue of the gastro-intestinal canal and by the secretions of the glands discussed in the last chapter. By these changes the food-stuffs are reduced to the form necessary for their rapid absorption, assimilation, and transference to the blood stream.

By "food-stuffs" in the widest sense, we mean all those substances which are normally contained in the blood plasma, or can readily be converted into the same, and which do not represent the end-products (or metabolites) of tissue consumption, destined as such to be eliminated from the body. A perfect diet must therefore contain (*a*) protein; (*b*) fats; (*c*) carbohydrates; (*d*) water; (*e*) various salts, the bases of which are Na, K, Ca, Mg, Fe, and hydrochloric, sulphuric, and phosphoric acid. The three groups of organic substances (proteins, fats, carbohydrates) are oxidisable, *i.e.* they contain potential energy which is greater or less in proportion to their capacity for oxygen; the mineral constituents (water and salts), on the contrary, are not capable of being oxidised, and are therefore useless as sources of energy, and merely fulfil the rôle of common solvent, or passive material of construction. We shall discuss the *physiological classification* of foods, according to the functions of each group of substances (which is fundamental to the *theory of nutrition*), elsewhere, when we consider *metabolism*, *i.e.* the material exchanges of the body as a whole.

Of the oxidisable organic substances on which we subsist, sugar

and certain proteins only are soluble in water; starch, coagulated protein (*e.g.* meat and boiled egg-white), and fats are insoluble. The mechanical and chemical object of digestion is to modify these substances, and to render them soluble and readily diffusible. Mineral constituents being soluble need undergo no change in the gastro-intestinal canal to fit them for entering the blood.

The mechanism of digestion is so bound up with its chemistry, that to treat them separately seems to us no less grave an error than to discuss the theory of nutrition before that of digestion.

I. The first series of methodical experiments on Digestion were those of Réaumur (1683-1757). The Accademici del Cimento, disciples of Galileo, and founders of the iatro-mechanical school, had previously experimented on ravens, and seen that the stomach of these birds is capable with its powerful muscles of pulverising the hardest bodies, which lent support to the view that digestion consisted essentially in *trituration* (Borelli, Pitcairn, Boerhaave). It was known, however, that in man and mammals, where the digestive powers are very great, the stomach has such thin walls that digestion can only be conceived as the effect of *chemical solvents* (Wepfer, Viridet, Valisnieri). In order to decide between the mechanical and the chemical theory, Réaumur carried out a series of experiments in which ostriches were made to swallow perforated metal tubes containing food. The first results were negative or very doubtful, but his later work on birds of prey, which have a membranous stomach, yielded conclusive results, and convinced him of the chemical character of the forces that, in the majority of cases, effect digestion. When, however, he attempted to digest *in vitro* by means of gastric juice obtained from sponges which his tame buzzard was made to swallow and then regurgitate, after which the fluid which the sponges had imbibed was squeezed out, his results were negative, and he gave up the experiments.

Nearly half a century later the same experiments were taken up again by Spallanzani (1783) with complete success, and he confirmed the discovery of Réaumur, and further demonstrated the possibility of artificial digestion *in vitro*, without the intervention of mechanical factors. He suspected the presence in the gastric juice of a ferment of neutral reaction, as discovered by Schwann in 1837, a ferment on which the solvent power of the gastric juice depends. Lastly he made a most important discovery from the standpoint of medicine and hygiene, *i.e.* the *non-putrefaction* of gastric juice, to which is due its sterilising action on the foods introduced; this being possibly, as we shall see, the most important function of the acid secretion of the stomach.

The Congress convened at Paris in 1823 by the Académie des Sciences with the object "de déterminer par une série d'expériences chimiques et physiologiques, quels sont les phénomènes qui se

succèdent dans les organes digestifs durant l'acte de digestion," led to the publication of two important monographs, one by Leuret and Lassaigne (1825), the other by Tiedemann and Gmelin (1826), in which the entire process of digestion was for the first time submitted to an experimental criterion. The work of the two German authorities in particular must be regarded as the starting-point of subsequent experimental researches, since they established the foundations on which the whole of the modern doctrine of digestion rests.

In collecting the gastric juice, Tiedemann and Gmelin introduced a modification of the method pursued by Réaumur and Spallanzani, since they caused dogs to swallow insoluble bodies in order to stimulate the walls of the stomach. They then killed the animals, collected the juice secreted, and studied its solvent action on food *in vitro*. A few years later (1833) Beaumont published his experiments on the Canadian trapper, Alexis St. Martin, who, in consequence of an accident, had a large gastric fistula, which made him a convenient subject for the study of the phenomena of natural digestion. And shortly after (1834) Eberle published his discovery of *artificial gastric juice* obtained from extract of mucous membrane, with which numerous series of *artificial digestions in vitro* were carried out by himself, by Joh. Müller, Schwann, Wasmann, Vogel, Valentin, etc. This return to Spallanzani's method indicates a marked progress in the positive knowledge of the nature and properties of the digestive process.

Among the more complete monographs on digestion, of special historical interest, are those of Blondlot (1843), Frerichs (1846), and Bidder and Schmidt (1852).

II. The Digestive System, which is a canal extending from the mouth to the anus, has on an average a length of about nine metres. The part that lies in the head, neck, and thorax measures from the mouth to the cardiac orifice of the stomach some 38 to 46 cm.; the remainder, situated between the abdomen and the pelvis, is almost twenty times as long. The former includes the mouth, the pharynx, and the oesophagus; the latter the stomach, the small intestine, and the large intestine. This anatomical division clearly indicates the lines we must follow in studying the mechanical and chemical changes in the food-stuffs introduced into the digestive canal.

The first secretion which the food encounters is the saliva poured into the buccal cavity, in a daily quantity (according to Bidder and Schmidt) of more than 1500 c.c. *Prima digestio fit in ore*, as the ancients phrased it. At first sight it appears as if the saliva, secreted in such abundance, must have a highly important chemical function. Everything, on the contrary, indicates that the operations effected on the food in the mouth are mainly of a mechanical character.

Fluids, whether taken into the mouth by sucking or drinking (*i.e.* imbibed or gulped down), are immediately swallowed; solids, on the contrary, are masticated before swallowing.

If a fluid is taken up by imbibing, this is effected by the negative pressure which is produced in the buccal cavity during an inspiration, provided the communication between the pharynx and the nasal fossae is closed by elevation of the palate. In order that the liquid shall be imbibed, the edges of the lips must be applied to the edge of the glass and to the surface of the fluid. When a fluid is gulped down, the mouth is half-open, and the lower lip makes a funnel which conducts the fluid to the mouth.

Sucking, by which the infant draws its nourishment from the glands of the breast, is effected by the vacuum produced in the mouth by depression of the roof, retraction of the tongue towards the throat, and sometimes by dropping of the lower jaw (Auerbach), while the lips completely enclose the nipple. The negative pressure which determines the flow of milk into the buccal cavity oscillates, according to Herz, between 3 and 10 mm. Hg; this last figure, however, seems to us exaggerated.

Mastication of solid foods is accomplished by the voluntary movements of the lower against the upper jaw, assisted by the movements of the tongue, by which the food is pushed between the two rows of teeth, which are the passive instruments of trituration; the canines and incisors serve particularly for pulling and tearing, the molars for biting up the food.

The teeth make their appearance in the first two years of childhood—these being the milk teeth destined to be gradually replaced by the permanent teeth from the seventh year onwards. The milk teeth are 20 in number: 8 incisors, 4 canines, 8 molars; the permanent teeth are usually 32: 8 incisors, 4 canines, 8 premolars, and 12 molars. Comparison of the form of the teeth in man and in the carnivora and herbivora, gives a plain anatomical proof that a mixed diet is that best adapted to the nature of man. This is confirmed by the length of his intestine, which holds the mean between that of herbivora, which is much longer, and of carnivora, which is much shorter.

Elevation of the lower jaw is effected by means of the temporal, masseter and internal pterygoid muscles; its depression, by gravity, and by the action of the anterior surface of the digastric, mylo- and genio-hyoid muscles, and the platysma; the forward movement by the simultaneous action of the external pterygoids; the retraction by the simultaneous movement of the internal pterygoids; and the sideway movements by the alternate action of the external pterygoids on both sides (Fig. 52, A and B).

The masticatory movement is regulated by the tactile sensibility of the teeth and the buccal mucous membrane, and by the

muscular sense of the muscles that come into play ; it is activated by the motor roots of the third branch of the trigeminals, aided by the hypoglossal and facial nerves. The immediate common centre of the masticatory movements, according to Schröder van der Kolk, lies in the medulla oblongata; this view is not, however, supported by any definite anatomical evidence. Since the movement is complex and voluntary, its centre probably lies in the so-called *motor zone* of the cerebral cortex. In fact, the electrical excitation of a circumscribed area in the lower lateral part of the cortex of the anterior lobe of the brain in rabbits readily produces

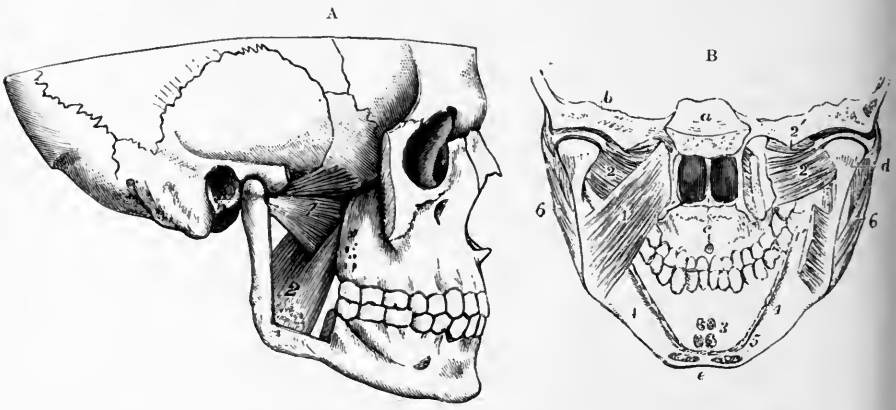

FIG. 52.—A, internal pterygoid muscles viewed from outside. (G. D. Thane.) The masseter muscle, greater part of zygomatic arch, temporal muscle with coronoid process, and a large part of the ramus of the jaw have been removed ; 1, external pterygoid, the figure is placed on the lower head ; 2, internal pterygoid. B, lower part of skull and face to show attachment from behind of pterygoids and some other muscles. (Bourgery.) *a*, body of spheroid, beneath which are the posterior nares ; *b*, section through temporal bone ; *c*, hard palate ; *d*, posterior part of condyle and neck of lower jaw, above which are the synovial cavities of the joint separated by the inter-articular fibro-cartilage ; *e*, symphysis menti ; 1, left internal pterygoid muscle ; 1', lower part of same muscle, on right side, the middle is cut away to show external pterygoid ; 2, lower head of external pterygoid ; 2', upper head of the muscle, attached in part to the inter-articular disc ; 3, origin of mylo-hyoid and genio-glossus muscles from the mental spines ; 4, origin of mylo-hyoid ; 5, attachment of anterior belly of digastric ; 6, 6, masseter muscles.

movements resembling those of mastication. The centrifugal paths from this area lead through the corona radiata to the median segment of the internal capsule, and may be followed into the anterior mesial part of the cerebral peduncle.

Simultaneously with mastication comes the insalivation of the food, by which its particles are worked into a mass, which, when carried to the back of the tongue, becomes rounded and is called the *bolus*. The movements of the tongue, besides shifting the food to and fro between the rows of teeth, help in shaping the bolus from the fragments already chewed and insalivated.

According to Gaudenz (1901) a mouthful suited for mastication normally has a volume of about 5 c.c. Its weight depends on the specific gravity of the foods. Such a mouthful in a normal man

is sufficiently chewed in half a minute to determine the reflex of deglutition, independent of the nature of the food. The masticated pulp contains a certain quantity of coarse particles from 7-12 mm. in diameter, according to the nature of the food; the smallest particles are only 0·01 mm. in diameter. Pieces larger than 12 mm. in diameter are retained in the mouth during deglutition of the pulp, and subjected to fresh trituration. As a rule vegetable foods are better masticated than animal matters.

The most important function of saliva is certainly the preparation of a bolus from the masticated food, which is then ready for deglutition. Saliva has no chemical action on the greater part of the food-stuffs, and is limited to the conversion of the starch into dextrin and sugar, with absorption of water. This action takes place rapidly on cooked starch, very slowly upon raw, and is due exclusively to the ptyalin, which acts in a slightly alkaline, or even in a faintly acid medium, so that its action must cease in the stomach, as soon as the acidity of the gastric juice exceeds that of 0·5 per cent HCl. The saccharifying power of the enzyme is less when it is made to act on a large amount of starch; moreover, it is easily exhausted.

Cannon and Day (1903) studied salivary digestion in the stomach of the cat by isolating the different parts of the stomach with ligatures, at a given time after the ingestion of food, and testing them singly for the sugar content. They found that in the fundus, the contents of which do not mix for a long time with those of the pyloric region in the cat, the saliva produces a conspicuous formation of sugar from the starch, without disturbance by the hydrochloric acid of the gastric juice.

The amylolytic or diastatic action of the saliva is accomplished in stages, *i.e.* it passes through certain intermediate products. The first stage of starch conversion is that of *amidulin* (Nasse) or soluble starch, which turns blue with iodine like insoluble starch; amidulin is then transformed into *erythrodextrin* (Brücke), which turns deep red with iodine; the *erythrodextrin* changes into *achroödextrin* (Brücke), which no longer stains with iodine; lastly, a portion of the achroödextrin is converted into *maltose* (von Mering and Musculus), and a small portion into *glucose* (Zimmermann), which give the ordinary sugar reactions.

Besides maltose, there is always a certain amount of dextrin and unaltered starch in the end-products of the amylolytic action of saliva, as exerted by ptyalin on starch. According to Sheridan Lea, 3·412 grms. of boiled starch, left to digest for a number of hours with 100 c.c. of saliva, yield 2·838 grms. of maltose, and 0·505 grm. of dextrin. On the other hand, it is certain that a small quantity of saliva suffices to saccharify a large amount of starch (Brücke).

Clemm (1902) showed that simple salivary digestion con-

tinued for three days at body temperature, produced sugar, both from animal starch (glycogen) and from vegetable starch (potato); the whole of the maltose was split into two molecules of glucose.

Surprising as is the readiness with which ptyalin acts upon cooked starch, the time of its action is very short, and incomparably less in intensity than that of the analogous enzyme of pancreatic juice.

Recent researches prove that salivary digestion has a much greater importance than was formerly supposed.

J. Müller (1901), *e.g.*, found that saliva converts 50-70 per cent and even more of the alimentary starches into soluble products closely related to maltose. In cases of weak acid secretions in the stomach, only very minute fractions of starch, as a rule, remain undissolved. The saccharification of starch is therefore most intense at the commencement of gastric digestion. Gaudenz (1901), too, found that in the ingestion of starchy foods, such an amount of saliva was secreted even after half a minute that it induces a peculiarly energetic process of saccharification, and is capable of dissolving large quantities of vegetable foods like macaroni, potatoes, turnips, etc., while animal foods are only dissolved to the extent in which they contain substances soluble in water.

The saliva of carnivora, although it is secreted in great quantities, is entirely destitute of ptyalin, as might be expected from teleological considerations. The saliva of infants, up to a year old, is also lacking in ptyalin, and therefore in diastatic properties (Schiff and others). This is the best proof that the principal function of the saliva is mechanical, *i.e.* formation of the bolus. It must, however, be added that saliva by its alkalinity also serves to protect the teeth from the corrosive action of acids, which are readily formed in the mouth by the fermentation and decomposition of alimentary residues. One argument in favour of this theory of Bunge is the fact that *Cetacea* that live in water are entirely destitute of salivary glands, which are rudimentary in the *Pinnipeda*. The emulsifying action of saliva on fats claimed by some authorities (Colin, Longet, Corona, Ellenberger, Hofmeister) is due to the mucin which it contains. According to others, saliva promotes gastric secretion when it reaches the stomach, by its alkalinity (Stricker); but this fact is not conspicuous or constant enough to render it of importance. Dogs are apparently none the worse for the extirpation of all the salivary glands, and only require to drink more frequently than usual during their meals (Fehr, 1862).

III. The formation of the bolus is succeeded by the act of Deglutition, which carries it from the mouth to the stomach, through the pharynx and oesophagus. The analysis of the

mechanism of this act is one of the most difficult problems: "*difficillima particula physiologiae*," as Haller termed it. Magendie (1808-13) was undoubtedly the one among modern physiologists who occupied himself most with this phenomenon, and his description, by its simplicity and clearness, leaves nothing to be desired. He was the first to distinguish three stages in deglutition: the first directed by the will, during which the bolus passes from the mouth to the isthmus of the fauces; the second involuntary, of a reflex character, very rapid and almost convulsive, in which the bolus passes the pharynx and reaches the upper part of the oesophagus; the third involuntary, very slow, carrying the bolus into the stomach. The mechanism by which these three acts are performed is essentially the same; it consists in a peristaltic movement by which the bolus is driven onwards and forwards—in the first period by pressure of the tongue against the palate, owing to contraction of the longitudinal lingual and the mylohyoid muscles; in the second by the contraction of the constrictors of the pharynx, which surround and constrict the bolus, carrying it forward, while the larynx and hyoid bone are elevated, and the passage of the bolus through the aperture of the glottis is accelerated; in the third by the progressive contraction of the circular fibres of the oesophagus, dilated by the pressure at which the bolus is driven forward by the contraction of the pharynx.

Many details in Magendie's description are the fruit, not merely of anatomical, but also of direct physiological, observation. This explains how his theory came to be generally accepted, subsequent physiologists only introducing slight modifications and additions, with the object of completing and perfecting it in various ways.

In 1880, however, after the work of Kronecker and his pupils and co-workers, doubt was for the first time cast on this doctrine in regard to its central concept, viz. that the passage of the bolus from the mouth to the stomach was effected by a comparatively slow peristaltic contraction, by which it was driven from section to section till it reached the stomach. In a paper with Falk, Kronecker notes that when iced water is drunk, there is a feeling of cold in the stomach directly after the first gulp, *i.e.* before peristalsis of the pharynx and oesophagus can occur. Forensic medicine, again, has described cases of poisoning by swallowing of corrosive fluids, which showed on examination that the oesophageal lesions were confined to certain isolated points, the greater part of the mucous membrane being uninjured—which would not be the case if the liquid swallowed were propelled down the tube by peristalsis. Pathological observation further shows that while paralysis of the oesophagus makes deglutition difficult it does not inhibit it. Kronecker concluded from these facts that the fluid or semi-

fluid bolus is shot into the stomach by the contraction of the striated muscles, before peristalsis of the oesophagus can take place. Manometric observations show that at the commencement of the act of deglutition there is a rapid increase of pressure equal to about 20 cm. water near the base of the tongue, and also in the gullet, but not in the stomach.

Meltzer performed an interesting series of experiments on himself, to prove that this increased pressure in the retro-buccal space at the commencement of deglutition suffices to drive the bolus rapidly into the stomach. When a sound with a very light rubber balloon at one end (see Vol. I. fig. 192, p. 429), and a recording tambour at the other, is passed down the oesophagus to various measurable depths, two elevations are marked on the

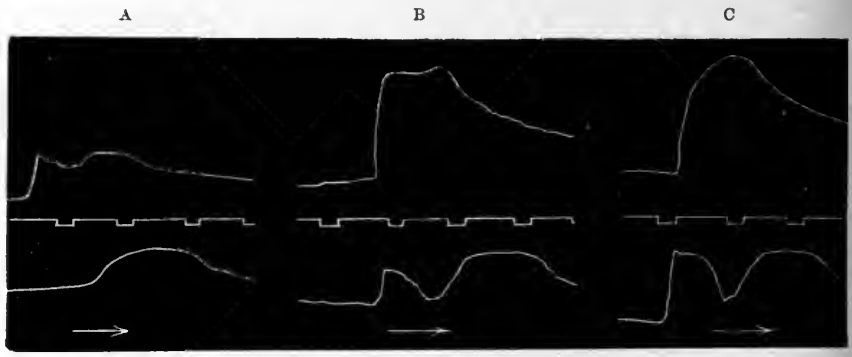

FIG. 53.—Curves of deglutition obtained from himself by Meltzer, on introducing two separate sounds into pharynx and oesophagus. *F*, tracing from pharyngeal sound; *E*, tracing from oesophageal sound, passed 4 cm. down the oesophagus; *s*, time tracing in seconds. A little liquid was swallowed at A; more at B; a large amount at C.

rotating drum at each act of swallowing, which Kronecker terms "signals of deglutition" (*Schluckmarken*): the first signal appears immediately after the act, independent of the depth to which the sound has been introduced into the oesophagus; the second, on the contrary, appears later in proportion as the sound goes deeper. On introducing a second sound into the pharynx, and repeating the above experiment, Kronecker and Meltzer obtained the curves of Figs. 53 and 54.

The rapid rise of the curve from the pharyngeal sound of Fig. 53 signals the moment at which the bolus (or liquid mouthful) shoots down the pharynx, and compresses the balloon. A, B, C show that the height of the elevation is in proportion with the amount of fluid swallowed. The oesophageal tambour marks no rise at A to coincide with that of the pharyngeal tambour, owing to the small amount of water swallowed; but at B and C the passage of the fluid into the oesophagus is clearly signalled by elevations which coincide with those of the pharynx. All three

curves then show a second elevation (about 1 sec. after the first), which depends on the contraction of the constrictors of the pharynx and oesophagus set up by the passage of the bolus. In

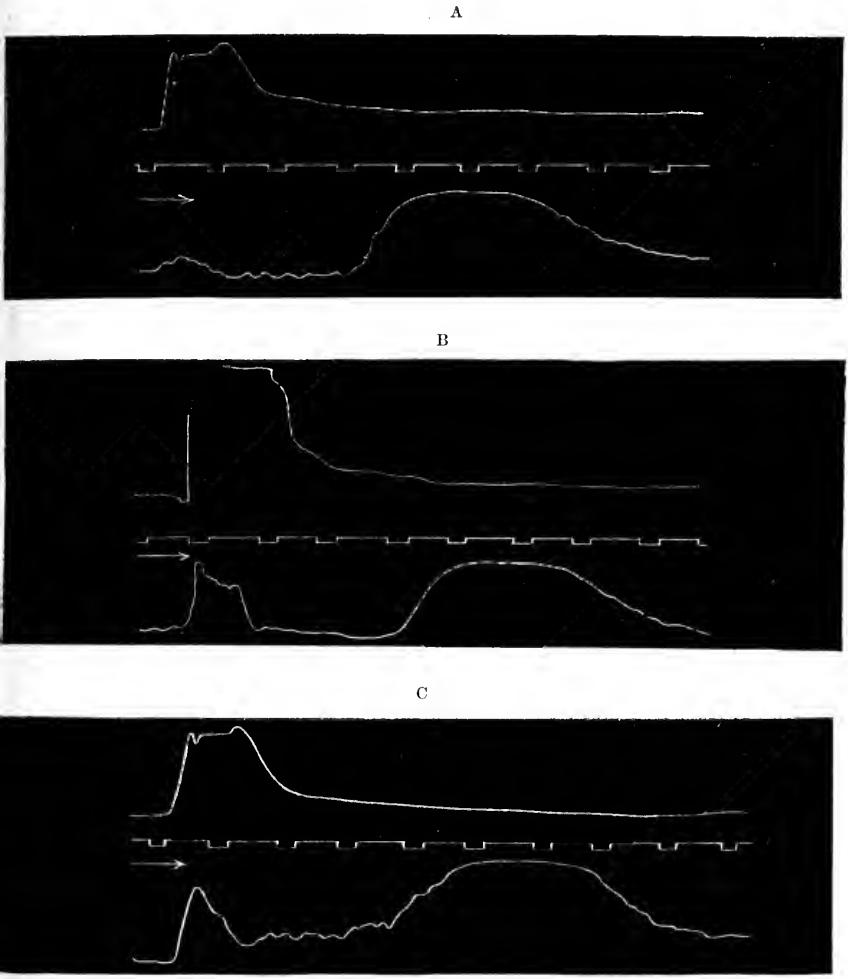

FIG. 54.—Curves of deglutition as in Fig. 53. In A and B the oesophageal sound was passed 12 cm. beyond the opening of the oesophagus; in C, 16 cm. Less water was swallowed at A and C than in B.

fact in the tracings of Fig. 54, in which the oesophageal sound had been introduced farther into the oesophagus, the second rise occurs much later than the first, which practically coincides with the pharyngeal signal.

The first signal indicates the rise of pressure in the gullet

owing to compression from the bolus (solid or liquid), which is driven through the oesophagus by the forcible contraction of the mylohyoid muscles; the second is due to the successive contraction of the pharyngeal and oesophageal constrictors of the pharynx and oesophagus. The increased pressure in the mouth determines the rapid propulsion of the bolus (fluid, or solid reduced to a pulp) into the cardia; the subsequent contraction sweeps away from the gullet any particles of food that are adherent to its walls, and overcomes the resistance of the cardia, driving the bolus into the stomach.

According to Meltzer, the human oesophagus does not contract by peristalsis, as is usually accepted, but in three sections (the first being 6, the second 9, the third 6-7 cm. long), each of which is emptied successively like the several segments of the heart. When the upper part is in maximal contraction, the lower part begins to contract, so that the solid bolus (which cannot like fluids be directly propelled by the thrust of the mylohyoid muscles) is forced to descend towards the stomach. Meltzer succeeded in determining the interval between the contraction of the mylohyoids and of the pharyngeal constrictors (0·3 sec.), between the contraction of the pharyngeal constrictors and that of the first section of the oesophagus (0·9 sec.), between the contraction of the first and second sections of the oesophagus (1·8 sec.), between the contraction of the second and third sections of the oesophagus (3·0 sec.). The sum of these differences represents 6 sec., which indicates the time necessary for the bolus to descend from the mouth to the extremity of the oesophagus, and to overcome the resistance of the cardia and enter the stomach.

Meltzer confirmed his theory by the simpler method of auscultation. On listening with the stethoscope in the region of the stomach, or laterally, at the xiphoid process, a murmur is almost always heard during the act of deglutition. This coincides with the moment at which the bolus (or fluid mass) overcomes the sphincter closure of the cardia and penetrates into the stomach, which takes place 6-7 sec. after the commencement of deglutition, and it is therefore called the *terminal* murmur. In a much smaller number of cases there is, on the contrary, at the initial moment of swallowing, a sharp whistling murmur, as if the liquid swallowed had been shot forcibly and directly into the stomach. When this sound, which may be called the *initial* murmur, is very distinct, the terminal murmur is not heard; when, on the contrary, it is very dull, the terminal murmur is clearly heard as well, though faintly. In a small number of cases no murmur is perceptible on auscultation during the deglutition of liquids.

Meltzer noted that many persons in whom the initial murmur

alone is heard, exhibit atony of the cardia, since during coughing regurgitation of food from the stomach into the oesophagus readily occurs; in those, on the contrary, in whom the cardia is normally closed, which prevents the bolus from entering the stomach immediately, it remains at the lowest part of the oesophagus, until the contractile movement of the latter overcomes the resistance of the cardia, and produces the terminal murmur, which, as seen above, occurs 6·7 seconds after the commencement of deglutition.

The human cardia is thus normally closed, so that the bolus (or fluid mass) must remain at the extreme end of the oesophagus, until the contractile movement of the latter forces it into the stomach. This closure of the cardia explains why the increment of pressure determined by Kronecker and Falk in the gullet during deglutition, does not occur within the stomach.

Kronecker, therefore, differs from Magendie, in not admitting three successive stages in the act of swallowing. He maintains that deglutition occurs in one single act in which the bolus (liquid or pulp) is shot with great velocity and under a relatively high pressure, as far as the cardia. This, he says, is the fundamental mechanism of deglutition, in which neither the muscles of the pharynx nor those of the oesophagus participate, the bolus being allowed to slide through passively. The whole canal contracts in successive sections only when the bolus has already reached the cardia, and this accessory movement is an act complementary to the normal act of swallowing, which may acquire vital importance in cases in which a bolus too large or too hard is being swallowed, and sticks in the oesophagus owing to the insufficient impulse, producing painful sensations of choking, which have to be removed by repeated acts of swallowing and drinking of fluid.

The principal factor in the normal act of deglutition is represented by the muscles of the mylohyoid group, as already recognised by Magendie, Tourtual, Ludwig. Of this we have direct evidence in the fact that on dividing the mylohyoid fibres of the motor branch of the fifth nerve, while the filaments that supply the digastric muscles are left intact, the animal is no longer able to swallow, unless it resorts to the expedient of throwing its head back quickly with the mouth open, so as to jerk the food into the throat, when the pharyngeal constrictors can come into play effectively. The muscles innervated by the hypoglossal are also important to the act of deglutition, which is disturbed by their resection, owing to the consequent paralysis of the longitudinal lingual muscle and of the hypoglossal. By the almost simultaneous contraction of this group of muscles (with which is associated that of the group of elevator muscles of the hyoid bone and larynx), the bolus conveyed to the back of the tongue is pressed between tongue and palate, and driven under strong pressure towards the point of least resistance, *i.e.* towards the retro-buccal cavity,—while the

surface of the root of the tongue, which in the state of rest is turned backwards, retracts, and carries the epiglottis with it, so that the glottis closes mechanically. At the same time, the palate is raised and stretched, not passively, but by the contraction of the elevator and tensor muscles of the palate, so as to occlude and separate the nasal from the pharyngo-buccal cavity, with the assistance of the palato-pharyngeal and the superior constrictor muscles of the pharynx, which contract and bring forward the

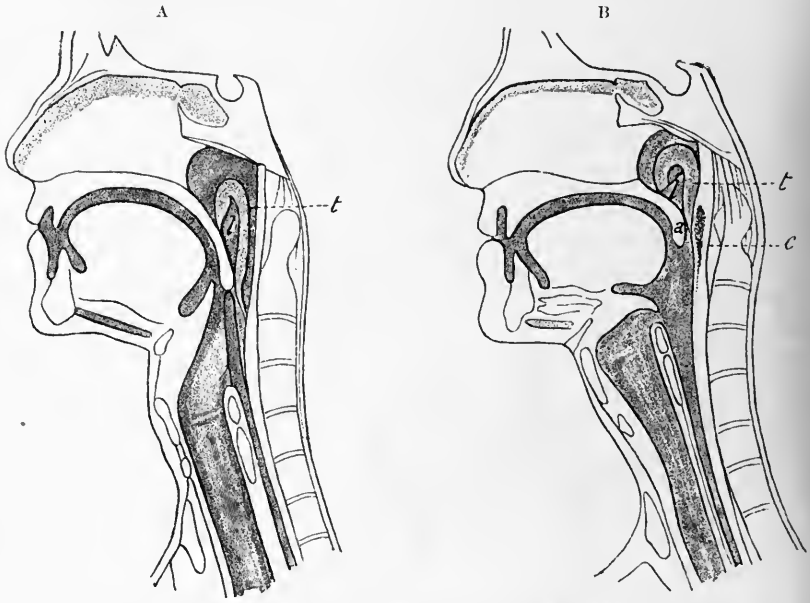

FIG. 55.—Diagram showing position of soft palate, tongue, glottis, pharynx, etc. A, at rest; B, during deglutition. (Zaufal.) *t*, Salpingo-pharyngeal fold; *l*, fold of levator palati; *c*, musculo-superior constrictor; *a*, azygos uvulae which completes the closure of the nasal cavity.

pharyngeal walls forming Passavant's swelling, as shown in Fig. 55. This, according to Kronecker, comprises the fundamental mechanism of deglutition: the rest, as minutely described by certain authors, is accessory, and serves principally to prevent the food or drink from taking the wrong path to the glottis or nasal fossae, and to clear the canal of the food residues, or to drive the bolus (when it is blocked at the lower end of the oesophagus) into the stomach, by overcoming the resistance of the cardia.

Another important fact discovered by Kronecker and Meltzer is that every active movement of swallowing carried out in the primary segment of the alimentary canal, particularly from the contraction of the mylohyoid or hypoglossal muscles, produces an inhibition of the movements of the deeper segments. When, on

drinking a fluid, a series of swallowing movements, separated by an interval of 1-2 seconds, occurs, the subsequent contraction of the oesophagus is produced only after the final gulp. This is easily proved by the method of the oesophageal sound, as seen in the curves of Fig. 56, which also show that the *pause* which occurs between the signal of the last act of swallowing, and that of the subsequent contraction of the oesophagus, is so much longer in proportion as the number of previous acts of swallowing is greater, —as if the production of the acts of deglutition gave rise to a

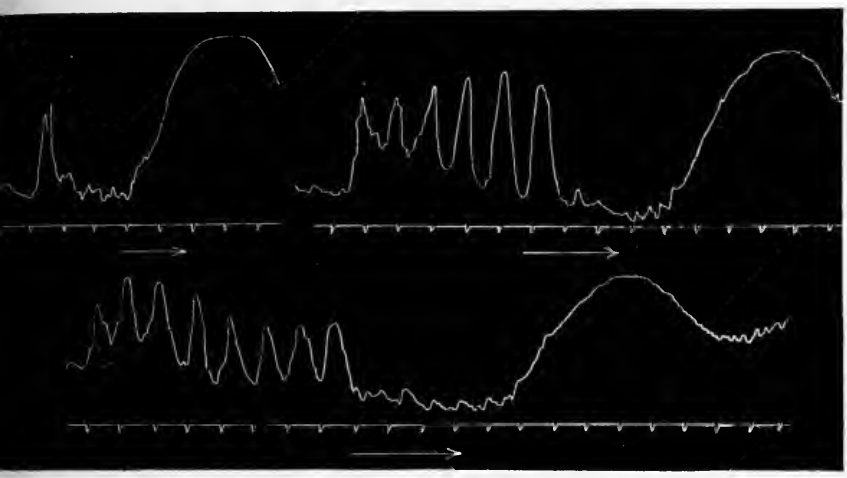

FIG. 56.—Signals of deglutition, recorded by Meltzer from himself, by oesophageal sound introduced as far as the second segment of the oesophagus, *i.e.* 12 cm. below its commencement. In curve 1 (top, left-hand) water was only swallowed once, and the second signal occurred 3 sec. after the first. In curve 2 (top, right-hand) fluid was swallowed six times, and the second signal occurred 4 sec. after the last swallow. In curve 3 eight acts of swallowing were performed, and the second signal occurred 6 sec. after the last.

delay in the conduction of the excitatory process by which the peristaltic movement of the oesophagus is developed.

But if this new theory of the mechanism of deglutition propounded by Kronecker and his school is applicable to fluids and to substances reduced to a pulp, it is doubtful whether it applies to soft alimentary boluses, and to solids, which are sometimes swallowed without, or with imperfect, mastication and salivation. We are indebted to Cannon and Moser (1898) for the valuable observations which have solved this doubt and elucidated the act of deglutition in birds and the higher mammals. They applied the Röntgen rays to this purpose, bismuth subnitrate being added to the food to render it opaque. The fluorescent screen employed was marked at intervals of centimetres with cross lines. A vibrator marking tenths of a second was interrupted whenever the shadow cast by the bolus passing through the gullet crossed a line.

By this method the following conclusions were arrived at:—

The mechanism of deglutition varies according to the animal and the nature of the food swallowed.

In fowls, the movement is slow and peristaltic whatever the consistence of the food. Any jerking of fluid is obviously impossible, because the parts surrounding the buccal cavity are too hard and rigid. Gravity has a predominating importance over the propulsive power of the mouth. Each time the mouth is filled with fluid the head is raised, so that the liquid descends by its own weight into the oesophagus, where it is carried forward by peristalsis.

In cats, according to these authors, the movement of deglutition is always peristaltic and much more rapid than in fowls. The bolus takes 9-12 seconds to reach the stomach. In the upper part of the oesophagus, fluids move more rapidly than semi-solids. In the lower or diaphragmatic parts the velocity, for both liquids and solids, is much less than in the upper parts.

In dogs, the bolus descends to the stomach in 4-5 seconds. It is always propelled rapidly in the upper part, and more slowly below. For fluids the rapid movement may be maintained even in the lower part.

In man and in the horse, fluids are shot into the oesophagus at a velocity of several decimetres per second, owing to the impulse from the rapid contraction of the mylohyoid muscles. Solids and semi-solids are propelled slowly forward throughout the gullet by peristalsis only, and Kronecker's theory is therefore justified in regard to the deglutition of liquids and pulp; but for the deglutition of solids and semi-solids the old doctrine of peristalsis still holds, although it must be understood in the restricted sense imposed by the experiments of Kronecker and Meltzer.

The later work of Zwaardemaker and Eykman, Schreiter, Kindermann and Kahn has not contributed anything really new to the subject.

IV. Deglutition is a characteristically *reflex* act. It is true that it commences as a voluntary process, but this, which Magendie regards as the first period of deglutition, during which the bolus reaches the isthmus of the fauces, has nothing to do with the act of deglutition proper and may be logically regarded as the final moment of mastication (Morat and Arloing, 1880). Magendie devised the following experiment in order to demonstrate the necessity of the peripheral stimulus—*i.e.* the bolus or fluid—to the act of deglutition:—

"Cherchez," he said, "à exécuter de suite cinq ou six mouvements de déglutition, dans lesquels on avalera la salive contenue dans la bouche: le premier et même le second se feront facilement; le troisième sera plus difficile, car il ne restera que très peu de salive à avaler; le quatrième ne pourra être exécuté qu'au bout

d'un certain temps, quand il sera arrivé de nouvelle salive dans la bouche; enfin le cinquième et le sixième seront impossible, parcequ'il n'y aura point de salive à avaler."

Since deglutition normally takes place when the bolus or fluid reaches the isthmus of the fauces, it is evident that the starting-point of the reflex is represented by the contact of the food with the sensory nerve-endings distributed to this region. Wassilieff (Bern, 1888), however, did not succeed in the human throat in finding any point on the tongue, palate, or posterior and lateral walls of the pharynx, at which mechanical, chemical, or electrical stimuli incite the act of swallowing, as the stimulation of the nasal mucosa incites sneezing, and contact with the glottis coughing; we must assume that preparatory movements in the isthmus of the fauces are required in order to excite swallowing in man, these being absent during experimental excitation when the throat is kept quiet. In the rabbit, on the contrary, deglutition is infallibly excited on touching the central part of the anterior surface of the soft palate, which is some 2-5 mm. broad, and 2 cm. long, extending from the hard palate halfway along the tonsils. The least contact in this region produces a complete act of swallowing. Wassilieff succeeded in evoking fifty in succession without finding any fatigue of the reflex nervous mechanism.

R. H. Kahn (1903), who did much careful work on the reflexes of deglutition, found that they were excited in the rabbit by stimulation of the soft palate (trigeminal), in the dog and cat by stimulating the dorsal surface of the pharynx (glosso-pharyngeal), in monkeys by stimulation of the upper part of the palatal arch (trigeminal).

Both in rabbits and in man, anaesthesia of the sensory region with a concentrated solution of cocaine (10-20 per cent) makes the swallowing reflex *impossible* for some time (about a quarter of an hour). This is the best proof that deglutition is not dependent on will, as the respiratory movements are under certain conditions.

The sensory fibres to the soft palate, which are the starting-point of the swallowing reflex in the rabbit, derive from the trigeminal, the sensibility of the palate to reflexes of deglutition being permanently abolished after intracranial division of this nerve.

In 1865 Bidder and Blumberg noted that stimulation of the central end of the superior laryngeal nerve also provokes movements of swallowing. This fact was confirmed by A. Waller and J. L. Prévost in 1870 for both cats and rabbits.

They further found to their surprise that section of both superior laryngeals produced no marked disturbance of deglutition, particularly in rabbits, which survived for months after this operation. On Kronecker's new theory this is not surprising, since division of the superior laryngeals leaves intact the essential

mechanism of the swallowing reflex, which is effected by way of the trigeminal.

As regards the glosso-pharyngeal nerve, both Schiff (1867), and Waller and Prévost found that swallowing was never excited by its stimulation, and concluded that it does not contribute in any way (at least in rabbits) to the reflex phenomena of deglutition. Schiff also noted that the division of those nerves in the same animals produced no disturbance of deglutition. It was left for Kronecker and Meltzer (1883) to discover that the glosso-pharyngeal must be regarded as a nerve which reflexly *inhibits* the swallowing movements. In order to bring out this fact Wassilieff performed the following experiment on rabbits. When, after lateral exposure of the superior laryngeals and glosso-pharyngeals, the former alone are excited, movements of swallowing are performed; when the latter are simultaneously excited with weak induction currents the phases of deglutition occur irregularly and are much delayed; when, lastly, they are stimulated with strong currents, the effect of the superior laryngeals is altogether abolished.

The inferior laryngeals or recurrent nerves also contain centripetal fibres which are capable of exciting the reflexes of deglutition. This fact, as already surmised by Valentin (1846), and by Waller and Prévost (1870), was fully elucidated by Kronecker and Lüscher (1897). They found in a series of experiments on rabbits that the recurrens sends four branches to the cervical part of the oesophagus, the lowest of which innervates the upper part of the thoracic oesophagus also (Fig. 57), and that when the peripheral trunk of one of these filaments is excited even with weak currents, a tetanic contraction occurs exclusively in that segment of the oesophagus in which it ramifies (Fig. 57). When, on the contrary, the whole trunk of the recurrens is excited, the entire cervical part of the oesophagus contracts simultaneously. The peristaltic form of the oesophageal movement that takes place in deglutition must accordingly depend on a delay in the excitation which descends to the three branches of the recurrens in succession from the nerve centre. This agrees with Mosso's earlier and important observation (1873), to the effect that the peristaltic wave of the oesophagus is not arrested in swallowing by ligation, nor by section, nor by extirpation of a quarter of its length; the wave continues to be propagated from the upper to the lower segments. It ceases only after division of the oesophageal nerves. This fact shows that the peristaltic wave of the oesophagus is not a local phenomenon propagated from tract to tract by the muscular coat, as in the intestine; but that it results from the nerve impulses that descend successively by the three branches of the oesophagus from the nerve centres.

Lüscher further noted that stimulation of the central trunk

of the recurrens in the rabbit produced the same effect as that of the superior laryngeal, *i.e.* a swallowing movement confined to the upper tract which is innervated by the trigeminal, the oesophagus being paralysed owing to the occlusion of the centrifugal paths contained in the two nerves resected. In morphinised rabbits, reflex deglutition from the two laryngeals occurs less readily than in the normal; sometimes, however, when the superior laryngeal is out of court, deglutition can be excited by the inferior laryngeal. After bilateral section of the two inferior laryngeals, rabbits die in a few days from pneumonia owing to the blocking of the oesophagus from the paralysis of its muscles.

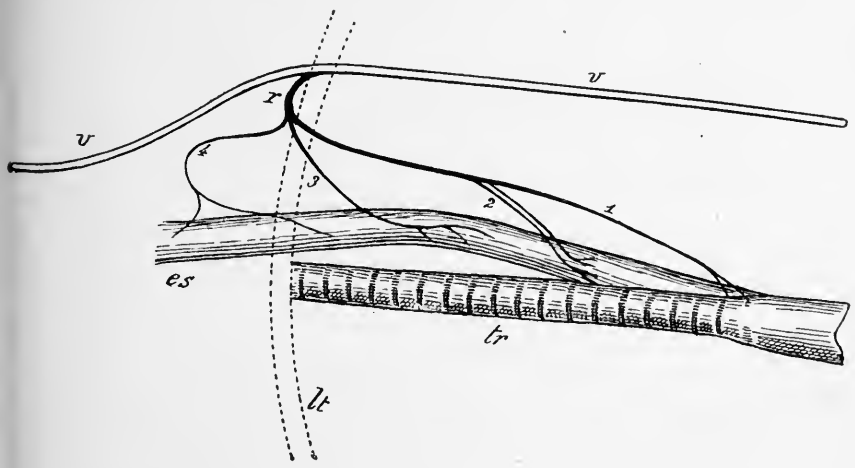

FIG. 57.—Diagram of the four branches of the recurrens which supply different parts of the oesophagus in rabbit. (Lüscher.) *v*, vagus; *r*, recurrens; 1, 2, 3, 4, its branches; *es*, oesophagus; *tr*, trachea; *lt*, border-line of thorax.

The nerve centres which preside over and co-ordinate the movements of swallowing lie in the upper part of the medulla oblongata, for destruction of the brain above the respiratory centres (more exactly above, and external to, the ali cineraee of the rhomboidal sinus) does not abolish the movements of deglutition (Wassilieff, Marckwald). We know, on the other hand, from pathology that the so-called *bulbar paralysis* produces disturbance or inhibition of the act of deglutition. Nothing, however, is known as to the localisation of these centres, on which depends the co-ordination of the successive movements in the various tracts (buccal, pharyngeal, oesophageal) of the alimentary canal.

The centrifugal paths (as may easily be inferred from the above experiments) lie in the motor portions of the trigeminal and hypoglossal nerves for the mylohyoid, hypoglossal, and lingual

muscles; in the vagi and spinal accessory for the muscles of the palate, pharynx, and oesophagus.

The cardia belongs by its movements to the oesophagus, its function being co-ordinated with the swallowing movements in the latter; it contracts after the last part of the oesophagus, and loses its tonicity when the oesophagus is relaxed under the inhibitory influence of the glosso-pharyngeal nerves.

V. On reaching the stomach the alimentary boluses remain there for several hours, according to the nature of the food, and suffer various changes of a chemical character. The importance of the stomach was formerly exaggerated, since it was held to be the centre of the digestive system; and the mass of the food-stuffs transformed by it was known as *chyme*, meaning by this term a pulp differing far more in constitution from the raw materials ingested than it does in reality. As it became recognised that the action of the gastric juice is almost entirely confined to protein, and that even this property is not limited to the stomach but is common to the intestine also, a more reasonable conception prevailed of the functional value of this viscus. The fact that food remains a long time in the stomach is not enough to give it a predominating importance in digestion. The surface of the stomach being relatively small in comparison with the ample surface of the intestine, while it secretes an acid peculiar to itself, it would be necessary (in order that the gastric juice may act effectively) to compensate the limited surface of the organ by a prolonged stay of the food within it. It has, on the contrary, been proved, as we shall see, that food remains longer in the small intestine as a whole than it does in the stomach. Lastly, it is important to note that surgeons (Czerny, Kaiser and others) have succeeded in keeping dogs and man in good condition for months and even years after the excision of practically the whole of the stomach. These facts show that the stomach is in no sense absolutely essential to life. In another connection we shall analyse the details and effects of the operation.

Two methods are employed to study the digestive action of the gastric juice: that of *natural digestion*, which consists in observing the changes the food undergoes in the stomach (when introduced in muslin bags by fistula); and that of *artificial digestion in vitro*, in which the various foods are brought into contact with natural or artificial gastric juice, at a proper temperature. The first method, inaugurated by Beaumont, serves to give an idea of the process as a whole; the second, instituted by Réaumur and Spallanzani, yields a minute analysis of the different phases of the process and the various products resulting from it.

It is easy with artificial digestions to show that the fundamental digestive action of the gastric juice consists in the so-called *peptonising* of the proteins, by which these substances,

whether dissolved, or coagulated and insoluble, are transformed into soluble and readily diffusible substances, called by Lehmann *peptones.*

We cannot enter upon the exposition and critical analysis of the various opinions successively put forward as to the nature of peptonisation, and must confine ourselves to enumerating the more positive of the experimental data:—

(*a*) No protein is (*caeteris paribus*) more readily digested by the gastric juice than fresh fibrin extracted from the blood, and it was therefore chosen by Brücke as the common measure of comparison between the digestive power of artificial and of natural gastric juice. Next to fresh fibrin, casein is the most rapidly digested; next, boiled fibrin; next again, coagulated egg-white. As a rule it may be said that proteins of animal origin are digested more easily than those of *vegetable origin.*

(*b*) Apart from the disparate nature of the proteins, the rapidity of their digestion and solution depends on the degree of temperature, the amount of pepsin, and the amount of acid which the digestive juice contains. The optimum degree of temperature is approximately that which is normal to the body. Below 35° C. digestion is retarded, at 0° C. it is entirely suspended. The amount of pepsin required to obtain a marked digestive action is very small, certainly less than 0·067 per cent. According, however, to Schütz (*infra*), when the amount of the enzyme is increased, the quantity of acid and protein to be digested remaining constant, then on estimating at regular intervals the amount of protein dissolved, it is found that *the rapidity of digestion increases in proportion with the square root of the concentration of the pepsin.* If the amount of acid is varied, while the amount of pepsin and of protein remains constant, it is found that excess or deficit of acid retards or suspends digestion, while the optimum amount of acid varies with the nature of the protein to be digested (*e.g.* for fibrin the optimum is 0·9 per cent of hydrochloric acid, for coagulated egg-white on the contrary it is 1·2-1·6 per cent).

An admirable method for the quantitative determination of the proteolytic power of the gastric juice and therefore of its pepsin content is based upon the Schütz law. This method, as first described by Mett (1894), can also be used for testing the digestive power of trypsin, and is as follows:—

Fresh, liquid egg-white is aspirated into a glass tube with a lumen of 1-2 mm., which is plunged for one minute into water heated to 95° C. The tube of coagulated albumin is then slowly cooked, and cut with a file into small pieces, taking care that the cylinders of egg-white fit exactly the end of each tube, so that no empty space is left in the latter. The glass tubes are then plunged into 1-2 c.c. of the digestive fluid and left for 10 hours at a temperature of 37-40° C. The albumin is evenly dissolved during this time from the outer end of the tube inwards. At the end of the time the length of the little tube and of the column of egg-white left undissolved are measured. The difference gives the length of the cylinder of digested egg-

albumin. Since by Schütz' law the rate of digestion or amount of protein dissolved in the time unit are proportional to the square root of the quantity of ferment, the quantity of pepsin or trypsin contained in the specimen investigated must equal the square of the length of the column of egg-white which it has digested in the given period. Supposing, *e.g.*, that the gastric juice *A* dissolves a column of albumin of 2 mm. while the juice *B* dissolves one of 3 mm., it follows that the amount of pepsin present is as 4 : 9.

(*c*) The presence of the digestive products, particularly of peptones, delays the final digestion of proteins and eventually suspends it. If the mixture be then diluted with water, digestion is resumed. If the peptones are removed by diffusion through a dialyser as fast as they are formed, so that the original concentration of pepsin and acid is maintained, the mixture recovers its initial digestive force. This must occur during natural digestion in the stomach, because the peptones are absorbed as fast as they are formed. In fact, only a mere trace of them can be found in the contents of the stomach during the digestion of protein. Brücke, on the strength of this, assumes that pepsin undergoes no change during its digestive action. Grützner's latest results, however, make it probable that a little of the pepsin is consumed, or loses its enzymatic properties (possibly by combining with other colloidal substances), because even under the most favourable circumstances the digestive power of any juice declines slowly.

(*d*) The addition of concentrated alkalies or acids destroys the digestive action of pepsin, as does heating to 70° C. Bile, too, suspends the action of gastric digestion *in vitro*, even in such a small quantity that the acidity of the juice is not neutralised. This seems, however, not to occur during natural gastric digestion, since Oddi noted no digestive disorders in dogs in which the gall-bladder had been put in communication with the abdominal cavity by a fistula. It is probable that the bile poured into the stomach under these conditions is rapidly absorbed again without admixture with the gastric contents. Or it may be assumed that the absence of digestive disturbance is due to the fact that in dogs the suspension of the gastric function is not of much importance, since it is readily compensated by a more active duodenal digestion.

(*e*) The peptonisation of proteins by the gastric juice is not immediate, but takes place in stages, several *intermediate substances* being formed before reaching the end-substances represented by the *peptones*—by a process analogous to the action of saliva on starch. These modifications of protein by the gastric juice can only be demonstrated by prolonged artificial digestion. After some hours of digestion *in vitro* (at 35-45° C.) of a given quantity of boiled fibrin (or cubes of coagulated egg-albumin) in a very active, artificial gastric juice, at least three different kinds of proteins can be detected in the mixture: an acid albumin or

syntonin, a proteose (formerly called by Schmidt-Mühlheim propeptone), and a peptone.

Syntonin is the first stage in the transformation of fibrin effected by the gastric juice. When the liquid is slowly neutralised by successive drops of sodium carbonate solution, the syntonin precipitates, and can be separated by filtration. To convert boiled fibrin into syntonin, it is only necessary to use a simple solution of 1 per cent HCl, keeping it in the warm chamber for 1-2 days. But if a little pepsin be added to the acid, the conversion into syntonin is much accelerated. Fluid egg-white, on the contrary, according to Meissner, is converted into syntonin in a few minutes, at 40° C. in simple acid solution.

The *proteose* differs from peptone in being precipitated with acetic acid and potassium ferrocyanide in the cold, and redissolved on heating. With concentrated nitric acid there is also a precipitate which disappears on warming and comes back on cooling. When treated with ammonium sulphate, it is thrown out like all other proteins, and this is the best method for separating and estimating the peptone, which remains in solution and passes through the filter.

The *peptone* which remains after separation of all the other proteins from the digestive mixture, occurs in comparatively small quantities, showing that gastric digestion is only partial, and is mainly a preparation of the alimentary proteins for more complete digestion in the intestine. On adding excess of caustic soda or potash and a few drops of copper sulphate to the mixture, it becomes pink (biuret reaction). But proteoses also give the same reaction. In a faintly acid solution the peptones precipitate with phosphotungstic and phosphomolybdic acid, which are therefore used for the isolation of peptone from all the other proteins. It is to be noted that commercial peptone contains a large amount of proteose and very little true peptone.

The proteolytic or peptonising process by which fibrin, egg-albumin, and the other proteins are transformed into syntonin, proteose, and peptone has been the subject of numerous and minute researches, particularly by Kühne and his school; these are to be found in special treatises of chemical physiology. Here we must confine ourselves to stating that the collective term *proteose* includes several similar substances, which are distinguished from one another by various more or less definite chemical characteristics, and that the end-products or *peptones* must also be distinguished according to the nature of the original protein from which they are derived.

This sequence of the transformations of proteins is not due to any specific action of the gastric enzyme: it can be obtained artificially by prolonged boiling with plain water or, better, dilute mineral acids, or by steam at high pressure, by treatment with strong alkalies, lastly by the putrefactive processes produced by bacteria. According to Neumeister, however, the products obtained by these different methods are not identical.

The gastric juice has a solvent action upon all proteins except certain sclero-proteins. It transforms collagenic substances into gelatin, which loses its faculty of coagulation, and is converted into the so-called gelatin-peptone. Mucin, too, is converted into

a carbohydrate substance akin to the peptones. On the other hand, the gastric juice has no effect on keratin, elastin, and certain other substances of this group.

The analysis of the percentage composition of proteins, proteoses, and peptones, as performed by Kühne and Chittenden, suggests that the proteolytic process effected by the pepsin and gastric juice consists not so much in a profound alteration of the structure of the large original protein molecule, as in its subdivision, accompanied by hydration, *i.e.* taking up of water. This theoretical concept explains why many properties are common to all the chemical aggregates represented by the products of digestion—in particular, the great facility with which the peptones and their amino-acid derivatives are reconverted into natural protein in order that the body may utilise them.

Gastric juice acts on the caseinogen of milk and clots it in virtue of its *chymosin* or *rennin*, which (as we saw in the last chapter) is an enzyme distinct from pepsin. According to Hammarsten's admirable researches, this curdling is a process quite distinct from the flocky precipitation of caseinogen, which takes place in the presence of hydrochloric acid, and redissolves on neutralisation. Chymosin splits the caseinogen of milk into two substances—a proteose, which remains dissolved in the serum of milk, and is not precipitated by boiling or the addition of acids, and the so-called casein or paracasein, which in combination with the calcium salts of milk forms the true clot or *cheese*, which is then digested by the action of the pepsin and hydrochloric acid.

A phenomenon apparently analogous with curdling is that first described by Danilewsky (1886) of the precipitation of a clot from a highly concentrated solution of proteoses and peptones (Witte's peptone) by chymosin, pepsin, and papain, as well as by extracts of many organs (pancreas, liver, small intestine, etc.). If the mixture is placed in the thermostat at 35° C., a more or less abundant precipitate is formed after a certain time, to which Sawjawlow gave the name of *plastein* and Kurajew of *coagulose*, and as to the nature of which nothing definite is known.

Since the normal stomach (or intestine) never contains a concentrated solution of proteoses and peptones, Danilewsky's phenomenon cannot be utilised in the complex study of digestion.

It was believed for a long time that the gastric juice had no important action on fats, starches, and sugars. According, however, to Cash (1880) and Ogata (1881), neutral fats can be split up in a minor degree, with liberation of fatty acids. Volhard (1900-2) demonstrated a lipolytic ferment in the gastric juice. His pupil, Stade, not only confirmed the existence of this ferment, but also showed that it conforms to the Schütz law.

On the strength of this, Connstein (1904) concluded that the lipolytic ferment is of great importance in the assimilation of

certain fats, particularly where, as in milk, the fats are emulsified. This especially affects the new-born, who have no pancreas to secrete ferments. The fact that after extirpation or destruction of the pancreas there can still be a certain cleavage and assimilation of alimentary fats, finds partial explanation by the presence of a lipolytic ferment in the gastric juice.

According to Nasse, hydrochloric acid has some solvent action on starch, transforming it into amidulin or soluble starch, which is then, according to Brücke, converted into erythrodextrin; according to Leube, saccharose and lactose are split into monosaccharides.

VI. The influence of the spleen on the digestion effected by the gastric juice deserves special consideration. This point was taken up in our laboratory by Tarulli and Pascucci (1901), who repeatedly compared on different dogs the digestive activity of the gastric juice, before and some days or weeks after the extirpation of the spleen, as well as the digestive power of the gastric juice in splenectomised animals before and after administration of a watery infusion of congested spleen, *i.e.* spleen excised from dogs in full digestion.

Tarulli and Pascucci collected the gastric juice from a fistula made in large dogs by Claude Bernard's method. Before feeding them with the experimental meal (100 grms. cartilage and tendons) which was to promote the flow of gastric secretion, they were given a preparatory meal (500 grms. cooked meat, 500 grms. broth, 200 grms. bread), with the object as far as possible of exhausting the pepsin accumulated in the gastric glands; and after 16 hours the mucous membrane of the stomach was washed out with an isotonic and slightly warmed solution of sodium chloride.

For digestion *in vitro*, a small cube of boiled egg-white weighing 1 grm. was placed in contact with 10 c.c. pure gastric juice at a temperature of 39° C. for 24 hours. From the loss of weight in the egg-albumin, the digestive power of the gastric juice could be determined with sufficient accuracy.

The results of the experiments performed by this method may be summarised in the two following propositions:—

(*a*) After extirpation of the spleen the digestive power of the gastric juice is constantly weakened in a greater or less degree.

(*b*) The administration by the mouth of an infusion of congested spleen 8 hours before the experimental meal increased the digestive power again for one, two, or even three days.

In order to form a concrete idea of these effects, three series of experiments performed on three dogs may be studied in a diagram (Fig. 58, A B C).

It should be noted that the lowering of the digestive power of the gastric juice after splenectomy is apparent not merely in the

first days after the operation, but even two to three months after the removal of the spleen. On the other hand, if splenic extract from an insufficiently congested spleen (excised 2-3 hours after food, or from fasting animals) be administered to the splenectomised animal by the gastric sound, there is no perceptible increase of digestive power in the gastric juice: whereas this is constantly

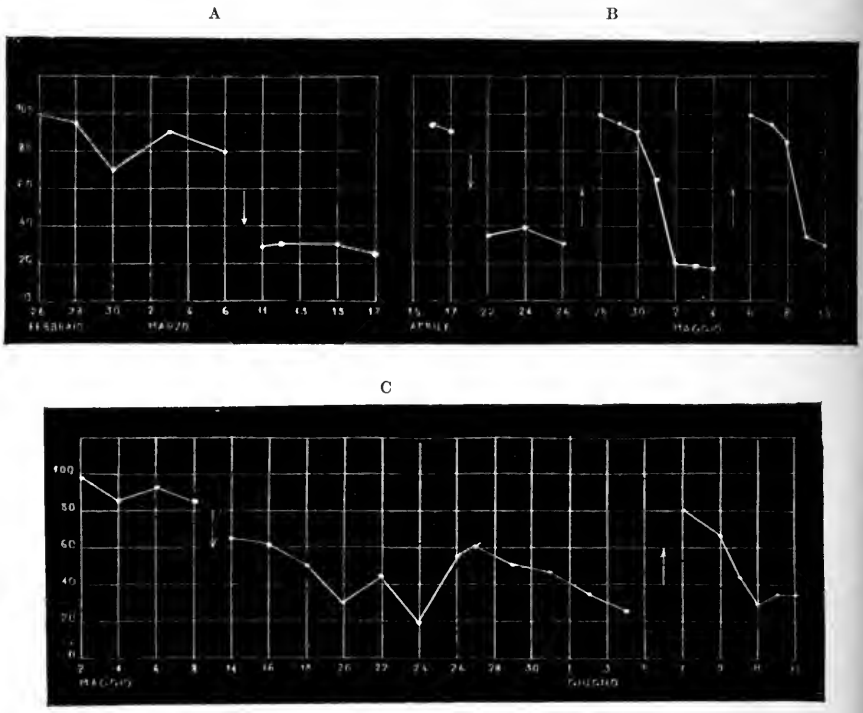

FIG. 58.—Diagram to show digestive power of gastric juice before and after splenectomy, and before and after administration of extract of congested spleen. (Tarulli and Pascucci.) The ordinates express the amount of boiled egg-white digested in cgrms.; the abscissa lines indicate the days on which the experiments were made; ↓ indicates the fall of digestive power consequent on ablation of spleen; ↑ shows the rise due to dosage with extract of congested spleen.

the case when a well-congested spleen (excised 5-6 hours after a meal) is used for the extract.

These results seem on the whole to agree with the old hypothesis of Baccelli as regards the influence of the spleen upon gastric digestion. It is, however, desirable to obtain more definite knowledge of this influence. From what was said above (p. 121), it seems that we may logically assume that the spleen during gastric activity elaborates a pepsinogenic substance which, when carried into the circulation and absorbed by the gastric glands, increases the amount of pepsin secreted.

VII. When we pass from digestion *in vitro* to consider the *natural digestion of food in the living stomach*, a preliminary question at once arises, to the effect that it is not possible from the peptonising power of the stomach, as described above, to arrive at any conclusion as to the process and the degree of digestion normally carried on in the stomach. How far do proteins undergo peptonisation in the stomach before they pass through the pylorus? Is it only the solid or coagulated proteins that are wholly or partially peptonised in the stomach, or the natural proteins as well, which we ingest already dissolved?

With the object of solving this problem, Jaworski and Gluzinski (1885) performed a series of experiments in the medical clinic of Cracow upon healthy individuals and on those who suffered more or less from digestive trouble, pumping out the contents of the stomach at different periods after a meal, in order especially to determine the quantity of pepsin contained, and the degree of acidity. The gastric contents of a healthy man pumped out three-quarters of an hour or one hour after the ingestion of egg-albumin *gave no peptone or syntonin reaction.* Seven hours after a meal of beefsteak the gastric contents of a healthy man, which were very abundant and acid, contained many fragments of meat, but only *traces of peptone,* although the filtrate was capable of digesting bits of coagulated egg-white in the warm chamber, and then yielded a strong peptone reaction. On the other hand, in a person suffering from febrile intestinal catarrh, the stomach, half an hour after the ingestion of an egg, yielded a highly acid fluid, which contained fragments of coagulated egg-albumin, and gave a *strong peptone reaction.*

From a number of fairly concordant experiments, these authors concluded that the formation of digestive products in the stomach is usually very small, and that under normal conditions of gastric digestion an accumulation of such products was never present. In pathological conditions, on the other hand, the acidity of the gastric juice and the amount of digestive products might be very much increased. They concluded that the egg-albumin introduced passed after a certain time (1 or 1½ hours) into the intestine, almost entirely undigested, and that the more quickly the stomach was evacuated, the more normal was its function. So that, according to Jaworski and Gluzinski, the stomach must be regarded less as an organ of chemical digestion, than as a receiver providing for the gradual transit of the food into the intestine where *true digestion* takes place. Gastric disturbance is thus the consequence of abnormally increased digestive chemistry.

This theory, which tends to minimise the digestive importance of the stomach, appears to us to be exaggerated. These observers have not reckoned with the probability that the stomach walls are capable of absorbing peptone as rapidly as it is formed, so that it

never accumulates in the chyme or pulp of the gastric contents during digestion. If this accumulation can take place under pathological conditions, the phenomenon most likely depends on the reduced absorbing capacity of the epithelium, consequent on its catarrhal alterations.

Still it is undeniable that the peptonisation of proteins is very imperfectly accomplished in the stomach, the dissolved protein passing from the pylorus to the intestine before it has time to become peptonised. This is evident from the observations made by Busch (1858) on the famous case of fistula established in the upper part of the jejunum in a woman of thirty-one. Four hours after ingestion of raw egg-white, a ropy fluid which was faintly alkaline, mixed with bile, and free of coagulum, began to flow from the upper end of the intestine; on dilution with water and heating, or treatment with nitric acid, this coagulated in large flocculi. It follows that a considerable part of the egg-albumin ingested passes not only the stomach but also the duodenum, without being attacked by the digestive juices. We shall return elsewhere to the significance of this fact.

Our knowledge of the changes which natural food-stuffs and viands, *i.e.* foods modified by cooking and other manipulations, undergo in the living stomach, rests more particularly on the classical work of Frerichs and Schröder, as confirmed by later observers.

Milk is curdled previous to peptonisation. The caseinogen of cows' and goats' milk forms a firm clot which is more resistant to the action of gastric juice than the caseinogen of human milk, the latter accordingly being the most suited for the alimentation of infants.

Of muscular flesh, viscera, and membranes of animals the collagenous substances of the connective tissues are first digested; they soften and become transparent and eventually dissolve; next follows the digestion of the muscular fibrils, and parenchymatous cells. The fat which infiltrates the connective tissues, and that with which many viands are impregnated, resists the digestive action of the gastric juice, and greatly delays the digestion of the proteins of which tissue protoplasm is built up. For this reason pork is more difficult to digest than the lean meat of beef or veal.

Bone, too, is digested by the combined action of the hydrochloric acid which attacks the phosphates and carbonates of calcium, converting them into soluble carbonates and phosphates, and the pepsin which digests the ossein.

Vegetables and plant tissues in general are more slowly digested than animal tissues, owing especially to the comparative resistance to the action of gastric juice of the cellulose and starch which surround the proteins. Bread, which is the commonest form of food, is reduced to a soft and partially digested pulp in

the mouth, and undergoes few changes in the stomach from the action of the gastric juice, which is confined to starting peptonisation in the gluten.

The duration of gastric digestion, *i.e.* the evacuation by the stomach of the food, varies with the quantity and quality of the latter, according to the individual and to the more or less normal state of the digestive organs. Busch stated that after a copious meal, the flow from the upper end of the fistula in the woman above referred to commenced about half an hour after the meal, and almost or entirely ceased after 3-4 hours.

Many of the sclero-proteins are refractory to the digestive action of gastric juice: *e.g.* elastin, chitin, fibroin, chondrin. The *nucleins*, too, are entirely exempt from the action of gastric juice, a fact utilised by Miescher in separating them. Lastly, *mucin* and the *amyloid substances* are also very resistant to the action of enzymes in general.

The *digestibility* of the various foods or viands, *i.e.* the time required for their digestion and absorption, can only be determined in the stomach by the very relative criterion of their longer or shorter retention there. The tables drawn up from the observations of Beaumont upon the famous Canadian, St. Martin, and his gastric fistula, have therefore little value. The same may be said of similar researches more recently made by other workers. Those of Fermi, however, have a certain value, particularly from the hygienic standpoint.

It is more important to form an approximate notion of the time that the foods which consist mainly of the proteins that can be digested by gastric juice remain in the stomach. In a dog with a gastric fistula, 100 grms. of boiled egg-white enclosed in a muslin bag are digested and disappear after 5 hours; 200 grms. of boiled and minced meat were not completely digested in the dog's stomach for over 12 hours (Schmidt-Mühlheim); 500 grms. raw minced meat were not all digested after 12 hours (Barbèra). All these facts confirm the statement that the task of the stomach is confined to merely initiating the digestion of proteins.

One very important function of the gastric juice is certainly that of sterilising the food and drink ingested, by killing the germs of putrefaction and innumerable pathogenic microbes, and destroying and rendering innocuous the toxines and ptomaines which are formed as the products of their metabolism, or from the putrid corruption of the tissues. This *sterilising and antiseptic action*, which constitutes one of the great defences of the organism to many morbigenic causes, results from the incapacity of the gastric juice to putrefy, and its antiseptic properties, discovered by Spallanzani (1780). He proved in a series of ingenious experiments, which Bunge justly praises as a model owing to the

scientific acumen they reveal, that the gastric juice kept for long periods in closed vessels does not putrefy, although it gradually loses its antiseptic properties; that fresh meat steeped in gastric juice keeps for a long time without putrefying; that putrid meat wholly or partially loses its bad smell in gastric juice, and that the foetid odour disappears in proportion as it is digested, when it is forcibly fed to ravens (attached to a thread by which it can be examined at different intervals); lastly, that when enclosed in finely perforated wooden tubes, and introduced into his own stomach, "it lost even the slightest trace of putrescence."

Modern workers have shown that the process of putrefaction is effected by specific bacteria, and that the antiseptic action of the gastric juice is due to its free hydrochloric acid. In fact Sieber (1879) found that the amount of HCl necessary to retard the putrefaction of meat is approximately equal to the normal acid content of the gastric juice, and that a 0·5 per cent solution of this acid suffices to hinder the development of the saprophytic bacteria. Miquel (1884) confirmed this observation, and found that the addition of 0·2-0·3 grms. HCl to 100 c.c. beef-tea prevented it from putrefying.

The antiseptic and bactericidal power of the gastric juice, of course, has its limits. Some bacteria, particularly in the spore stage, exhibit such resistance to chemical agents that they are only destroyed by hydrochloric acid at a higher degree of concentration than that of the gastric juice. Falk (1883) found the latter inadequate to destroy the tubercle bacillus, while it did kill the anthrax bacillus, leaving the spores intact (Perroncito). According to Nicati and Rietsch, and to Koch (1884), the cholera bacillus is easily killed by a dilute solution of HCl, so that introduction of this culture into the stomach of an animal does not infect it. On the other hand, infection ensues if the culture is introduced into the small intestine or the stomach, after injection of a soda solution. According to Fermi (1894), the gastric juice has no sterilising action on hyphomycetes and blastomycetes, which therefore develop in it and alter its digestive activity. The bacteria of lactic and butyric acid fermentation also seem to resist the gastric juice, since after ingestion of much carbohydrate there is nearly always a slight fermentation with development of lactic and butyric acid. With abnormal catarrhal conditions of the gastric mucosa, the amount of free HCl in the gastric juice diminishes in proportion with the increased secretion of the alkaline mucus. Under these conditions all the bacteria that excite fermentation, particularly those of lactic, butyric, and also acetic and alcoholic fermentation, are able to germinate freely in the stomach. In consequence of this fermentation lactic, butyric, and acetic acid and alcohol develop at the expense of the carbohydrates ingested. At the same time gases are developed, *i.e.*

carbonic acid, hydrogen, methane or marsh gas, and occasionally sulphuric acid (Kuhn, Boas, 1892).

VIII. The effects of complete or almost complete resection of the stomach are highly important from the physiological point of view, in order to form a clear concept of the significance as a whole of its digestive and protective functions.

The dog which survived the almost complete extirpation of its stomach by Czerny and Kaiser, was able 2 months after the operation to nourish itself on the mixed diet of a normal dog, without vomiting or other disturbance. Its weight, 5850 grms. previous to operation, rose in 9 months to 7000 grms. The faeces were normal in constitution. When it was killed 6 years later the post-mortem showed that only a small portion of the stomach was left near the cardia, which had assumed the form of a bladder filled with food.

Ludwig and his pupil Ogata employed another method to suppress the influence of the stomach on the digestion. They introduced the food directly into the duodenum by a fistula made near the pylorus, and to prevent the gastric juice from entering the intestine, closed the pylorus by a small rubber balloon, the distension of which was regulated by means of water introduced through the neck of the balloon, which projected from the gastric fistula. The various foods introduced in large quantities directly into the duodenum (beaten-up eggs, minced meat) were perfectly digested without producing any disturbance. Two injections a day sufficed to keep up the animal's weight. Microscopic examination of the faeces showed that the connective tissue of *raw* meat was not perfectly digested; *boiled* flesh was not digested, and was excreted by the rectum after a few hours, little or not at all modified. *Raw* pork was hardly digested at all, *cooked* pork was to a much larger extent. These authors concluded that the stomach was not absolutely necessary to the nutrition of the body, either as a reservoir of food or in the formation of gastric juice.

In 1893 Carvallo and Pachon successfully repeated the almost total extirpation of the stomach on a dog; in the first 20 days after the operation, the animal only tolerated milk, which was imperfectly digested. Two months later it was still unable to digest the connective tissue of meat. Three months or more from the operation, it was estimated from the nitrogen content of the food and the faeces, that the digestion of cooked foods had become almost normal, while that of raw foods was still imperfect. Five months after, the animal was made to eat putrid meat without any ill effects, a fact which does not minimise the antiseptic importance of the gastric juice, because after such a long period some functional adaptation might have occurred in the animal to compensate for the lapsed antiseptic function of the stomach.

De Filippi in another dog, on which Monari (1893) had performed almost total gastrotomy, repeated the results of Carvallo and Pachon. The latter (1894) also succeeded in keeping a cat of 2 kilos. alive after total excision of the stomach. After 25 days the animal weighed 420 grms. less. The milk administered was not well digested, and clots of it were seen in the faeces.

Among the cases of gastrotomy performed on man was one recorded by Schuchardt, at Stettin. In 1895 he excised the stomach of a patient to a somewhat smaller extent than in Czerny's dog, and the man lived two and a half years in good condition. At first he was only able to take small quantities of food at each meal, but eventually he fed like a normal individual. At the post-mortem a small stomach (formed from a portion of the cardia that had been left) was found which had gradually acquired a capacity of 500 c.c.

The case of the Zurich surgeon Schlatter was more remarkable. In 1897 he excised the whole stomach from a woman of fifty-six in whom it had formed into a hard tumour. Being unable to suture the cardia to the duodenum, he turned the latter into a blind sac, and bound the cardia with a loop of the small intestine. The patient survived this amazing operation, and increased in weight. During the first 8 weeks the food had to be given in very small quantities, and always in a liquid or finely minced form.

A month after the operation, Wroblewski examined the urine and faeces of this patient. For 13 days he found indole in the urine to an amount in excess of the normal, and for 3 days in normal quantity; the scatole was also rather in excess of the normal.

Four months after the operation, Hoffmann made further investigations on the same case and estimated the nitrogen introduced with the food and eliminated with the faeces and urine. He found that the proteins were digested and absorbed in a ratio approximating to the normal. The same was found of the fats.

Five months after the operation, as an index of the putrid processes in the intestine, he determined the amount and ratio of the inorganic sulphuric acid and the ethereal sulphuric acid in the urine. He concluded that, after 5 months, putrefaction was not in excess of the normal. Seven months after the operation the patient had put on about 6 kilos. weight.

In November 1898, Tricomi succeeded in operating on another woman of forty-eight with complete success. This patient suffered from diffuse cancer, like Schlatter's case, and here the very small portion of the cardia that had remained healthy was utilised for the suture, so that this may be regarded as an almost

total gastrotomy. On suturing the duodenum into a blind sac, the continuity of the digestive canal was re-established by uniting the cardia with the duodenum.

Some time after the operation, Deganello performed an interesting series of experiments on this patient with the object of determining (*a*) the digestion, assimilation, and consumption of proteins, which he calculated from the amount of nitrogen introduced and excreted by the faeces and urine; (*b*) the intensity of the putrefactive processes in the intestine, calculating from the ratio between the inorganic and the conjugated sulphuric acid, and the amount of aromatic substances in the urine, more particularly of the phenol, indigo blue, and indigo red.

The most interesting of his results may be summarised as follows:—

(*a*) Forty days after the operation (first period in Deganello's experiments) the digestion and assimilation of nitrogenous substances were not normal. The faeces, under the microscope, showed almost intact muscle fibres; and of the ingested nitrogen 18·22 per cent was eliminated with the faeces, the physiological average of excreted nitrogen not exceeding 6-11 per cent.

(*β*) At this time the faeces also gave indications of very intense putrefaction, as shown not merely by their foetid odour, but also by the marked reaction of indigo blue and red, and by the ratio between the ethereal and the inorganic sulphuric acid of the urine, which had altered from 1 : 4·5 to 1 : 1·72.

(*γ*) Three months after the operation (second experimental period) the digestion and assimilation of proteins had considerably improved, the nitrogen excreted in the faeces having come down to 12·92 per cent of the nitrogen ingested. This agrees perfectly with the data of Carvallo and Pachon, De Filippi, and Hoffmann, who made their observations some time after the operation and found that nitrogen assimilation was almost normal.

(*δ*) In this second period the ratio between the ethereal and inorganic sulphuric acid varied between 1 : 8·4 and 1 : 5·6, showing a marked diminution of the putrefactive processes in the intestine as compared with the first period. This result agreed with that obtained by Hoffmann, who investigated Schlatter's patient 5 months after the operation, and found the ratio almost normal.

From these complex results we may conclude that the stomach is not absolutely indispensable to life. After its total resection the digestion and assimilation of proteins diminish in a first period, while the putrefactive processes of the intestine are much increased. In a second period all these processes are improved and gradually approximate to the normal, by a process of compensation as to the nature of which we are ignorant. At the end of February 1900 (*i.e.* more than 2 years after the operation) this patient was reported by the surgeon to be well, and

able to take nourishment of all kinds in frequent, though not abundant meals.

IX. While the stomach is, in virtue of its glands, a digesting organ, it is from its muscular coats an organ of *special movements*, which serve in the first place to churn up the ingesta and bring them into contact with the gastric juice, and in the second place, to propel the semi-digested chyme onwards into the duodenum.

Beneath the external serous coat the stomach has three layers of plain muscular tissue. These are (from the direction of their fibres) the longitudinal (outer), the circular (middle), and the oblique (inner). The longitudinal fibres are directly continuous with those of the oesophagus; they radiate from the

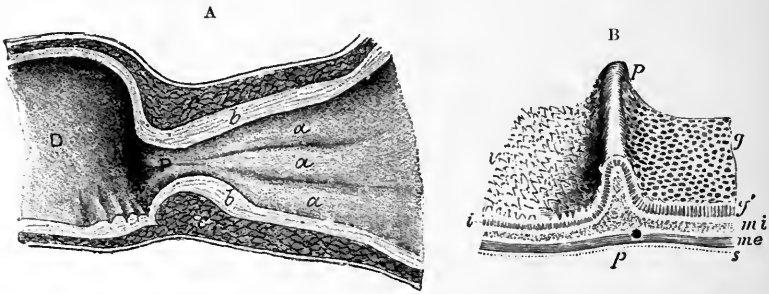

FIG. 59.—A, section through pyloric part of stomach and commencement of duodenum, from specimen hardened *in situ*. (J. Symington.) *a*, *a*, *a*, longitudinal folds of mucous membrane in pyloric part of stomach; *b*, section of mucous membrane; *c*, circular muscular fibres of stomach; the longitudinal fibres are just visible to the naked eye as a narrow line internal to the circular fibres; D, duodenum; P, pyloric orifice. B, diagrammatic view in perspective of portion of coats of stomach and duodenum, including pylorus. (Allen Thomson.) *g*, inner surface of gastric mucous membrane; *g'*, section of mucous membrane with pyloric gastric glands; *v*, villous surface of mucous membrane of duodenum; *i*, section of same with crypts of Lieberkühn; *p*, *p*, ridge of pyloric ring, with section of its component parts; *m i*, circular layer of muscular fibres, seen in the section to form pyloric sphincter; *m e*, longitudinal layer of muscular fibres; *s*, serous covering.

cardiac orifice, are more abundant along the curvatures, and thinly scattered over the remaining surface of the stomach as far as the pylorus, where they form a thick uniform layer, which passes over the pylorus and becomes continuous with the longitudinal fibres of the duodenum. The circular fibres form a close and complete layer over the whole of the stomach. At the pyloric end they become much thicker, and at the pylorus itself they form a bundle within a circular fold of the mucous membrane, known as the pyloric sphincter. Lastly, the oblique fibres are continuous with the circular fibres of the gullet on the left of the cardiac orifice, where they form a considerable stratum; from this point they descend obliquely, and spread out in different directions upon the anterior and posterior surfaces of the stomach; they disappear at the pyloric antrum, mingling with the circular fibres which predominate there (Fig. 59).

In proportion as the stomach fills with food, it dilates, and

changes its form and position; the lower, great curvature moves forward, and the upper, small curvature turns backward. This is effected, when the walls become distended, by a *passive rotation* of the stomach round its axis, which passes through the fixed points represented by the cardia and the pylorus.

As the stomach fills with food, a series of *active movements* are set up which proceed from the cardia along the body of the stomach, and terminate at the pyloric orifice. They are peristaltic in character, the mass of ingesta being churned up, and driven towards the pyloric antrum and back along the lower curvature, so that the upper portion of the gastric contents is continually forced down below. These peristaltic movements are sometimes accompanied by antiperistaltic contractions, which originate in the pylorus, and proceed towards the cardia, but usually stop about half-way down the stomach. The double movement helps to mix up the mass of ingesta, and to saturate it with the gastric juice. At the beginning of digestion the contractions are weak and irregular; afterwards they become more active, to decrease and die away when the formation of chyme is completed.

The evacuation of the stomach during digestion is commonly supposed to be effected by a rhythmical closing and opening of the pyloric sphincter.

These data are mainly due to the observations of Wepfer, Schwartz, Haller, Spallanzani, Magendie, Beaumont. Wepfer (1679) was the first to describe active peristaltic and antiperistaltic movements of the stomach; Magendie (1838) first noted a constriction of the stomach due to the muscles of the pyloric antrum; Beaumont (1834) first observed most of the phenomena enumerated in man. Pönsgen (1882) published a monograph on the motor functions of the stomach, which reviews the entire literature of the subject, and cites over 500 authors.

Morat (1882) used a gastric sound attached to a large rubber balloon with thin walls, which could be inflated with air, the other end of the sound being connected with a tambour. With this he recorded three kinds of abdominal movements on man and dogs—respiratory (predominating), cardiac, and gastric; but this method obviously tells nothing as to the form and localisation of the peristaltic movements.

Pfungen (1887), by the manometric method, succeeded in counting on an average three contractions of the antrum per minute, each lasting 6-12 secs. He noted, in confirmation of an observation by Hofmeister and Schütz, that solid bodies introduced into the antrum were driven back towards the fundus of the stomach by an antiperistaltic movement.

Moritz (1895), with an elastic balloon of medium size attached to the end of a flexible sound passed through the oesophagus, registered the variations of gastric pressure, and recorded the

movements exactly. According to his observations the fundus and the pyloric antrum must be distinguished: the former has mainly a *digestive*, the latter a *motor* function, as exhibited in rhythmical contractions varying in number from 2-6 per minute. Since the antrum fills in consequence of slight peristaltic waves in the fundus, which are set up under very low pressure (2-6 cm. water), the passage of the solid constituents of the gastric contents into the duodenum is prevented. But the balloon which Moritz introduced into the fundus is unable to transmit the peristaltic movements as they succeed each other in the individual segments, and minimises or cancels their effect on intra-gastric pressure. On the other hand (given the relatively small size of the pyloric antrum, and the almost synchronous systolic or diastolic movements of its walls), it is obvious that the elastic balloon can record considerable rhythmical variations of pressure, up to a maximum of 50 cm. of water.

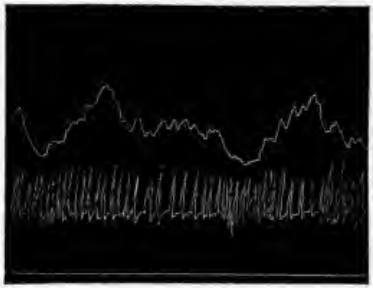

FIG. 60.—Oscillations of tonus in cardiac part of stomach, obtained with a sound introduced into dog by gastric fistula. (Ducceschi.) The lower tracing represents the respiratory movements recorded by a Marey's pneumograph.

Ducceschi (1897) took up this interesting question again in Fano's laboratory, and published an accurate account of the excellent results he obtained, which covered many lacunae and conduced to a clear and satisfactory theory of the active movements of the stomach in relation to gastric digestion.

His experiments were carried out on four large hounds previously provided with a gastric fistula. This operation abolished the negative pressure which distends the stomach; its walls therefore tend to adhere, and a small balloon, 4-5 cm. in diameter, inserted between the two surfaces of the abdominal walls, transmits the movements of the part of the stomach in which it is placed to a tambour with tolerable accuracy.

The animal is made to lie quietly on its side on a table (at least 6 hours after a meal) and the cannula placed in the fistula is opened; through this the sound fitted with the balloon is introduced into the part of the stomach to be explored. Next the balloon and sound are emptied of air by aspiration, and filled with water, and then connected with a vertical glass cylinder, closed above by a cork provided with two glass tubes, one long and dipping into the water, the other short and communicating with the column of air above the water. On joining the latter to a Marey's tambour, the gastric curves are directly recorded, the respiratory curves often being registered as well by a second

tambour connected with a pneumograph. The distension of the exploring balloon is regulated by raising or lowering the cylinder which is fixed in a holder.

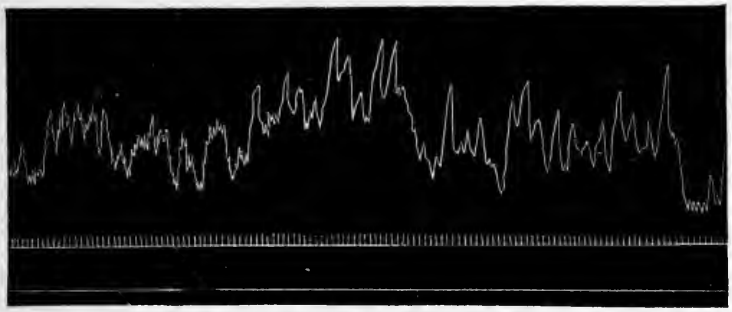

FIG. 61.—Oscillations of tone in cardiac stomach, complicated by more rapid contractions and passive respiratory movements, recorded from dog, as in Fig. 60. (Ducceschi.) Time tracing marks intervals of 5 sec.

When the sound is passed into the cardiac, fundic, or middle region of the stomach in a state of comparative rest, slow, irregular contractions, slight in degree, are observed, which are probably automatic oscillations of tonicity in the gastric muscles (Fig. 60). In a period of greater motor activity, other more rapid, simple contractions appear along the line of this slow primary wave, which are comparable with those that commonly appear in plain muscle (Fig. 61). These oscillations of tonus and contractions vary considerably in duration and intensity; they are never regular and rhythmic. The primary waves on an average last 50-60 secs., the secondary 15-30 secs.

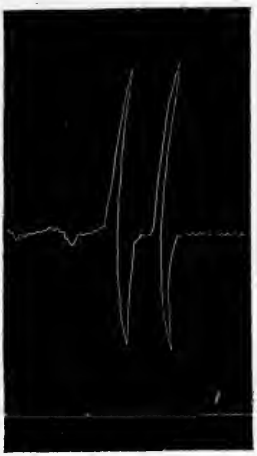

FIG. 62.—Tracings of peristaltic movements obtained under same conditions as Fig. 60, with sound introduced into cardia and fundus of stomach. (Ducceschi.)

If the glass cylinder be somewhat raised so as to increase the swelling of the balloon, and with it the distension of the gastric walls, another form of movement appears with a highly characteristic curve. This is very probably an expression of the peristaltic movement propagated through the stomach from cardia to pylorus. A schema of this movement is shown in Fig. 62. More frequently, however, the tracing of this wave is less simple, and is interrupted by slight notches due to the respiratory movements; the succession of these is very irregular, and abortive forms and a variety of combinations with the oscillations of tonicity already referred to are not

infrequent. These waves have a period of 35-55 secs.; their amplitude usually exceeds the excursion of the writing lever.

When the sound is introduced into the pyloric antrum, a very distinct form of rhythmical movement appears, consisting of systoles and diastoles in regular succession, which are determined by the total contraction or relaxation of the muscles of the antrum (Fig. 63). Each revolution takes 10-30 secs., *i.e.* a shorter period than each peristaltic wave. No other form of contraction due to the tonic state of the walls is ever seen in the antrum, probably because the circular fibres predominate so largely.

The study of the conditions which produce these movements of the stomach and their co-ordination with the several phases of gastric digestion was very incomplete prior to Ducceschi's observations.

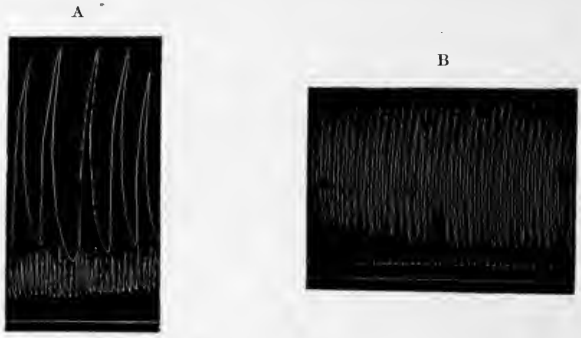

FIG. 63.—Rhythmical systolic and diastolic movements obtained with introduction of sound into pyloric antrum. (Ducceschi.) A, the lower tracing represents the respiratory rhythm. B, time tracing marks 10 sec.

According to some authors, the gastric movements after a meal begin after a brief period of tonic contraction, *i.e.* shortly after the ingestion of foods (Eberle, Blondlot, Brinton, Beaumont, Busch, Kussmaul). According to others, on the contrary, the meal is followed by a period of tonic contraction lasting about an hour, after which the movements set in with increasing intensity, reaching their maximum after 3-4 hours (Magendie, Adelon, Schiff, Leven). All, however, agree that liquid foods pass rapidly through the pylorus into the duodenum a few minutes after ingestion. The best observations have been made on man, or on dogs with a duodenal fistula (Busch, Kühne, Hirsch, v. Mering, Moritz), which show that the contents of the stomach, particularly the liquid parts, are spurted into the duodenum a few moments after the meal.

Leven (1902) specially investigated the time during which fluids remain in the stomach. A measured quantity of water was administered to dogs that had fasted for 24 hours; they were

then killed at different periods, and the quantity of water left in the stomach was measured. In the first 12 minutes nothing was absorbed or expelled by the pylorus; after 15 minutes evacuation commenced and was completed after 30 minutes.

In children the water in the stomach can easily be detected radioscopically. The rapidity of expulsion varies very much; in some children it begins at once, in others after 13 minutes. In some the horizontal level of the fluid sinks gradually, no waves of muscular contraction being perceptible; 100-125 c.c. of water required 8-13 minutes for evacuation; 250 c.c. 19 minutes; warm water disappears faster than cold; the presence of solids in the stomach delays evacuation to a remarkable extent. In another group of children muscular contraction obviously co-operates. The time required by the stomach for evacuation varies considerably, according to the nature and quantity of the food. Nearly every one, however, agrees that after 5-7 hours the stomach is usually almost empty, unless there has been an excessively abundant meal, as we saw in discussing gastric digestion.

By some the distension of the stomach walls by the presence of food is held to be a mechanical stimulus to the excitation of gastric movements. Spallanzani first pointed this out in birds. A guinea-fowl that had fasted for a day was made to swallow hazel-nuts, and its stomach watched through an aperture made in the abdomen. "As long as the stomach contained only a few nuts, no movement was visible, but as it became filled I saw it swell out, and suddenly get flat again," *i.e.* it exhibited systoles and diastoles similar to those observed in the dog's pyloric antrum.

Schütz observed regular peristaltic movements in a dog's stomach, isolated from the body, after insufflations of air through a cannula tied in the oesophagus. This is a reflex phenomenon, discharged by the mechanical stimulus, and effected by the ganglion plexus situated in the stomach.

Many authors have verified Magendie's discovery that a solid body introduced into the pyloric antrum is at once shot out, and falls into the fundus. This proves the excitability of the stomach to mechanical stimuli, under conditions not far removed from the physiological.

Some interesting details can be deduced from the work of Ducceschi. Twenty-four hours after a meal the stomach is immobile, its movements commencing immediately after food. Introduction of an exploring balloon into the empty stomach, however, at once excites the movements. In proportion as the distension of the balloon increases by the introduction of a constantly increasing amount of water, the gastric movements become more ample while their rhythm is approximately constant. There is, however, a limit to the distension of the stomach,

after which its movements diminish, and are finally abolished (Fig. 64).

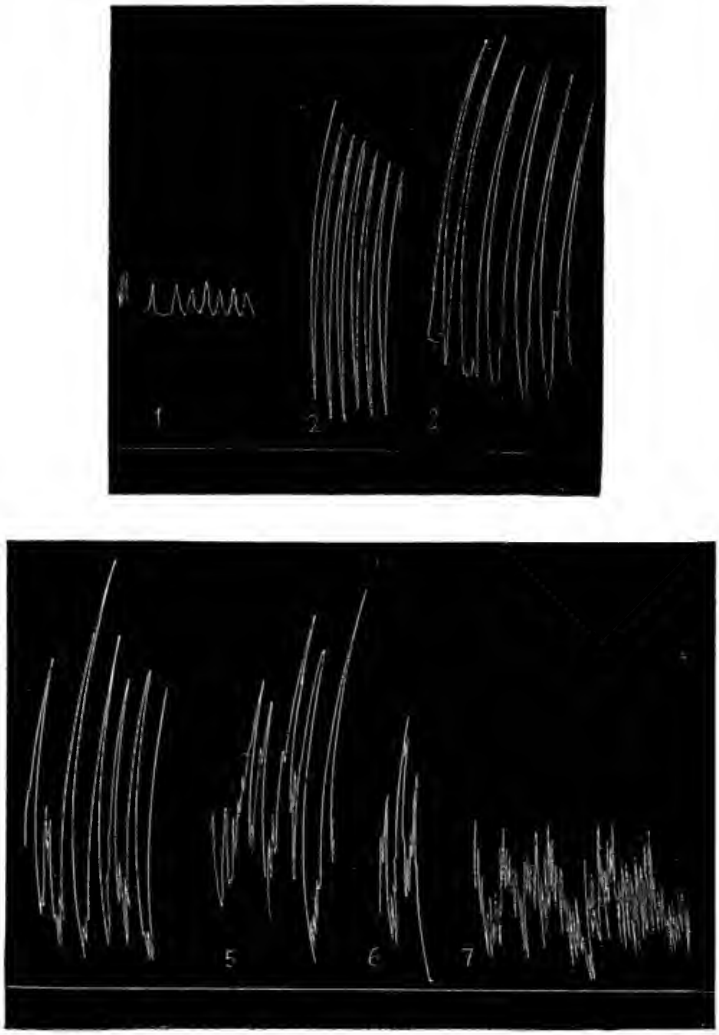

FIG. 64.—Tracings of pyloric rhythm and its variations under the influence of progressive increments of pressure. (Ducceschi.) At 1, the exploring balloon exerted very weak pressure on the walls of the antrum; at 2, the pressure was increased by addition of 50 c.c. water; at 3, 4, 5, 6, 7, respectively, 50 c.c. water were added, by which the balloon became more and more distended.

On exciting the stomach by a sound with a rough surface, peristaltic movements are set up in the cardiac portion and fundus; in the region of the pyloric antrum, on the contrary, the rhythm

becomes disorganised, antiperistaltic waves occur, or there is tetanic contraction of the walls (Figs. 65 and 66).

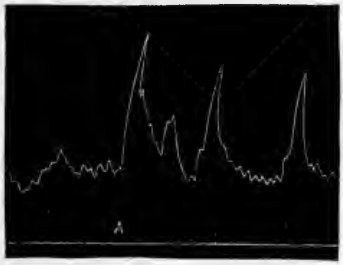

FIG. 65.—(Left.) Tracing of pyloric rhythm and its modifications under rapid mechanical excitation. (Ducceschi.) At *A*, the experimenter jerked the sound. Time tracing marks each 5 sec.

FIG. 66.—(Right.) Tracing from fundus of stomach. (Ducceschi.) At *A*, a marked increase of movement was obtained by rapidly shifting the sound.

As regards the chemical stimuli that excite movements in the stomach, Brücke ascribes great importance to the acid content of the gastric juice, and proves that the movements are more or less energetic in proportion with the digestive work. According to Schiff, on the other hand, chemical stimulation of the stomach is more particularly due to copious absorption of the digestive product (peptone), which is supported by the fact that towards the end of digestion there is constant reinforcement of the movements of the stomach.

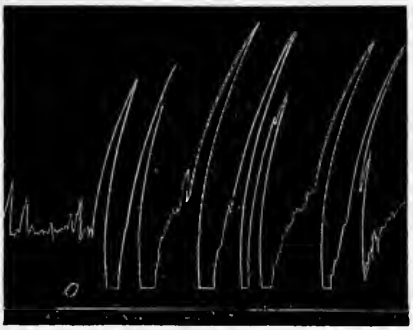

FIG. 67.—Tracing from cardiac stomach in which peristaltic movements were excited by introduction of HCl solution. (Ducceschi.) At *O*, 40 c.c. of 0·25 per cent HCl were injected near the exploring balloon.

Ducceschi, to test these views experimentally, introduced 30-50 c.c. of 0·15 per cent HCl in the vicinity of the exploring balloon, and found that in the region of the cardia and fundus, particularly in the former, movements were clearly excited, so much so as to produce typical peristaltic waves (Fig. 67). In the region of the antrum, on the contrary, he obtained quite different results; a 0·1 per cent solution of acid

produced a delay in the systolic and diastolic rhythm; stronger solutions disorganised its course, and weakened its intensity; stronger solutions still were able to arrest it, or to incite anti-peristaltic movements (Fig. 68).

On injecting solutions of peptone (1-2 per cent), Ducceschi obtained increased tonicity of the gastric walls, and reinforcement of the movements proper to the several regions of the stomach.

These and other effects of thermal and electrical stimuli on the different parts of the stomach, led Ducceschi to conclude that the excitability of the neuro-muscular apparatus of the stomach did not merely vary *quantitatively*, but was also *qualitatively*

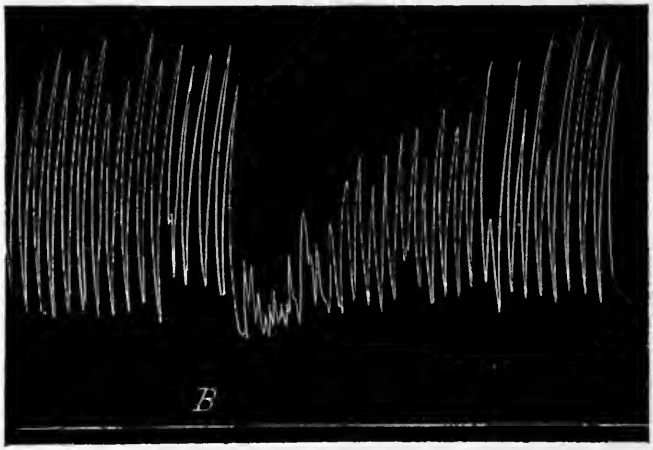

FIG. 68.—Tracing of rhythm in pyloric antrum, profoundly altered by excitation due to introduction of HCl solution. (Ducceschi.) At *B*, 40 c.c. 0.4 per cent HCl were injected near the exploring balloon.

different and almost antagonistic in the region of the pyloric antrum, as compared with other regions of the stomach.

This important conclusion agrees perfectly with the results arrived at by Openchowski and his school (1889) in their valuable work on the innervation of the stomach, to which we shall refer below.

Ducceschi reconstructs the motor functions of the stomach, in co-ordination with its digestive processes, as follows: The descent of the food into the stomach produces distension of its muscular coats, which determines the peristaltic movements in the region of the cardia, fundus, and body of the stomach, while the secretion of the gastric juices occurs at the same time with an increasing degree of acidity. This factor again reinforces the movements, and in proportion as the digestive process advances, the tonic and partially motor action of the peptone is added to the motor action

of the hydrochloric acid. This explains how the movements arise and are kept up in the greater part of the stomach.

The rhythmical movements of the pyloric antrum follow a different course, in consequence of the same mechanical and chemical stimuli. The food which fills and distends this region suppresses the rhythmical movements by the acidity of the juice with which it is saturated and the solid particles which it contains, obstructs the pyloric orifice, and produces antiperistaltic waves, which carry the food back towards the middle and fundus of the stomach. The pyloric antrum thus contributes to the churning up and mixing of the ingesta, which is a necessary condition in order that they may be saturated with the secretion, and digested.

At a certain stage in digestion the motor processes of the stomach undergo an important modification. The solid constituents of the food-stuffs are almost entirely dissolved, or at any rate the mechanical effects of contact are much diminished, and the acidity of the chyme reduced, on which the antiperistaltic motions of the antrum subside, and it resumes the rhythmic (systolic and diastolic) movements proper to it, while the tonic spasm of the sphincters or pyloric valve ceases. Then at each revolution of the antrum there is a little spurt of chyme into the duodenum, synchronous with the opening diastole of the pyloric orifice, as has often been observed directly in duodenal fistulae.

There is thus, according to Ducceschi, a complete correspondence between the chemical and dynamical functions of the stomach, which justifies the assumption that (like the adult heart, according to Kronecker) it possesses a nervous, self-steering, regulating apparatus, for its functions as a whole (*infra*).

Moritz (1901) has recently investigated the influence of the nature of the food-stuffs on the rate of gastric evacuation in dogs with duodenal fistulae and in man. The experiments on man (principally on Moritz himself) were conducted as follows: Some time after a test meal of known quantity and quality, a measured amount of a known solution of some chemical product which can be readily estimated and is not normally present in the ingesta, was introduced into the stomach by the sound. After thoroughly mixing the liquid with the gastric contents, by introducing air into the stomach and violently shaking the body, a portion of the mixture was drawn out again by the sound. From the lowered concentration of the test substance (usually glucose), it was easy to determine the quantity left behind in the stomach. Moritz found that the mechanical consistency of the food was an essential factor in the evacuation of the stomach. The gastric contents are not passed on into the intestine in the form of solid pieces, nor exclusively in the fluid state, but largely in the form of pulp. Fluid foods (broth) are, however, more rapidly evacuated than thick soups or sops.

The consistency of the food is not, of course, the *sole* factor that determines the rate of gastric evacuation. If this were so, all mobile fluids would leave the stomach with the same rapidity, which is not the case. On introducing half a litre of water, 60 per cent is eliminated in 15 minutes, while if the same quantity of beer is introduced, only 11 per cent is excreted. Milk, soup, sops, again, stay longer in the stomach than would be expected, judging merely from their consistency. Moritz interprets this fact as meaning that all these substances (unlike water, which is an indifferent substance) function as stronger chemical, and partly also as mechanical stimuli, as shown also by a greater secretion of acid. On the strength of this fact, Moritz holds soups to be a food, particularly adapted to prepare the stomach for the introduction of more solid viands.

The application of *radioscopy* (by admixture of bismuth subnitrate with the food) to the study of the movements of the stomach in digestion, has led to a distinct advance in methods and comparative results. The most interesting researches in this direction are those of Cannon (1898), and Roux and Balthazard (1907), both with the usual animals experimented on and with man.

According to these authors the stomach may functionally be divided into two portions, the fundus (or cardia) and the pylorus. The latter is mechanically the most active part of this organ, and exhibits, radioscopically, ample peristaltic movements throughout the whole period of digestion.

The cardiac region only shows rare waves of contraction which propel the food-stuffs towards the fundus. In the fundic part the chyme travels very slowly in the direction of the pyloric antrum. The movements of the pyloric antrum are set up in the part nearest the fundus (pre-antral constrictions), and are mainly effected by the circular fibres; the antrum contracts vigorously and assumes the form of a tube. The (peristaltic) contraction waves are separated, both in animals and in man, by an interval of 10-20 secs. The pyloric orifice rarely opens in the first period of digestion, while towards the close it relaxes in response to each contraction of the antrum.

The chyme is almost stationary in the fundus: it passes slowly into the pyloric antrum where the food is thoroughly mixed with the digestive juices and dissolves, owing to the vigorous movements in this region. The alimentary mass, while continually passing from fundus to antrum, perpetually flows back (especially in the first periods of digestion) from antrum to fundus owing to the increased pressure, which gives rise to the peristaltic waves in the antrum when the pylorus remains closed. The chyme passes more quickly and in larger quantities into the intestine, in proportion as it is softer and more liquid in consistency. The pyloric orifice opposes the passage of solid foods. On mixing

some hard boluses of bismuth subnitrate with the soft foods, the pyloric sphincter is seen, radioscopically, to close sharply on the arrival of the bolus.

These results are particularly important because they confirm to a great extent for uninjured man or animals, the observations made by means of fistulae, or other methods, in which the normal conditions of gastric digestion have been more or less modified.

X. Since it is one of the most important modifications of the ordinary motor processes in the stomach, special attention must be given to *vomiting*. In the majority of cases it is a pathological phenomenon, but is under certain conditions a true physiological act, by which the body relieves the stomach of excessive work, and eliminates noxious substances ingested or developed *in situ* by abnormal processes of fermentation. Vomiting is excited either by excessive distension of the stomach, or by the acrid substances developed in abnormal digestive processes, or by the action of the so-called *emetics* which are particularly adapted to excite the nervous mechanisms that give rise to vomiting.

The fundamental question in regard to the mechanism of vomiting is to decide what part the stomach plays by its contractions, and what is due to *abdominal compression*, which consists in the synchronous contraction of the abdominal and diaphragmatic muscles.

The older physicians held vomiting to be purely an effect of the antiperistaltic movements of the stomach, with simultaneous closure of the pylorus and dilatation of the cardia. Bayle and Chirac, and after them Magendie, sustained the opposite opinion, viz. that the stomach was passive in vomiting, and that the process rests upon the violent impulse of abdominal compression.

Schwartz demonstrated that the stomach, when exposed and freed from the pressure of the abdominal muscles and diaphragm, was no longer capable of emptying itself by vomiting on injection of tartar emetic. He did not, however, deny the active participation of the stomach. Magendie (1813), went farther. He was unable to convince himself of such participation, either by palpation or by inspection. It appeared to him to be an *experimentum crucis* that vomiting was accomplished perfectly when the stomach was replaced by a pig's bladder filled with water. Giannuzzi (1866) supported this theory by his observation that curarised dogs could not vomit when tartar emetic was injected.

But this fact does not prove that the stomach is passive, only that vomiting requires the aid of abdominal compression. Tantini (1825) was the first to prove this by a modification of Magendie's experiment in which he substituted a bladder for the stomach, but without interfering with the cardiac orifice. Under these

conditions the stomach was not evacuated in spite of the most vigorous impulses of abdominal compression.

On the other hand, we know that in coughing and in defaecation, when the abdominal muscles and diaphragm come energetically into play, there is no vomiting, because the stomach remains passive. Schiff (1867) further noted that in certain nervous affections vomiting is inhibited, notwithstanding the most powerful efforts of abdominal compression. He also adduced the fact that in fistula-dogs it has been proved by introducing a finger in the direction of the cardia that it dilates actively during vomiting, owing to the contraction of the longitudinal fibres which spread out from the oesophagus into the cardia. In fact, when these fibres were divided in the dog he found that vomiting no longer occurred.

At the commencement of vomiting, Schwartz often observed contraction of the longitudinal layer of gastric muscle fibres, which commenced at the pylorus, and brought it nearer to the fundus. The surgeon Patry (1863) made observations on vomiting in a young man who was wounded after a heavy meal and had an abdominal aperture and protrusion of the stomach. On replacing it in the peritoneum vomiting ensued, during which strong but slow contractions were seen from pylorus to cardia, until the stomach had entirely emptied itself without assistance from the diaphragm and abdominal muscles.

In order to demonstrate the active participation of the stomach in vomiting, Openchowski (1889) paralysed its movements by ligation of the thoracic aorta above the diaphragm. After inoculations of apomorphine or lobeline he saw energetic spasms of sickness, without the least regurgitation of the gastric contents. On removing the ligature from the aorta, regurgitation occurred regularly. He described the modifications of the normal peristalsis of the stomach under the action of emetics (copper sulphate, apomorphine). There is at first disquiet of the intestines, then spasm of the pylorus, followed by contractions of the antrum, which are propagated as antiperistaltic waves to the lower and middle third of the stomach, while the upper or cardiac part widens at the same time, so that the viscus finally assumes the form of a pear with its dilated part turned upwards—the contents of the stomach being forced out at the oesophagus. In most cases the dilatation of the cardiac part precedes the antiperistaltic motions of the remainder which (particularly at the pyloric antrum) are the main factors in the act of vomiting. This cycle of phenomena is repeated many times, periodically, in the form of spasms.

Lüttig (1873) was the first to note at the beginning of vomiting a strong inspiration and closure of the glottis, which must produce considerable negative pressure inside the thorax, sufficient to

aspirate the contents of the stomach into the oesophagus, if the cardia be opened simultaneously. This mechanism is facilitated by the simultaneous rise in abdominal pressure owing to the contraction of the diaphragm and abdominal muscles. The *retching* which precedes evacuation of the gastric contents is due to this oesophageal aspiration.

Lastly, in vomiting, there is an elongation of the oesophagus, caused by the contraction of its longitudinal fibres, and by the movements of mouth, pharynx, and larynx, as thoroughly worked out by Dzondi (1831). The closure of the pharyngo-nasal cavity and glottis is effected by a mechanism identical with that which occurs in the act of deglutition; but, contrary to deglutition, the tongue and roof of the mouth are not raised but are lowered, because in vomiting the mouth must be open. According to Dzondi the mouth, which is relaxed in deglutition, must contract in vomiting, to resist the passage of the contents of the stomach by the choanus.

XI. The *innervation* of the gastric muscles is still a very obscure and imperfectly studied field. The observation of various experimenters, particularly Hofmeister and Schütz, to the effect that the stomach, when excised from the body and brought into a warm glass chamber, is capable, like the heart, of performing spontaneous movements, shows that it possesses in itself all the conditions necessary to its movements,—its automatic and reflex centres being probably represented by the gangliated groups in Auerbach's plexus. This fact, however, does not exclude the controlling and regulating influence of the cerebrospinal nervous system, transmitted to the stomach by way of the vagi and splanchnics.

Longet first suggested that the vagi exercise a motor influence on the stomach, which, however, in his opinion is manifested only after a meal, and not on the empty stomach. S. Mayer, Russo-Giliberti, and Morat confirmed this influence of excitation. Division of the vagi, on the contrary, gives very uncertain results: according to some the gastric movements persist (Magendie, Bidder and Schmidt, Donders, Schiff); according to others they are suspended or at least much attenuated (Rawitsch, Milne-Edwards, Joh. Müller, Longet).

A fact worth noting, as deduced from physiological research and anatomical control, is that the two vagi are not (as commonly stated in the text-books) distributed, the right to the posterior surface and the left to the anterior surface of the stomach. Both in the higher mammals and in man, the two vagi course together and form in the lower part of the oesophagus, with fibres common to both, one trunk which runs to the anterior plexus, and a second which is continuous with the posterior gastric plexus (Ducceschi, Dorello).

The action of the sympathetic system is less well established. Some deny that it has any effect on the movements of the stomach (Joh. Müller, Oehl, Longet); others credit it with a motor influence (Budge, Donders, Brinton, Schiff, Adrian, Goltz, Russo-Giliberti); others, again, recognise in the splanchnics and the sympathetic fibres from the caeliac plexus in general, inhibitory or moderator nerves of the gastric motions (van Braam-Houckgeest, Morat, Convers).

The numerous researches of Openchowski and his pupils, v. Rosen, v. Knaut, Dobbert, Hlasko, Fransen, on rabbits, cats, and dogs, which are collected in two publications (1889), led to a remarkable consensus of results in regard to the central and peripheral nervous mechanisms that regulate and co-ordinate the movements of the stomach. In order to facilitate this point, Fig. 69 reproduces Openchowski's schema.

In the stomach of new-born rabbits, treated with gold chloride, Openchowski discovered ganglionic nodules which are distinct in structure and position from those of Auerbach's plexus, and resemble Remak's and Bidder's ganglia in the heart. They are scattered in the serous coat, and are in relation with the fibres of the vagus and the sympathetic system, which run to the stomach. Eleven such groups can be distinguished in the cardia, and seven in the pylorus (G G of figure). In the walls of the stomach they are fewer, and consist of a smaller number of cells. He believes that the movements of the stomach which persist after its separation from the cerebrospinal centres depend on these ganglia, to which he assigns an automatic function. This part of Openchowski's theory calls for direct experimental confirmation.

According to the Dorpat physiologist, the cerebrospinal centres on which the regulation of the movements of the stomach depends, are situated in the posterior corpora quadrigemina, in the nucleus of the corpora striata, the cortex of the sulcus cruciatus, the olivary bodies, and the grey matter of the upper tract of the spinal cord. The efferent paths run in the vagi, the splanchnics, the spinal chain of the sympathetic, and the caeliac plexus. The afferent paths leading directly or indirectly to these centres have not been exactly determined, but must, as we shall see, be very numerous.

Excitation of the median part of the sulcus cruciatus of the cerebral cortex causes a slight dilatation of the cardia associated with the contraction of the pylorus. It therefore contains two centres which have an antagonistic action, probably because they produce the contraction of the longitudinal muscle fibres, which predominate at the cardiac orifice, and of the circular fibres, which constitute the pyloric sphincter. The efferent paths for these two centres run exclusively with the vagus nerves.

The caudate and lenticular nuclei contain more important

centres which act in the same way and with more effect, on both cardia and pylorus, causing the former to dilate, and moderating the movements of the latter, without, however, causing it to open. The efferent paths from these centres also run in the vagi.

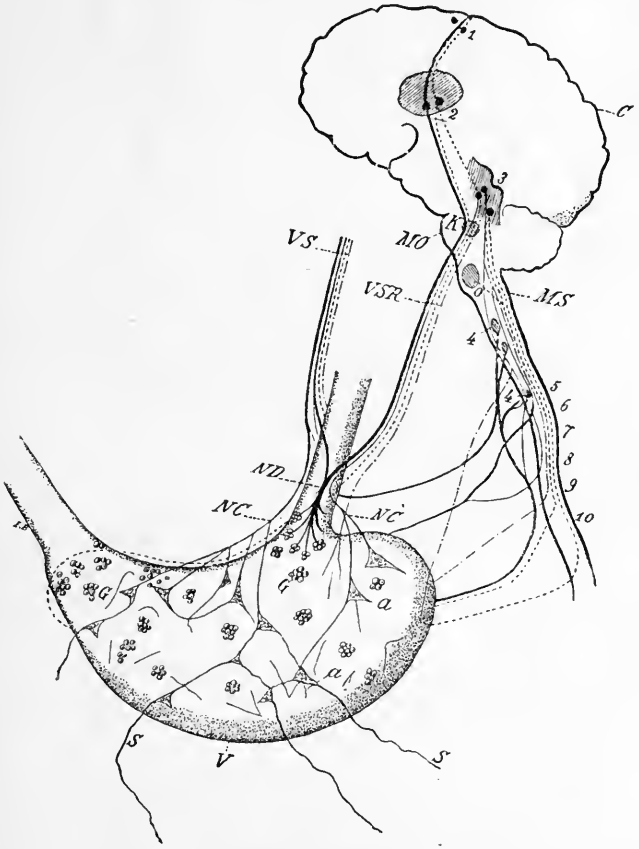

FIG. 69.—Diagram of nerves and nerve centres that regulate movements of stomach. (Openchowski.) *C*, brain; *V*, stomach; *MO*, medulla oblongata; *MS*, spinal cord; 5–10, level of corresponding dorsal vertebrae; *VSR*, trunk of right vagus; *VS*, trunk of left vagus; *ND*, dilator nerve of cardia; *NC*, constrictor nerves; *c*, plexus of Auerbach; *G*, ganglia described by Openchowski; *S*, *S*, fibres from sympathetic plexus, which are in relation with Auerbach's plexus. 1, Sulcus cruciatus; 2, corpus striatum; 3, corpora quadrigemina; *K*, nucleus of vagus; *o*, olive; 4, 4, spinal centres for orifice of cardia. The black lines represent the nerves to the cardia; the broken lines the nerves to the pylorus; the broken and dotted lines the nerves to the fundus and body of stomach.

The principal cerebral centres for the movements of the stomach lie in the posterior corpora quadrigemina, which influence not merely the cardia and the pylorus, but also the entire body of the stomach. Excitation of these produces a general constrictor effect. The efferent fibres run for the most part in the vagi.

Other fibres traverse the anterior column of the spinal cord, and leave by the anterior roots of the tract that extends from the 5th-10th dorsal vertebrae; they then unite with the splanchnics and to a less extent with the sympathetic chain.

In the olives of the bulb there is, according to Openchowski, an inhibitory centre that determines the opening of the pylorus by fibres which descend in the cord, and unite after leaving it with the sympathetic.

In the upper part of the cord, again, there are centres, which on excitation cause the cardia to open. The efferent fibres descend in the anterior cord, and then leave the anterior roots, and unite with the dorsal sympathetic chain, with the aortic plexus, and the small splanchnic.

Although the afferent paths, which by acting on these centres may reflexly determine the movements of the stomach, have not been fully worked out, it is proved by Openchowski's work that excitation of the kidneys, uterus, bladder, loops of the intestine, and sciatic of animals in which all the nerve paths and centres are intact may induce opening of the cardia. This fact accounts for *reflex vomiting*, which not seldom accompanies diseases of these parts, like that which is easily induced in man merely by slight mechanical stimulation of the roots of the tongue, the pharynx, and the palate.

An important contribution to our knowledge of the significance which must be attributed to the afferent paths, and, generally speaking, to the peripheral stimuli, in the production and normal course of vomiting has recently been made by A. Valenti (1906). Experimenting with dogs and cats, he found that if a well-defined zone of the pharyngeal mucous membrane was anaesthetised with cocaine, between the lower part of the buccal cavity and the higher part of the oesophagus, the animal lost the capacity of expelling substances from the stomach, although on the action of emetics (apomorphine, tartar emetic, copper sulphate) all the other phenomena of vomiting were exhibited. This incapacity is due to the fact that under such experimental conditions the active opening of the cardiac sphincter does not come off. This opening is, however, a reflex act, due to excitation of the said zone of the pharyngeal wall. According to Valenti this reflex has no connection with the reflex of deglutition, the peripheral area of which lies, as we have seen, in a more anterior region of the soft palate. In normal vomiting this region of the mucous membrane is stimulated, according to Valenti, by waves of peristaltic contraction from the oesophageal walls, or more probably, perhaps, by the passage of the saliva, which is regularly swallowed prior to vomiting.

Valenti's work accounts clearly for the mechanism of reflex vomiting on tickling of the fauces, since it is evident, as we have seen, that pharyngeal-oesophageal anaesthesia is capable of pre-

venting the cardia from dilating, while excitation of the same region must, on the contrary, provoke a violent and forcible dilatation of the cardia, and reflex emission of the gastric contents.

Lastly, Muratori's experiments in our laboratory (1909) on dogs with a gastric fistula, through which a long semi-rigid sound (provided with electrodes) can easily be passed to the various regions of the mucous coat of the stomach, show that the whole surface is not capable of exciting reflex vomiting on artificial stimulation with electrical and mechanical stimuli. It is the cardiac region proper, which is distinguished from the rest of the gastric mucous membrane by the property of determining reflex vomiting, the pyloric region being destitute of this capacity. Division of the vagi in the neck abolishes all reflex vomiting, while sensibility to pain remains. These observations of Muratori are not entirely new, Bulatowicz (1858) having noted analogous data.

The theory of the mode in which the action of the many centres of gastric motion is associated and co-ordinated in the performance of the acts that normally occur in vomiting, has still to be worked out. Certain observations of Openchowski, Tumas, and Ducceschi, however, bear on this question.

Among the fibres of the vagus coming from the corpora striata, Openchowski (1883) discovered in the rabbit a nerve which, on peripheral excitation, produces contraction of the pylorus as well as dilatation of the cardia. The two antagonistic effects, which are eminently adapted to bring about or favour vomiting, are synchronous.

Openchowski distinguishes two groups of emetics: those which act directly on the centres, and those which promote vomiting by reflex paths. Apomorphine and lobeline, which belong to the first group, transmit the central excitation through the paths of the spinal cord, so that it is a mistake to consider (as stated in many text-books) that the vagus is the only nerve of vomiting. With emetics of the first group vomiting becomes impossible after the destruction of the corpora quadrigemina; after division of the cord or its anterior columns to the level of the 5th vertebra; after section of the thoracic chain of the sympathetic at the height of the 6th and 7th ribs; after extirpation of the 5th, 6th, and 7th spinal roots; lastly, after complete separation of the splanchnics. Under all these conditions the characteristic movements of the stomach also come to a standstill. It has hitherto proved impossible to give any adequate explanation of these phenomena. Apomorphine may perhaps paralyse the motor nerve fibres which end in the cardia and upper third of the stomach, with simultaneous excitation of the inhibitory fibres, which causes dilatation of the whole cardiac region.

Valenti saw that interruption of the peripheral sensory paths

(anaesthesia of the vagi in the neck, anaesthesia of the glosso-pharyngeal, anaesthesia of the pharyngo-oesophageal region) is capable by itself of inhibiting evacuation of the stomach, even when emetics with a central action (apomorphine) are administered. This fact can be explained on the assumption that emetics with a central action raise the excitability of the centre, on which the normal stimuli reaching it by sensory paths can induce vomiting. After complete anaesthesia of these sensory paths the hyper-excitability of the centre produced by the emetic is not of itself sufficient to determine vomiting.

The action of emetics of the second category (copper sulphate, tartar emetic) is transmitted solely by the vagi, hence the possibility of vomiting ceases when they are divided. In some cases vomiting ceases in dogs after destruction of the corpora quadrigemina and the corpora striata. According to certain observations incidentally made by ourselves when studying the cerebellum, partial destruction of the posterior corpora quadrigemina gives rise in dogs, for 4-5 days in succession, to repeated vomiting, which then ceases entirely with the disappearance of the excitatory phenomena. It is clear that the emetic action of these substances is mainly due to reflexes by the afferent paths, whatever the situation of the part on which they act. Vomiting, in fact, follows not merely when the emetic is introduced into the stomach, but also when it is injected into a loop of the intestine, which explains the vomiting that accompanies certain intestinal diseases.

It is still doubtful whether, in order to explain the specific behaviour of the nerve centres in vomiting, we should assume the existence of an *isolated centre for vomiting*, or a specific association and co-ordination of the separate motor and inhibitory centres for the different parts of the stomach as pointed out by Openchowski, as well as active intervention of the bulbar respiratory centres. Tumas (1887) assumed a *unitary centre for vomiting*, situated bilaterally in the depth of the medulla oblongata near the calamus scriptorius. He saw in effect that in dogs destruction of the median line of this region made vomiting impossible. Openchowski, on the contrary, doubted the existence of a special centre of vomiting, and thought it probable that Tumas' results depend on the interruption of the nerve paths which descend from the corpora quadrigemina to the bulb, and thence to the anterior columns of the spinal cord.

He showed by many observations made in collaboration with Hlasko, that apomorphine-vomiting is inhibited after destruction of the posterior corpora quadrigemina, while that from copper sulphate is violently excited. This fact shows that there must be two distinct central nuclei that act as centres for vomiting. He further saw that vomiting ceases immediately after the section of

the cord above the striae acusticae, but after 4-5 hours apomorphine produces vomiting of a special kind, which sets in suddenly, as if an inhibitory influence had expired, so that the

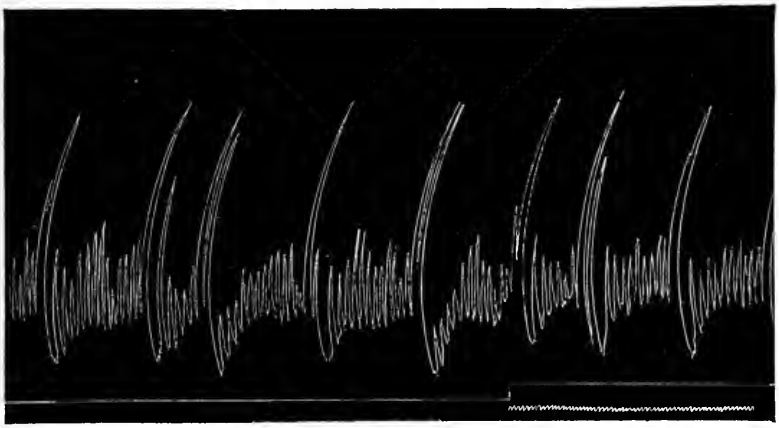

FIG. 70.—Tracing of rhythmical and periodic movements obtained in the pyloric region, after extirpation of caeliac plexus. (Ducceschi.)

action of the spinal centres which are simultaneously trying to induce vomiting, come into play. In any case, it is certain that the respiratory centres of the bulb are quite distinct from the vomiting centres. In fact, when the conditions for vomiting fail

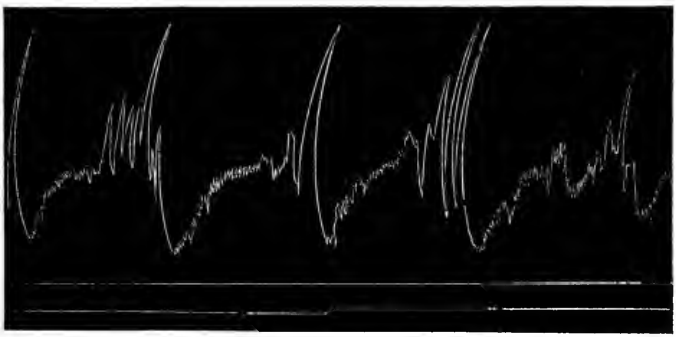

FIG. 71.—Tracing of periodic movements in cardiac region, after extirpation of caeliac plexus. (Ducceschi.)

owing to central lesions, an excessive tachypnea can be observed. As on the other hand abdominal compression, *i.e.* the synchronous contraction of diaphragm and abdominal muscles, intervenes actively in the production of vomiting, we must, in order to sustain the doctrine of a special unitary centre for vomiting also

show the existence of a centre for abdominal compression, closely connected with the former, in which no one has yet succeeded.

Another fact worth noting, which may serve as a point of departure for further work, is that observed by Ducceschi after section of the vagi and caeliac plexus, as performed on dogs under Fano's directions. While on section of the vagi there is, according to Ducceschi, no very striking modification in the form and course of the normal movements of the stomach, excision of the caeliac plexus, which sends branches into the stomach in connection with Auerbach's plexus, sets up movements with a periodic course, which arise from the grouping and combination of rhythmical movements, peristaltic waves, and oscillations of tonus, constituted into successive groups of fairly regular form (Figs. 70 and 71). This phenomenon (which recalls the analogous effect already studied on the heart and in the respiratory movements) is never seen under normal conditions. Subsequent division of the vagi modifies the groups, without, however, suppressing them.

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CHAPTER IV

MECHANICS AND CHEMISTRY OF DIGESTION IN THE INTESTINE

CONTENTS.— 1. Artificial digestion with the three intestinal secretions: pancreatic juice, bile, succus entericus. 2. Mechanism of bile-excretion in the intestine, and innervation of muscles of common bile-duct. 3. Natural digestion of chyme in small intestine. 4. Putrefactive processes in the intestine. 5. Effects of extensive resection of small intestine in animals and man. 6. Peristaltic movements of intestine. 7. Central and peripheral innervation. 8. Post-mortem autodigestion. Why it does not occur during life. Bibliography.

THE last chapter proves, as already stated, that the digestion of food-stuffs in the mouth and stomach is very imperfect. Contrary to earlier opinions, the acid pulp, known by the name of Chyme, does not differ, chemically speaking, in its essentials from the mass of the food-stuffs ingested, whether these be raw or modified by cooking. The changes which the foods undergo in the mouth are principally mechanical; those which they undergo in the stomach are principally antiseptic. But if not absolutely indispensable to life, both these changes serve to prepare for and to facilitate the true and complete digestion that takes place in the small intestine, which is the subject of this chapter.

I. The acid chyme, after passing into the duodenum, encounters three alkaline secretions—*pancreatic juice* and *bile* in the duodenum, *succus entericus* throughout the small intestine—by which it is gradually neutralised. It is only in the last part of the small intestine that the intestinal contents give an alkaline or neutral reaction. The cause of the acidity of the intestinal contents has been studied by many authors (Nencki and Zaleski, Moore and Rockwood, Hemmeter, Gillespie, C. Foà, U. Lombroso, etc.).

According to most authorities the acid reaction of the intestinal contents is due to a complex of factors, *e.g.* acidity of the gastric juice, the fatty acids liberated from alimentary fats, the lactic acid developed during digestion of the carbohydrates, the carbonic acid formed by the action of stronger acids on the carbonates, etc.

C. Foà (1906), who undertook to control and confirm the observations of various authors in regard to the *actual* and *potential reactions* of the digestive secretions (which all present an almost neutral actual reaction, the gastric juice alone giving a strongly

acid actual reaction), suggested that the acidity of the intestinal contents might be due to the fact that the pancreatic juice and the succus entericus were unable to neutralise the acidity of the gastric juice. U. Lombroso, however, contemporaneously with G. Rossi (1907), objected that in this case it would be, not the actual, but the potential, reaction that must be considered, and that the alkaline potential reaction of pancreatic juice is very strong.

Foà (1908) accepted this criticism, but maintained that the acid reaction of the intestinal contents was due solely to the hydrochloric acid of the gastric juice. He observed that no free hydrochloric acid was to be found in the filtrate of the gastric and intestinal contents in the dog after a meal of flesh or milk, but only hydrochloric acid combined with proteins. Examination of the filtrate, however, does not exactly account for the various acid constituents of the intestinal contents, since we know that the higher fatty acids to a large extent remain on the filter. We cannot therefore attribute the acidity of the intestinal contents solely to the combined hydrochloric acid, but must admit (particularly in view of the known data as to digestion and absorption of fats which we are about to discuss) that all the other factors above enumerated contribute to it.

In the preceding chapters we have already referred to the specific enzymic activity of the various digestive secretions. It is now time to determine more exactly the mode in which these various factors in the complex problem of alimentary digestion come into play—what favours and what thwarts their function—and how that functional correlation is effected between the different secretions which is necessary to the conversion of the food-stuffs into the form that precedes their absorption.

In virtue of its enzymes, *pancreatic juice* acts, as we have seen, on the three different groups of alimentary substances, viz. carbohydrates, fats, and proteins. Its action *in vitro* can be studied either with natural juice or with the extract of the gland.

The *saccharifying* action of pancreatic juice on starch (due to *amylopsin*) is similar to that of saliva, but much more energetic, since at body-temperature (37-40° C.) it acts rapidly on boiled as well as on raw starch. The rapidity of this conversion, and the intensity of the effect, are astounding. Thus if pancreatic juice be dropped into a test-tube containing starch paste stained with a drop of tincture of iodine, the deep-blue colour disappears, and is replaced by a violet-red (*erythrodextrin*), then by pink, until finally it becomes colourless (*achroödextrin*). Minkowski suggested a method for the rapid estimation of amylolytic activity, based upon this sequence of readily observed phenomena.

According to Roberts, one part of amylopsin is able to convert 40,000 parts by weight of starch in less than a minute.

Like saliva, the pancreatic juice does not convert the whole of the starch into sugar, after it has passed through the intermediate products of erythrodextrin and achroödextrin, but *dextrin* always appears as one of the end-products, along with the sugar, which mainly consists of *maltose* (von Mering and Musculus). Glycogen undergoes the same conversion. Pancreatic juice also dissolves cellulose and gum (Schmulewitsch)—to a much larger extent in herbivora than in man and in carnivora.

This digestive action of the pancreatic juice on the polysaccharides, which reduces them, with absorption of water, to smaller and more soluble molecules, that can be easily absorbed and assimilated, is of great importance in frugiverous birds, for if the pancreatic secretion is drawn off externally, by a fistula, in pigeons they die of progressive emaciation after a short time if sugar be not administered, the giving of which delays their fate (Langendorff).

Little is known of the origin of the zymogen of amylopsin, and the factors which convert it into the enzyme. According to some authors, the centro-acinar cells elaborate the *zymogen*, and the epithelium of the ducts pours out a *kinase* by which it is activated.

Both entero-kinase and bile undoubtedly increase the amylolytic activity of the pancreatic juice (Pawlow). This action comes off also in a slightly acid medium, which is very favourable to the digestion of carbohydrates; in fact, we have seen that the greater part of the intestine presents an acid medium. According to Grützner, weak acids, as also 0·7 per cent sodium chloride, increase the action of the amylolytic enzyme, while more concentrated solutions inhibit it, as do also alkaline salts, sulphates, alcohols, chloroform, ether, thymol, etc.

After a few hours in the thermostat at 37° C. pancreatic juice loses its amylolytic activity (also its other enzymic properties, the lipolytic first, and the proteolytic more slowly).

The *lipolytic* action of pancreatic juice (due to *steapsin*) is exercised on the neutral fats, which are first emulsified permanently and completely, and then decomposed into glycerol and fatty acids, with absorption of water. The power of emulsifying fats is common to all alkaline fluids, but in a less perfect and less stable degree, according to the quantity of free fatty acids which Hoffmann finds to be present in all the fats. Alkali, in presence of fatty acid, combines with it to form soap, which as Brücke demonstrated, has the power of penetrating into neutral fat and dividing it up into minute drops separated by a thin film of soap.

In order to prove that pancreatic juice really has the property of decomposing neutral fats, they must first be freed from the fatty acids which they contain by dissolving them in ether and shaking, after which the ethereal layer is separated and slowly evaporated, leaving a residue of perfectly neutral fat, which on

dissolving in alcohol no longer reddens litmus. On mixing this purified fat with fresh, alkaline, pancreatic juice, and keeping the mixture in the warm chamber at 37° C. with the addition of a little litmus solution, the alkalinity gradually diminishes, till the mixture finally gives an acid reaction owing to the hydrolytic cleavage of the neutral fat, as first perceived by Ch. Bernard and Berthelot. We shall presently see the great importance of the lipolytic action of the pancreatic juice for the utilisation of the ingested neutral fats.

On adding succus entericus to pancreatic juice the lipolytic activity of the latter is a little increased. It is much reinforced by the presence of bile, even in a small amount. According to Bruno the lipolytic activity of pancreatic juice can be increased 20 times with bile. But if the experiment *in vitro* be prolonged beyond a certain time, the difference in activity between the pancreatic juice alone, or with bile, diminishes. From the teleological point of view it is an important fact that on adding bile the pancreatic secretion retains its lipolytic activity much longer.

The lipolytic activity of pancreatic juice is aided by a slightly alkaline medium, but takes place in an acid medium also.

In order to measure the lipolytic action of pancreatic juice, a certain quantity of the juice and of pure oil is placed in the thermostat at 37° C., and the quantity of $\frac{1}{10}$n solution of alkali required to neutralise the fatty acid formed is estimated.

The *proteolytic* action of pancreatic juice (due to *trypsin*) is certainly its most important property. It acts on all proteins with greater or less rapidity.

Raw fibrin is more readily dissolved than other proteins, at 37-40° C., in 30 min. to 3 hrs. for large quantities, with a small amount of trypsin, and without any symptom of putrefaction. With other proteins that are more slowly digested (coagulated albumin, cheese, meat, etc.), a little salicylic acid, or thymol, chloroform, or ether (Kühne) may be added to the extract to exclude any trace of putrefaction, or, still better, a small quantity of iodoform, which according to Vandevelde (1907) does not interfere with the action of the enzyme.

Trypsin, unlike pepsin, digestion takes place both in an alkaline and in a neutral or slightly acid medium. The *optimum* of digestion occurs with an extract made alkaline with 0·3 per cent solution of sodium carbonate. The addition of free mineral acids, even in small quantities, entirely inhibits digestion. The acids combined with metaproteins (at least in small quantities) neither hinder, nor sensibly delay, digestion (Chittenden and Cummins).

A further difference in the action of gastric and pancreatic

juice is that with the latter boiled egg-white and other solid foods are softened and split up without previous swelling, and that only the muscular fibrils of meat are digested, while the connective tissue and the collagenic tissues in general are left undigested (Ludwig and Ogata).

The proteolytic activity of the pancreatic juice has been estimated by different methods with results that are not always comparable; and there are conflicting opinions as to the laws by which the digestive power of the pancreatic juice is developed. According to Mett's method, trypsin digestion follows the law of Schütz and Borissow; according to Gross, on the contrary, it is in direct ratio with the concentration of the ferment.

Method of Gross (1907). One or two drops of the fluid to be examined (or more if required) are placed in test-tubes containing 10-20 c.c. of a 0·1 per cent solution of caseinogen and sodium carbonate. This is placed in the thermostat, and samples taken at intervals of a few minutes of the mixture, into which is dropped a 1 per cent solution of acetic acid. When the mixture no longer becomes turbid, this shows that the caseinogen is entirely decomposed.

Hedin's Method (1904). After making a digestion with protein of any type, the liquid in which the digestion has taken place is precipitated with an equal volume of a solution consisting of tannic acid 70 grms., acetic acid 500 grms., sodium chloride 100 grms., water 1000 grms.; this is filtered, and the nitrogen of the filtrate estimated by Kjeldahl's method.

The protein cleavage effected by trypsin is shown by the work of Kühne and his school (1867-93) to be very complicated. Kühne proved that it differs essentially from that effected by pepsin, and may lead to a greater cleavage or disintegration of the complex molecule of natural protein, independent of the intestinal bacteria of putrefaction. The special text-books of chemical physiology must be referred to for the study of all the products into which proteins successively break up by the action of trypsin. We must confine ourselves to stating that the first direct products of cleavage are the secondary proteoses (*deutero-proteoses*), and not primary proteoses (*protoproteoses*), as occurs in pepsin digestion, and that the *peptones* are formed directly from the deuteroproteoses. According to Kühne pancreatic digestion differs from gastric digestion, in that two kinds of peptones are formed: a *hemipeptone*, which on the protracted action of trypsin readily breaks up into leucine, tyrosine, aspartic acid, and other products that are not exactly characterised, and an *antipeptone* which resists the disintegrating action of trypsin, and can only be decomposed into amino-acids on boiling, with addition of dilute sulphuric acid. The molecular aggregate of protein is thus composed of two complex groups, the first of which splits up easily, the other with difficulty; both, however, contain nuclei of the aromatic series as well as the fatty series. In the peptone of gastric digestion, the two groups are still united, from which

Kühne gave it the name of *amphopeptone.* In pancreatic digestion, on the contrary, the two groups of amphopeptone are split up, and give rise to *hemi-* and *anti-peptone.*

There can be no doubt that hemipeptone breaks up under the proteolytic action of trypsin, independent of any process of putrefaction, for when pancreatic extract treated with salicylic acid is digested *in vitro* for a long time, amino-acids and other products of protein decomposition are constantly met with.

Before inquiring whether this advanced proteolytic process takes place under physiological conditions in the intestine, as it does in artificial digestions, we will examine the chemical action of *bile* and *succus entericus* upon the food-stuffs.

The digestive action of bile *in vitro* is very insignificant. It has no stronger solvent action on proteins than water. Some authors (Kühne, v. Wittich, Giannuzzi, and G. Bufalini) have recognised a slight diastatic action on starch from the bile of man and some other mammals, which is probably due to small quantities of ptyalin or amylopsin from the salivary glands or from the pancreas, absorbed by the roots of the portal system, and reconducted from the liver to the intestine with the bile.

The emulsifying (not lipolytic) action of the bile upon the alimentary fats, which invariably contain a small amount of free fatty acid (*supra*), is more important. As early as 1858 Marcet noted that if bile be added to fats mixed with oleic, palmitic, or stearic acid, a part of the latter at once decomposes the bile salts, and combines with the liberated alkalies to form soaps, which produce a fine emulsion of neutral fats. When the ordinary alimentary fats are employed, however, the emulsion produced by the bile is rather coarse and unstable, owing to the small amount of free acids which they contain.

In studying the digestive action of succus entericus *in vitro,* either the glycerol extract of intestinal mucous membrane or the juice that flows from a Thiry-Vella fistula after injection of pilocarpine, may be employed, or the juice can be collected on small sponges introduced into the loop of intestine. In these artificial digestions, all trace of putrefaction must be avoided by adding a few drops of alcoholic solution of thymol or salicylic acid (Masloff), or still better iodoform (Vandevelde).

Provided the digestion of succus entericus *in vitro* proceeds under aseptic conditions, it has been proved to exert no action on protein, *e.g.* meat, egg-white, etc. On the other hand, O. Cohnheim finds that it does act on proteoses and peptones, which are split into amino-acids, owing to the specific proteolytic action of *erepsin.* It further has the property of curdling milk by a process of caseification, which, unlike that in the stomach, occurs in an alkaline medium (Vella). This effect is due to *chymosin,* which is present in small amounts in the succus entericus of certain animals.

Boiled starch is rapidly converted into maltose. According to Rohmann the glandular crypts of the jejunum secrete a juice that has a more pronounced diastatic action than that from the crypts of the ileum. Owing again to the action of *invertin* and *lactase* enzymes peculiar to the succus entericus (though some hold that they exist in minute quantities in pancreatic juice as well), saccharose and lactose are hydrolysed and converted into monosaccharides, in which form the carbohydrate introduced with the food is constantly present in the blood. Thus the succus entericus completes the metamorphosis of this important group of food-stuffs, the conversion of which commences in the mouth with the action of the saliva, and is continued with increasing intensity in the duodenum by the action of the pancreatic juice (Paschutin, Rohmann, Bastianelli, Brown and Heron). Lastly the succus entericus, from its alkalinity, co-operates with the bile and the pancreatic juice in neutralising the chyme, in emulsifying the fats, and perhaps also in their cleavage.

Taken as a whole the results of these experiments *in vitro* upon the digestive action of the succus entericus secreted by the small intestine bear out the general theory formulated by Hermann—to the effect that digestion in the intestine converts the greater part of the solid or colloidal, insoluble and indiffusible substances, represented by the protein compounds, the polysaccharides, and the fats, into their respective decomposition or cleavage products or units, which are soluble, readily diffusible, and easily absorbed by the intestinal epithelium, *e.g.* peptones and amino-acids, glucose, soaps, and free fatty acids.

II. In order to form a more adequate notion of the sum of the chemical processes which go on in the intestine, it is necessary to examine the changes that take place successively in the acid mass or chyme in the different parts of the gut, owing to the synchronous action of the three secretions whose activity we have been separately considering, in so far as it can be detected from artificial digestions of the natural food-stuffs.

But there is a preliminary question. In Chapter II. we saw that the secretion of bile from the liver is continuous, unlike the other digestive secretions, which take place only during digestion, and cease entirely, or almost entirely, during abstinence (see pp. 134-138, Fig. 51). But while the *secretion* of bile is continuous, its *excretion* or output into the duodenum is not continuous, but periodic, and coincides exactly with that period of digestion in which the acid chyme is spurted by rhythmical jets from the stomach to the intestine. It is therefore evident that in the intervals between digestion, the bile secreted by the liver must all collect within the gall-bladder, which is a lateral diverticulum of the excretory bile-ducts, where the bile becomes condensed by absorption of water. What is the mechanism by which the bile

collects in the gall-bladder during abstinence, and is poured out into the duodenum by the common bile-duct during digestion?

In 1887 Oddi, with the object of determining the functional importance of the gall-bladder, attempted to produce a continuous flow of bile into the intestine by completely removing the gall-bladder in dogs, an operation previously performed by Zambeccari, as suggested by Galileo. The animals operated on recovered quickly, without exhibiting abnormal phenomena of any significance. But the sections made some time after showed the hepatic duct, cystic duct, and common bile-duct to be dilated to twice or even three times their normal calibre. The cystic duct, in fact, seemed to be transformed into a reservoir for the bile, and had the appearance of a newly formed gall-bladder. This experiment has been utilised in surgery, since in cases of stones in the gall-bladder (producing severe colic) it is possible successfully to open, empty, and excise the gall-bladder abnormally distended by the presence of calculi. To explain these results it must, of course, be assumed that in animals deprived of their gall-bladder a powerful obstacle is opposed to the continuous outpouring of bile, and promotes the marked dilatation observed in the bile-ducts.

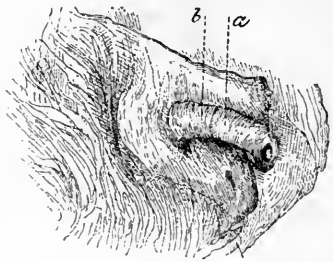

FIG. 72. — Dog's bile-duct obtained by maceration with nitro-glycerin. Macroscopic view. (Oddi.) *a*, *b*, plain circular fibres of sphincter of bile-duct at the point at which it passes through the coats of the intestine.

This legitimate assumption led Oddi directly to the discovery of a special sphincter of plain muscle, situated at the duodenal end of the common bile-duct, a sphincter which is entirely independent of the muscular coat of the intestine. It is visible even to the naked eye in some animals (sheep, dog, ox, pig), in which the bile-duct, before opening into the duodenum, runs for a certain distance between the muscular coats of the intestine (Fig. 72). In sheep and dogs, owing to the robust nature

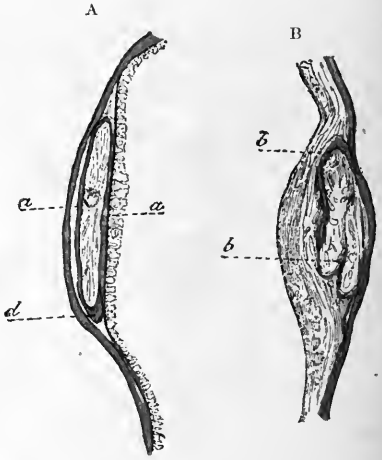

FIG. 73.—Sections of intestine transverse to axis of bile-duct, A, of sheep; B, of man. Carmine preparation. (Oddi.) *a*, *b*, sphincters of bile-duct; *d*, muscular fibres of intestine, independent of fibres of sphincter.

of the bundles that form the muscular hoop, and their independence of the muscular coats of the intestine, it is very conspicuous under the microscope, even with a low power, in sections parallel with the long axis of the intestine (Fig. 73, A). In man, on the contrary, owing to the delicacy of the muscle fibres, and the twist in the lumen of the bile-duct, during its very brief passage through the intestinal walls, the sphincter-like arrangement is less striking and characteristic (Fig. 73, B.).

Oddi further succeeded in showing that the sphincter of the bile-duct, like all other sphincters, has a tone of its own, which is able to resist a column of 50 mm. Hg (= 675 mm. H_2O). This explains why the sphincter resists the pressure of the bile, even when the gall-bladder is full and distended, showing that its tonic resistance exceeds the normal secretory pressure of bile by quite 475 mm. H_2O.

To complete his experiments, Oddi also proved that the tone of the sphincter of the common bile-duct is allied to the function of certain ganglia in its vicinity, which have specific cytological characteristics by which they are differentiated from the plexuses of Auerbach and Meissner, of which we shall speak later (Fig. 74). According to Oddi, the presence of these ganglia explains why, after separating the tract into which the bile-duct opens from the remainder of the intestine, that orifice can remain closed for a long while owing to the tonic-spastic contraction of the sphincter.

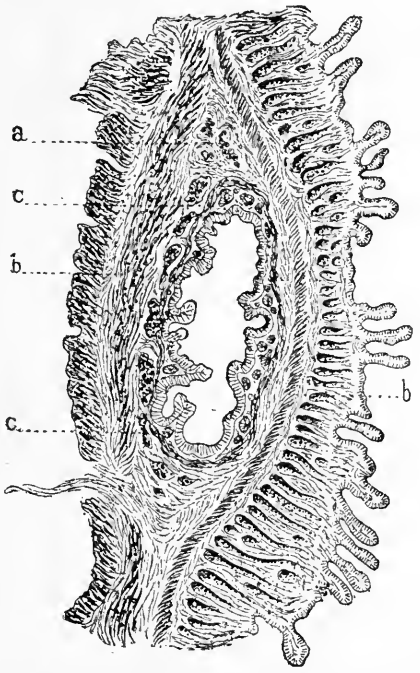

FIG. 74.—Oblique section through dog's bile-duct, at the angle of convergence between the thick muscular coat of the intestine and the thin muscularis mucosae, 35 diameters magnification. (Oddi.) *a*, group of ganglion cells which regulate the tone of the sphincter of the bile-duct; *b*, muscular coat of intestine; *b*, muscularis mucosae; *c*, Oddi's sphincter.

In a later series of researches, Oddi succeeded in proving the existence of a spinal centre, by which the tone of the sphincter of the common bile-duct is regulated. In dogs this centre is level, or at least in relation, with the first pair of lumbar nerves. The afferent paths, according to Oddi, are represented by the

sensory nerves in general, and particularly by the centripetal fibres of the vagus and sympathetic: the efferent by the anterior roots of the first lumbar pair. The mechanism by which the flow of bile into the intestine is brought about consists in a reflex diminution of tone in the sphincter of the common bile-duct, caused by the distension of the intestine and entrance of the acid chyme from the stomach. It is, therefore, an inhibitory reflex, discharged from a higher centre (of which the localisation is entirely unknown), by which the tonic action of the lumbar centre is suspended.

More minute researches into the contractility of the excretory bile-ducts, by the graphic method, were carried out in Morat's laboratory, and published by Doyon in 1893. According to Doyon the contractility of these ducts is perfectly similar to that of all other organs with plain muscle cells. They exhibit automatic, rhythmic oscillations of tonus, similar to those above described for the stomach. This rhythm can be seen in mammals, but is particularly visible in birds (pigeons). After inoculation of pilocarpine, Oddi's sphincter enters into spastic contraction, and for a long time resists the efflux of bile into the duodenum.

The great splanchnics, according to Doyon, contain the motor nerves to the bile-ducts, since on stimulating them the whole of the excretory biliary system contracts. It is possible that the splanchnics receive fibres from the anterior roots of the first lumbar nerves, and from Oddi's spinal centre. Dilatation of the common bile-duct is usually obtained by reflex only, by excitation either of the central end of the splanchnic (which causes dilatation of the gall-bladder), or by the central end of the vagus (which produces dilatation of Oddi's sphincter with simultaneous contraction of the gall-bladder). Asphyxia causes constriction of all the bile passages, as of the blood-vessels; curarisation produces the opposite effect. Injection of pilocarpine acts like asphyxia, atropine poisoning like curare.

Bruno (1899), in Winogradsky's laboratory, with the object of better determining the relations between biliary excretion and digestion, excised in a dog the part of the duodenal wall which contains the papilla of Vater, with the orifice of the common bile-duct, and sutured it to the edges of the abdominal wound, after stitching up the aperture into the intestine. On recovering from the operation, this dog was for about a month the subject of many interesting observations, from which the following conclusions may be taken:—

(*a*) The flow of bile occurs only when the stomach contains food. (*b*) The flow of bile commences after a latent period of 15 or more minutes, and continues till the stomach is completely emptied of chyme, after which biliary excretion ceases. (*c*) Not all food-stuffs are active, *i.e.* able reflexly to determine dilatation

of Oddi's sphincter and outflow of bile. This is effected by fats, proteins, and also by the extractives of meat. Carbohydrates seem to have no definite action on biliary excretion. (*d*) The course of biliary excretion is more or less typical for the different classes of food-stuffs. Generally speaking, it may be said that excretion is due to the exciting action, not of the food-stuffs, but of their digestive products. In fact, raw egg-white, which passes undigested from the stomach to the intestine, is unable to produce excretion of bile, even if it be introduced into the stomach in large amounts. Boiled egg-white, on the other hand, which remains in the stomach and is digested there, regularly excites a flow of bile. (*e*) Psychical influences seem to produce no effect on the flow of bile. No bile flows when the animal is brought into the presence of foods, or given milk while the cannula in the gastric fistula is kept open, so that the food runs out of the stomach as fast as it flows in (sham feeding). When, on the contrary, the gastric fistula is closed, ingestion of milk is regularly followed by a flow of bile after 12-17 minutes.

III. Various methods have been employed for studying *natural digestion* in the intestine. The animal can be killed at different periods of digestion to examine the contents of the several parts of the intestine. Intestinal fistulae can be established in animals, or pathological cases of intestinal fistula (*anus preternaturalis*) can be utilised in man, both at the extreme end of the small intestine and nearer the duodenum.

The fact that bile is inert when set to digest with proteins gives no idea of its action on the same substances when they are already acidified and partly digested by the gastric juice, nor of the inhibitory or coadjuvant influence which it may exert on the digestive power of the gastric juice, the pancreatic juice, or the succus entericus, with which it necessarily mixes in the duodenum. If bile be added to the chyme collected from the stomach of an animal killed in full digestive activity, a precipitate is immediately formed, even when the added bile is not sufficient to neutralise the acidity of the mixture. Bernard was the first to draw the attention of physiologists to the thick layer of caseous substance, which adheres tenaciously to the villi of the duodenum of dogs killed in full digestion. This layer results from the precipitation of syntonin (metaprotein) and of the proteoses or propeptone, by the alkali of the bile, the bile salts decomposing under the action of the gastric juice. It is generally held that the gastric acid combines with all the bases of the bile salts, throwing out the syntonin, whilst the liberated bile acids combine with the proteoses or propeptone, and precipitate them, the pepsin also coming down mechanically (Brücke, Burkart, Moleschott, Almquist, Hammarsten).

This process would result in the immediate suspension of

pepsin digestion, even before the acidity of the chyme had been neutralised. But when the alkaline pancreatic juice and the free alkali of the bile have neutralised the mixture and rendered it faintly alkaline, the syntonin and propeptones thrown out dissolve again, and the pancreatic ferment once more acts energetically in the alkaline medium.

Bile therefore aids the pancreatic juice in its digestive function, by checking peptic digestion in an acid medium, and promoting pancreatic digestion in an alkaline or neutral medium.

From the work of Maly and Emich, it would seem that special importance attaches to the taurocholic (not glycocholic) acid, liberated by the action of the hydrochloric acid of the chyme. It has the property of throwing out the albumin and the gelatin, on which the pepsin also comes down in the precipitate, while neither the albumin-peptone nor the gelatin-peptone is precipitated. In consequence of this action of the taurocholic acid, the peptone must therefore be separated in the duodenum from the proteins that are little or not at all modified by the gastric juice; the peptone can at once be absorbed, the proteins, on the contrary, must remain in the duodenum and be acted on by the pancreatic juice. But, as we showed in the last chapter, the chyme which passes from the stomach to the duodenum normally contains either no peptones or hardly a trace of them; this process of separation of peptone from the still incompletely digested proteins is therefore of little importance.

That bile inhibits the enzymic action of pepsin, and thus reduces or entirely suppresses the digestive function of the gastric juice, is an undoubted fact which was confirmed by the work of Bruno (1899), carried out by methods that leave nothing to be desired in their accuracy. It is, however, very difficult to determine by what process this phenomenon comes to pass. To the hypothesis that bile effects the destruction of pepsin, we may oppose the fact that Hammarsten succeeded in isolating a pepsin from gastric juice that had lost its digestive power by admixture with bile, which on the addition of hydrochloric acid recovered its digestive efficacy. It is possible that bile modifies proteins by entering into combination with them, as Hammarsten thinks, and thus rendering them indigestible by gastric juice; it is also possible that it modifies the enzymic property of pepsin without destroying it.

Bruno also points out that the bile which flows into the intestine during the first hour of digestion exerts, *caeteris paribus*, owing to its greater density, a more pronounced depressing action on the gastric juice than the bile poured out in the succeeding period. This still further emphasises the physiological function of the bile, in destroying the enzymic action of the gastric juice in favour of that of the pancreatic.

It is probably for this purpose that there is at the close of gastric digestion (particularly if rich in proteins, and therefore more stimulating to pepsin secretion) an abundant reflux of bile from the duodenum into the stomach. This fact, observed by Pawlow and his pupils, has been studied in detail by Boldireff, who brings out its constancy and modifications.

But the rôle of the bile is not confined to making possible the digestive action of the pancreatic juice; it conspicuously increases it, by promoting the enzymic activity of trypsin upon proteins, of amylopsin upon starch and polysaccharides, of steapsin upon fats. This is plain from the work of Martin, Nencki, and others, and is confirmed and extended in the careful experiments of Bruno, who compared the digestive power of a mixture of pancreatic juice and bile in different proportions for boiled protein, starch, and neutral fat.

The following are the most important of Bruno's conclusions:—

(*a*) Bile added to pancreatic juice raises its proteolytic activity by 1·68 times on an average, *i.e.* it increases the solvent action on protein, as if the pancreatic juice contained 1·68 times more trypsin. The maximum reinforcing action of bile is obtained when the quantity added to the pancreatic juice is not large.

(*b*) Bile added to pancreatic juice in the most favourable proportions reinforces the amylolytic power of the latter to an amount equal to increase of amylopsin by 2·43 times. But unlike what has been stated for the action of bile upon trypsin, the reinforcing action of bile on amylopsin increases in proportion as the quantity of bile is greater.

(*c*) Bile also reinforces the lipolytic power of the pancreatic juice, due to steapsin; this action on the fat-splitting enzyme is indeed, the most marked. The bile excreted after a meal of milk is the most active; it increases the lipolytic action of the pancreatic juice 20 times. Even boiled bile is capable of reinforcing the action of the lipolytic enzyme (although to a less extent).

These results justify the conclusion that the influence of bile on pancreatic juice is precisely opposite to that which it exerts on gastric juice. It is obvious that acquaintance with the action of bile must throw not a little light on the work of digestion as a whole, when it is accomplished under natural conditions in the duodenum.

Careful study of the effects of *intestinal acholia* in dogs operated on by a complete biliary fistula, confirms the coadjuvant action of bile in the processes of intestinal digestion; at the same time it shows the capacity of the body to compensate itself completely for total absence of bile in the intestine.

All the dogs operated on by Schwann with a complete biliary fistula died shortly after; but Bidder and Schmidt discovered that they could live a long while when fed more abundantly than

usual. It was, however, found that defaecation was infrequent and difficult; that the faeces assumed a fatty appearance, grey or brown in colour, and had a putrid odour; that much gas was developed in the intestine and produced fetid flatulence; and that the expired air had a bad smell, both in fasting and after a meal. In a word, dogs with a biliary fistula suffered owing to intestinal acholia from exaggerated putrefaction in the intestine, which caused progressive emaciation, and death. The autopsy showed no particular lesion of the organs, such as would induce a fatal result.

These observations gave rise to the conjecture that bile normally exercises an anti-putrefactive action on nitrogenous food-stuffs. But bile in itself is an effusion, that putrefies readily with much evolution of gas (Giannuzzi and G. Bufalini) and development of indole from the decomposition of the mucin (Ernest). We know, however, that the bile salts are decomposed in the duodenum, and that the free taurocholic acid actually exercises a certain anti-putrefactive power (Lindeberger, Gley and Lambling), as does also cholalic acid, which is a cleavage product of the former (Bufalini, Albertoni, Limbourg).

The anti-putrefactive action of bile can also (it seems to us) be regarded as an indirect effect of the excitatory action that it exerts, more particularly by its free acids, upon the muscle fibres of the intestine, increasing the peristaltic movements that serve to expel the faeces. This is proved by the fact that intestinal acholia produces constipation, on which the alimentary residues remain longer in the bowel, and reach a more advanced stage of putrefaction.

Lastly, the fact that in intestinal acholia there is almost always a considerable quantity of fat that has escaped absorption, shows that bile, besides favouring the digestion of fats, facilitates their absorption. This fact depends essentially on the property of the bile acids of dissolving the fatty acids liberated by the lipolytic action of the steapsin. According to Marcet (1858), whose experiments were subsequently confirmed by Moore and Rockwood, bile acids, at body temperature, dissolve fatty acids to the amount of 2-6 per cent. These authors hold that the fatty acids are absorbed in this state, and not in the form of emulsion. We shall return to this interesting point. Meantime it may be added that according to C. Voit, Röhmann, Fr. Müller, the faeces in jaundice contain 55-78 per cent of the fats ingested, while in normal individuals they contain only 7-10 per cent. The greater part of the fat in the faeces is present in the form of free fatty acids, or combined as soaps with lime and magnesia. Neumeister explains the influence of bile on fat absorption by assuming that it is capable of dissolving these otherwise insoluble soaps; this does not, however, exclude the well-established power of bile acids to dissolve

the fatty acids that have been liberated by the action of the pancreatic steapsin.

Whatever the importance of this coadjuvant function of bile in the processes of digestion and, more particularly, absorption in the intestine, there is no need to exaggerate its significance, and to hold that an animal with a complete and permanent fistula of the gall-bladder must inevitably be considered moribund. The intestine, like all other organs, possesses in a marked degree the power of gradually adapting itself to deficiency of bile. Many animals, when provided with a biliary fistula, as Barbèra (1896) observed, recover their original weight, and may live for a long time in perfect health. This occurs with strong dogs operated on in summer. Those, on the contrary, which are operated on in winter and in very cold climates, grow more and more emaciated and eventually perish from marasmus. The former pass the period of adaptation to want of bile in a season at which there is little need of fat as a thermogenic substance, and when the cold weather comes they have established functional adaptation, and bear it without disturbance of nutrition. In the latter, the disturbance of intestinal functions due to the sudden deficit of bile occurs just when there is great need of thermogenic substances to keep up the equilibrium of the thermal balance, and for want of it they consume their own tissues, lose flesh, and die of marasmus.

Digestion of proteins *in vitro* by pancreatic juice or extract shows that the complex protein molecule may (independently, according to Kühne, of the processes of putrefaction) undergo such decomposition and hydrolytic cleavage as to give rise to amino-acids and other simple substances.

In many analyses of the intestinal contents of dogs fed with flesh, however, Schmidt-Mühlheim finds either no tyrosine, leucine, and aspartic acid, or merely traces of them. Nencki arrived at the same result on examining the matter that escaped from a fistula at the extremity of the small intestine in a woman. All experimenters agree, again, in saying that hardly any peptones occur in the intestinal contents at any period of digestion.

These differences in the results of artificial and of natural digestion are readily explained on the assumption that the peptone formed is rapidly decomposed, owing to the proteolytic enzyme of the pancreatic juice, more particularly by the intervention of the *erepsin* of the succus entericus, the crystallisable products that arise (amino-acids) being promptly absorbed and utilised as fast as they are formed. Confirmation of this important statement will be found in the next chapter, when we shall study the absorption of the digestive products of the alimentary proteins.

The functions of the succus entericus also stand out more clearly and have more significance, when we pass from the results of experiments *in vitro* to investigation of the physiological

conditions under which it acts in the intestine. We have shown that it may co-operate in the emulsifying of fats, by partially neutralising the acidity of the intestinal contents due to the development of butyric and lactic acids, which are normally present in the intestine in large quantities, owing to the fermentation of carbohydrates effected by the intestinal bacteria.

Bunge in this connection attributes great importance to the large amount of sodium carbonate, which causes the succus entericus to effervesce when treated with acids. The greater the acidity of the intestinal contents, the more active, according to Bunge, is the reflex secretion from the crypts of Lieberkühn, as already assumed by Thiry and Quincke.

He asserts that the intestinal mucous membrane tends rapidly to neutralise the strong acids that are experimentally brought into contact with it. Lombroso noted that when a solution of hydrochloric acid is passed into a short Vella's loop, its acidity is reduced and practically neutralised in a few minutes. But if the acid be combined with pepsin or protein, the neutralisation takes place rather more slowly (U. Lombroso, C. Foá). How this neutralisation occurs is not exactly known. If we consider the quantity of succus entericus excreted by the loop, and its potential alkalinity, this is obviously much less than is required *in vitro* to effect an equal reduction of acidity in the fluid in Vella's loop. The same phenomenon does not occur when the higher fatty acids are introduced into the loop instead of strong acids. In this case the reduction of acidity is much less, and corresponds pretty accurately with the potential alkalinity of the copious secretion called out. We shall return to this interesting phenomenon as demonstrated by Lombroso in our laboratory (1907-8), in treating of fat absorption.

The sodium carbonate of succus entericus comes from the decomposition of sodium chloride effected by the parietal cells of the gastric glands, from which hydrochloric acid and sodium carbonate are formed. The first is secreted, the second absorbed by the glandular lymphatics, and passes into the blood. This hypothesis is confirmed by the fact which Baldi (1885) established in a number of experiments carried out in our laboratory: to wit, that the blood examined during fasting is less alkaline than that during gastric digestion, and that the greater alkalinity observed during this period depends on the increased quantity of sodium carbonate. The diminished acidity of the urine (Beaunis) and the greater alkalinity of the bile (Gaglio) in gastric digestion evidently result from the increase of sodium carbonate in the blood, when the gastric glands are forming and secreting hydrochloric acid. It therefore seems to us reasonable (although direct experimental proof is still wanting) to admit that there is a certain relation between the amount of hydrochloric acid

secreted by the stomach and the amount of sodium carbonate secreted by the intestine.

To this sodium carbonate Bunge assigns yet another function. As fast as it is secreted, it diffuses in the acid mass of the intestinal contents, leading to a fresh formation of sodium chloride, with evolution of free carbonic acid, which makes the whole mass spongy and permeable to the pancreatic juice, thus assisting the digestion or solution of the food-stuffs.

IV. To the chemical action of the secretions poured into the intestine during digestion, must be added the constant action, even under normal conditions, of the Bacteria that inhabit the intestine.

Their presence in the intestinal contents has been known ever since the microscope was first applied to the phenomena of life (Leeuwenhoek). The problem of determining their true physiological significance is, however, beset with difficulties, and we cannot at present claim that any definite theory has been arrived at. We must here confine ourselves to a very general survey of the subject.

There can be no doubt that the bacteria of the intestine penetrate from outside, along with the food, the fluids, the air that we swallow; and that the development of the gases within the intestines, as well as a considerable part of the substances that compose the faeces, are due to the fermentations they excite, and the further putrefactive decomposition which they produce in the food-stuffs partially digested by the enzymes. We know, in fact, that during the whole foetal period up to birth, there is no fermentation in the intestine, which is sterile and destitute of faeces. With the first frothy saliva, *i.e.* that mixed with air-bubbles, swallowed with the milk by the new-born infant, the first organic germs are introduced into its body. Many of these are destroyed by the acidity of the gastric juice, but others pass into the intestine, where they excite fermentative processes with evolution of gas.

It is evident that the bacteria introduced with the food and drink must be the same which act in the open air on the fermentable and putrescible matters. From the intestine of the new-born, that have sucked milk, very few kinds of bacteria are, however, secreted with the meconium in the 4th-10th hours after birth (Escherich, 1875). All the other germs have been destroyed by the bactericidal action of the gastric juice, or fail to find the necessary conditions of their existence in the intestine of the sucking infant.

In adults, too, although an enormous variety of germs continually pass by the mouth into the gastro-intestinal tube, the gastric bacteria consist almost exclusively of Blastomycetes and Sarcinae, organisms accustomed to live in an acid medium, and

the intestinal bacteria almost exclusively of the species *Bacterium coli* and its varieties, to which the *Bacillus mesentericus* (which resembles that of typhoid) is frequently added. It is true, that not a few authors (Macfadyen, Nencki and Sieber, Gessner, Ciechowsky and Jaworsky), have described 7 species in the human intestine under normal conditions, and Vignal 10 distinct species, 4 of which live in the mouth as well; but in all probability many of these bacteria must be regarded not as permanent but merely as casual inhabitants of the intestine. Innumerable researches of many workers in hygiene and pathology (Maggiora, Jensen, MacWeeney, Laveran, Celli, and others) on the faeces not merely of normal individuals, but also of persons affected with dysentery and *cholera nostras*, have yielded only pure or almost pure cultures of *Bacterium coli* and its varieties.

Bacterium coli under the microscope appears as a bacillus, 1-5 μ long, 0·3-0·5 μ broad. In gelatin cultures the colony assumes the form of a small, round, greyish-white protuberance. On studying its metabolism *in vitro*, it has been found to produce partial alcoholic fermentation of glucose, lactic fermentation of lactose, and direct cleavage of amygdalin into benzoic aldehyde and hydrocyanic acid, with consumption of glucose. It does not liquefy gelatin: it has the property of slowly coagulating milk (in 4-5 days) and of slowly digesting fibrin, but not coagulated egg-white; lastly it gives off a strong and disagreeable smell of putrefaction to the culture medium. It is, however, very probable (*infra*) that under the special conditions of temperature and environment in which their activity is manifested in the intestine, these bacteria are capable of a more varied and energetic metabolism, which is normally not pernicious, but may even be useful, if not indispensable, to their host.

The cause of this relative constancy of the intestinal bacteria, notwithstanding that the most varied species of microbes continually penetrate into the digestive tube, presents an interesting problem. That Blastomycetes and Sarcinae alone can live normally in the stomach is readily explained by the acidity of the medium; but why *Bacterium coli* and its allied species or varieties alone take up their permanent abode in the intestine, is not easy to explain (as Fermi noted) by the reaction of the environment, since this should be suitable for the development of the most varied species of microbes.

It is a fact that *Bacterium coli* is far less plentiful in the air, in water, and in the soil than many other microbes, which must therefore penetrate in much larger numbers into the digestive canal (Schardinger). It is a fact that it is not the most resistant to the action of the gastric juice, and that, on the other hand, many microbes penetrate per anum, and are therefore not exposed to the sterilising action of the gastric juice (Escherich, W. Schild).

It is a fact that it does not exhibit more rapid development and greater vitality than other microbes, since in faeces exposed to the air, in dead bodies, and in putrid matter in general, it gradually diminishes and disappears, and succumbs in the fight with *B. pyogenes, B. liquefaciens, Vibrio rugula*, and others (Dallemagne, Bordas, Gilber, De Dominicis).

Fermi also excludes the hypothesis that the almost absolute supremacy of *B. coli* in the intestine depends on the reaction of the intestinal contents on the bile, on the enzymes of the secretions, or the excreta separated by the mucous membrane acting as an excretory organ, which might favour the development of *B. coli*, and impede the development of other species. He proved, indeed, that the proteolytic enzymes and bile exert no action on microbes in general, and that many kinds of bacteria flourish luxuriantly in the intestine post mortem, or on its previously sterilised contents. He concludes that there must be a reciprocal adaptation between the epithelia of the normal mucous membrane and *B. coli*, a kind of *symbiosis*, while there is between these epithelia and the other species of bacteria (even such as develop more rapidly, and have a greater capacity for resistance and higher fermentation power) a kind of antagonism which obstructs their germination. Fermi finds confirmation of this hypothesis in the fact that when the intestinal mucous membrane is injured by different means, which cannot in any way affect the intestinal bacteria, the latter are profoundly modified, *B. coli* being reduced, with an invasion of numerous Vibrios, Protozoa, etc. After peritoneal injections of typhoid toxin, Vibrios and also Amoebae appear in the intestine of the guinea-pig, while *B. coli* is reduced in number and its virulence increases (Sanarelli). When venous stasis is artificially produced in the intestinal walls, the virulence of *B. coli* increases in the injured loop (Klecki). The same thing occurs in profound lesions of the mucous membrane caused by cholera or dysenteric infections (Dreyfus, Lesage and Macaigne, Jensen).

These and other similar facts demonstrate the adaptable character or variable attributes of *B. coli*, which facilitate the interpretation of certain physiological data that must now be considered.

From our point of view the most important question is whether the fermentative and putrefactive processes normally effected by the intestinal microbes in the food-stuffs modified by the digestive secretions, are or are not to be considered as a *second* or *complementary digestion*, useful to the body inasmuch as it completes the chemical work of the enzymes and utilises a greater or less amount of alimentary material which would otherwise be lost with the foetal dejecta.

The chemical processes which the microbes set up in the

contents of the intestine must be very complex, to judge from the copious and dissimilar products that result. There can be no doubt that the intestinal bacteria have a transforming action on carbohydrates, on fats, and on proteins.

From carbohydrates there arise by fermentation, alcohol, lactic, acetic, benzoic, succinic, butyric, and valerianic acid, with development of carbonic acid gas, methane or marsh gas, and hydrogen (Nencki). What is of greater importance—not merely starch, but also cellulose can be digested and decomposed by bacterial activity. Schmulewitsch observed that cellulose can be partly digested by pancreatic juice, because after ligation of Wirsung's duct the quantity of cellulose excreted with the faeces is somewhat increased. But Tappeiner has shown that the greater part of this conversion is effected by the intestinal microbes. On taking weighed parts of the intestinal contents of freshly killed animals, and dividing each into three samples, the first of which is immediately set to digest as it is at body-temperature, the second after sterilisation with an antiseptic, the third after boiling —it is seen that the cellulose disappears only in the first sample. If pieces of paper or cotton are placed in the mixture they are dissolved. The importance of this is obvious, particularly for those animals that live exclusively on vegetable matters, since they are enabled not only to utilise a substance that is difficult to digest, but also to render the nutritive substances enclosed in the cuticle of cellulose accessible to the action of the enzymes. In this connection it is interesting to note that if newly hatched chickens are brought up on sterile food, they rapidly decrease in weight, and die, like the controls that are kept fasting (Schottelius, 1902). The presence of intestinal microbes is therefore essential to the life of these animals.

The acid reaction of the contents of the small intestine is due principally to development of the organic acids above enumerated.

Neutral fats may break up in consequence of intestinal putrefaction into glycerol and fatty acids, and the latter may eventually undergo further cleavage, giving rise to the development of simpler fatty acids. The steapsin of the pancreatic juice is not capable of effecting this, so Landwehr assumed that the capacity of splitting up the higher fatty acids belongs exclusively to the bacteria, since, in his opinion, it ceases altogether in perfectly aseptic, artificial digestions. But this view was shown to be erroneous by Bruno's latest work, referred to above.

Still more important is the putrefactive action of the intestinal bacteria upon proteins. This is not confined to splitting the large protein molecule into proteoses, peptones, and amido-acids (leucine, tyrosine, aspartic acid), as is the case with pancreatic digestions in an aseptic medium *in vitro* (Kühne, Salkowski, Salomon, Hüfner); but the decomposition is carried further, to the development of

nitrogenous bodies of the aromatic series, *e.g.* indole, scatole, phenol, paracresol, phenyl-propionic acid, and other aromatic acids (Nencki), with simultaneous development of gas (sulphuretted hydrogen, carbonic acid, methane, hydrogen). When they act on gelatin, the intestinal microbes also produce glycocoll or glycine along with much leucine, ammonia, lactic acid, butyric acid, and carbonic acid. Besides these well-defined chemical compounds, the so-called ptomaines appear when the intestinal microbes are cultivated on gelatin; these are little-known alkaloids, which often act as powerful toxins.[1]

It is obvious that if all these putrefactive decompositions of protein occurred inside the intestine with the same intensity as they do outside the body, they would not only fail to benefit the organism but would be actively injurious, and mankind would be in constant danger of fatal auto-intoxication. Maly expressed the opinion that the limitation of our existence depends on a series of continual and gradual modifications to which the body is subject owing to the putrefactive processes of the intestine, and repeats with Brieger, *Homo non vivit quia putrescit.* We believe (as will presently be shown) that the true cause of natural death is neither extrinsic, nor to be sought in the intestinal contents, but is seated higher, *i.e.* in the *intrinsic* nature of the living protoplasm and its metabolism. To Brieger's apothegm we would oppose the affirmation that *Homo morietur quia vivit.*

There must therefore be conditions in the normal state of the intestine which tend to keep the putrefactive processes due to microbes within narrow bounds, so that they shall subserve the digestive functions of the secretory enzymes and not damage the economy of the system. It is only necessary to assume that the food-stuffs are absorbed as fast as they are sufficiently digested, and carried away from the intestine, which removes them from the further action of the bacteria. The acidity of the gastric juice, again, fulfils an important bactericidal function in limiting the entrance of germs into the intestine; while the acid reaction is also preserved in the jejunum and ileum, as far as the ileo-caecal valve, not by hydrochloric acid, but by the organic acids developed by the bacteria. These create a medium unfavourable to the putrid decomposition of protein, and the excessive multiplication of bacteria.

The observations made on man in cases of fistula of the upper part of the small intestine confirm the importance of the complementary digestive function accomplished by the intestinal bacteria, as also the natural limitation of the putrefactive processes which go on in the intestine.

[1] The recent work of Dale and Barger and others has added considerably to our knowledge of the origin and nature of these bodies, and their papers should be consulted. (*Journ. of Physiol.*, 1908-11.)

We have already referred to a remarkable case of *anus preternaturalis* in the upper part of the small intestine in a woman. Busch, who described this case, was able to produce considerable improvement in nutrition and increase of body weight, by introducing food through the intestinal fistula where neither bile nor pancreatic juice could penetrate. This case was cited by Herzen in support of Schiff's theory, which endowed the succus entericus with the power of digesting natural proteins. Now that the impossibility of this assumption has been established, Busch's observations are of still greater importance, because they show that in the early stages of the putrefactive process the intestinal bacteria are able to convert proteins into proteoses and peptones, on which the digestive ferment, *erepsin*, can then act. Vizioli repeated and confirmed the observations of Busch on another case of fistula of the small intestine.

No less interesting are the studies of Macfadyen, Nencki and Sieber, on another woman with a fistula in the lower part of the small intestine. They showed that the bacteria confine themselves in this region to the decomposition of carbohydrates, and that putrid decomposition of protein does not take place, or only to a very limited extent. In fact, it was found impossible to extract even the primary products of the putrid decomposition of protein, leucine, and tyrosine from the contents of the small intestine, probably because they are absorbed as fast as formed. On the other hand, the acid reaction of the contents does show the presence of organic acids derived from decomposition of carbohydrates. Jakowski, on examining two other cases of intestinal fistula in man, obtained fresh confirmation of these conclusions.

That the intestinal bacterial processes differ essentially from those of ordinary putrefaction outside the body, may also be concluded from the fact that normally, according to Brieger, Baumann and Udransky, ptomaines are not found in the intestinal contents, even when extracted some days after death. It is possibly the bile acids that make the intestines unsuited to the development of the ptomaines.

Generally speaking, the presence of aromatic products (phenol, indole, scatole) may be taken as the sign of putrefactive processes in the intestine. Part of these products are absorbed and partially oxidised: the indole is converted into indoxyl, the scatole into scatoxyl, and they are for the most part coupled with sulphuric acid, reappearing in the urine as indoxyl and scatoxyl sulphuric acid. The classical proof that the origin of these aromatic substances depends exclusively on the life of the intestinal bacteria is the fact of their invariable absence from the contents of the foetal intestine and the meconium excreted by the new-born.

V. In order the better to appreciate the functional importance

of the small intestine, and particularly to determine the limits of its adaptability, it is useful (as in the preceding chapter, *in re* gastric digestion) to consider the effects of more or less extensive resection of the several parts of the gut. Many of these operations were initiated by surgeons, either on dogs with the simple object of exploring in order to make clinical application of the results, or on man with the therapeutic object of relieving cancer and intestinal strictures consequent on strangulated hernia, cicatrised constriction of the bowel, volvulus, traumatic rupture of the small intestine, tumours of different sorts developed in the walls of the intestine, and so on.

Senn was the first who undertook a series of experiments of this kind on animals, and he came to the conclusion that the resection of a third of the small intestine is a hazardous operation, which results sooner or later in the death of the animal from marasmus. Trzebicky (1894) continued the experiments, removing first the upper portion of the jejunum, next the middle part of the small intestine, then the extreme end of the ileum. In all the dogs thus operated on, he found a diminution in the total weight of the animal, proportional to the absolute or relative length of intestine resected. When the excised loop does not exceed certain limits, the loss of weight is arrested after a time, and is succeeded by an increase which sometimes surpasses the initial weight of the animal.

Unlike Senn, he found that dogs were well able to bear the loss of half the small intestine, the duodenum of course being excluded. Even when these limits were slightly exceeded the animal could survive with a properly selected diet. Removal of two-thirds of the gut, on the contrary, inevitably caused the death of the animal, owing to insufficiency and disturbance of the digestive function and absorption, as shown in obstinate diarrhoea, followed by vomiting. The animal has a furious appetite, and eats enormously, but still grows thinner from day to day, and perishes of inanition. The autopsy shows typical death from starvation, characterised especially by the almost total disappearance of adipose tissue. In the intestine there is, moreover, a conspicuous dilatation of the part lying above and below the suture, but without compensatory hypertrophy of the intestinal walls, as supposed by Senn. Trzebicky was eventually convinced by his experiments that resection of the higher part of the small intestine (jejunum) is more serious than that of the lower part (ileum). Owing to its great physiological importance, this conclusion deserves to be confirmed by further experiments under conditions as far as possible identical and comparable. If established, it would show that the functional value of the small intestine for digestion decreases from above downwards, *i.e.* is greatest in the duodenum, moderate in the jejunum, least in the

ileum, below which (large intestine) it is *nil*, as already pointed out in discussing the digestive secretions (see p. 128).

Even more interesting from the physiological point of view is the experiment in intestinal resection carried out on a bitch by Monari and De Filippi (1892). They succeeded in keeping the animal alive after extirpation of 1·90 m. of the small intestine. During the first 13 days there was a progressive diminution in weight, from which, however, the bitch recovered on a suitable diet. Five months after the operation she was normally delivered of 4 puppies, one of which was suckled for 3 weeks by the mother. A year after the operation the animal was killed, when it was found that only 25 cm. of the small intestine were left, *i.e.* $\frac{1}{8}$ of the total initial length! This observation shows that the adaptability of the digestive functions is immense in a strong subject, far in excess of what Senn and Trzebicky admitted.

Surgical operations on man in which short lengths of the small intestine are successfully removed are common. On the other hand, there are very few cases on record in which the patient has survived the resection of long tracts of the bowel. A woman on whom Boum operated in 1884, by removing 1·37 m. of the intestine, died of marasmus in 4 months. Kocher in 1886 saw a man in good health from whom he had removed 1·60 m. of small intestine. Four years later this patient showed no sign of gastro-intestinal disturbances. In another with intestinal rupture from a railway accident, Kocher removed 2·08 m. of small intestine. The man recovered, but was subject to frequent diarrhoea. Schlange in 1892 excised 1·35 m. small intestine in a female, who was completely cured, with no sequelae from intestinal disturbance. Trombetta (1883) operated on a woman suffering from sarcoma of the small intestine. He cut away 1·10 m. along with the mesentery and some hypertrophied lymph glands. The course of the malady after this severe operation was favourable, and the patient was cured.

The case described by Ruggi in 1896 deserves more detailed consideration. This is perhaps the most classical experiment that physiologists can bring forward in man, to demonstrate the great functional adaptability of the intestine where the patient combines the favourable conditions of strength, youth, and perfect health of the viscera. In a boy of 8, who had a large wound on the abdomen at the level of the umbilicus, Ruggi, after two preliminary operations in the hope of averting intestinal stricture by simply dividing the tissues, was obliged to perform a third operation 13 days after the second, the symptoms of intestinal stoppage having again set in acutely. On making a large opening in the abdomen, he saw that owing to an adhesive peritonitis the greater part of the intestinal loops were knotted up into a huge skein and could not be disentangled without freeing the loops

from the mesentery. He was accordingly forced to cut away the entire segment of intestine, which was covered with the exudates produced by immobility of the intestine. When the operation was complete he saw that the lower incision was 15 cm. above the ileo-caecal valve; the part removed, measured immediately after the operation, was 3·30 m. long; obviously therefore the upper incision must have been in the jejunum.

A series of measurements carried out on the dead adult subject in the Anatomical Institute of Cracow showed that the length of the small intestine may vary in man from a minimum of 5·60 m. to a maximum of 8·70 m. More than half the small intestine therefore was removed in the boy on whom Ruggi operated.

The post-operative history was unexpectedly favourable. After a few days the patient was fully convalescent, but for at least 20 days he cried day and night from hunger, although he was allowed a relatively large amount of food. At the end of a month, his nutrition improved, and all bodily functions became regular, defaecation included. It should be noted that the child had no fever throughout the course of his illness.

A month after the operation Saggini made experiments (unfortunately incomplete) on 3 consecutive days, on this boy's metabolism, from which the following positive data can be utilised. In the 3 days of experiment the boy's weight increased 500 grms., as he was fed on an abundant diet, rich in nitrogenous and starchy foods. The faeces only contained small quantities of nitrogenous matters, carbohydrates, and fats, as compared with the amount ingested in the food, showing that the processes of digestion, absorption, and assimilation went on physiologically, in spite of the serious anatomical loss of small intestine.

On repeating the same experiments on metabolism, 3 months after the operation, for another 3 days, he found a marked increase in weight as compared with the first experiments (17·600-23·100 kgrms.), and an almost perfect equilibrium of balance between intake and output, as deduced from the fact that during the 3 days of investigation the boy's weight went neither up nor down as a whole perceptibly. This shows that, in 3 months after the operation, the child had made up the loss of weight due to obstructed digestion during the period of illness prior to the operation, and the enforced abstinence or scarcity of food in the post-operative period.

Everything in this rare case of extensive resection of the small intestine indicates that the functional adaptability of this organ, which is the principal factor in digestion, is much greater than we should suppose *a priori*.

VI. Owing to its muscular coats the intestine is an *organ of movement*, with the office of gradually driving forward the chyme

or alimentary pulp, in order to mix it with the digestive secretions, to facilitate the absorption of the products of digestion, and finally to expel the undigested and unabsorbed residues of food, along with the excreta that collect in the gut.

The several parts of the intestine, morphologically speaking, show a gradual differentiation, from which a correlative differentiation of function may be argued. The *duodenum* is distinguished not only by the absence of a mesentery, and by being only partially covered with peritoneum, but also by presenting the widest and most muscular part of the small intestine. Its total length varies between 25 and 30 cm., its breadth from approximately 35 to 50 mm.

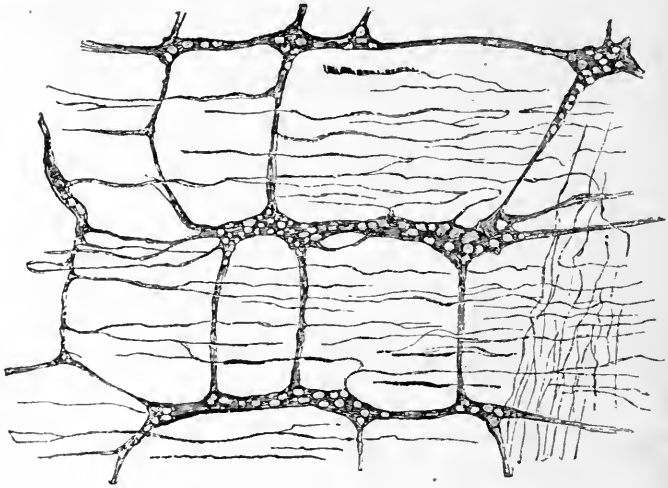

FIG. 75.—Auerbach's plexus between the two muscular coats of the intestine. Gold chloride method. (Cadiat.)

The remainder of the small intestine, which has a mesentery, is arbitrarily divided into *jejunum* (upper $\frac{2}{5}$) and *ileum* (lower $\frac{3}{5}$), which have no distinct morphological boundaries. But the portion between the commencement of the jejunum and the end of the ileum (where the ileo-caecal valve is situated) gradually alters in structure and appearance, so that the two ends of the segment can be readily distinguished. The jejunum is larger and more muscular; the ileum is narrower with thinner and paler coats, the valvulae conniventes are smaller and gradually disappear at the lower end, the villi are shorter, the groups of Peyer's patches larger and more numerous. Owing to all these differential characters, any part of the jejunum weighs more than a corresponding portion of the ileum. The diameter of the jejunum is about 3·25 cm., that of the ileum 2·60 cm. They vary considerably in length, with age and with different individuals, as we have

seen in another connection—probably in relation with the predominatingly vegetable or animal character of the usual diet.

The structure of the walls of the small intestine differs in no essential from that of the oesophagus and stomach. The muscular coat is composed of plain muscle. The *longitudinal* fibres form a comparatively thin layer which becomes denser along the free border of the intestine, the *transverse* or *circular* fibres are thicker and more distinct: the first in contracting can only dilate and shorten the intestinal tube (Exner); the second, on the contrary, constrict and lengthen it. The longitudinal cells which thicken along the free border of the intestine must stretch and distend the numerous folds or convolutions.

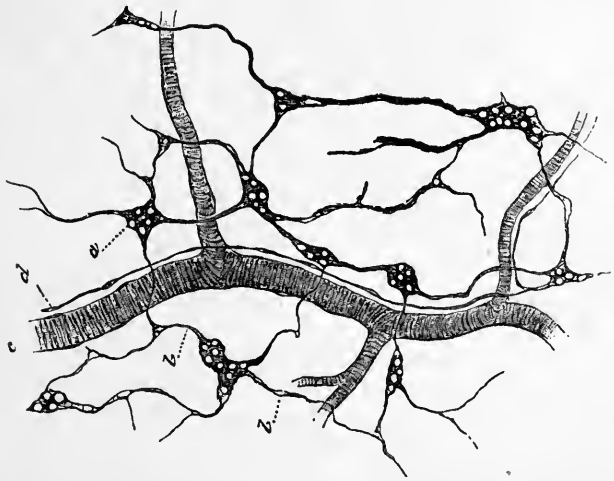

FIG. 76.—Meissner's plexus, from submucous layer of intestine. Gold chloride method. (Cadiat.) *a*, *a*, ganglia; *b*, *b*, cords of plexus; *c*, small blood-vessel; *d*, nerve filaments that accompany the small artery.

A gangliated plexus lies between the two muscular coats, and is in relation with the caeliac plexus, and branches of the vagus and great splanchnic, and is known as the plexus myentericus or plexus of Auerbach. It is principally composed of non-medullated fibres, which give off a number of fine branches to the longitudinal and circular muscle-cells (Fig. 75).

Other, larger branches pass through the circular bundles of fibres to reach the submucous layer, where they form a second gangliated plexus, the filaments of which are much finer than those of the preceding; this is called the plexus of Meissner (Fig. 76). From this plexus, nerve fibres pass into the muscular layer of the mucous membrane, breaking up into fibrils that ramify in the proper tissue of the mucous coat and villi, and terminate, according to Berkley, in small pear-shaped or globular dilatations.

On opening the abdomen of a recently killed animal, so as to expose the intestines, they are seen to be the seat of writhing or *vermicular* movements. At first these are hardly perceptible, and are confined to the upper part of the small intestine, but they soon become more ample and extend over its entire length to the last section of the ileum, with decreasing vigour. They consist of contractile waves propagated peristaltically, and preceded by waves of dilatation; the coils of intestine are displaced and move forward, some being pushed down, while others come to the surface, sliding one over the other. The irregularity and simultaneous appearance of these vermicular movements in different parts of the intestine confuse the observer, so that it is impossible to grasp the rhythm, or the ascending or descending direction of the motion. After reaching their maximum intensity, the waves gradually diminish, and die out. But after the spontaneous movements have ceased, it is possible to start them again by various stimuli. Haller excited intestinal movements in a dog an hour after death, Colin in the horse after about 50 minutes.

The movements observed in animals with an open abdomen, such as Haller described, are, however, quite unlike the true physiological phenomenon, *i.e.* the movements normally serving in the intestine to propel and churn up the chyme, and to facilitate intestinal absorption. They result from the abnormal conditions of the intestine exposed to the air after the death of the animal, when it becomes hyperaemic, cooled, and dried up.

If immediately after opening the animal's abdomen it is filled with physiological saline, warmed to body-temperature: or better, if the abdomen of a living rabbit be opened after fixing it in a holder, and plunging the whole into a bath of the same saline at 38° C., as first attempted by Sanders-Ezn and von Braam-Houckgeest (1872), the duodenum and the jejunum alone exhibit very slight movements, which can be separated into two groups, according to whether or no they assist the progress of the intestinal contents towards the large bowel: the former, known as *peristaltic* movements, originate in a ring of constriction which travels like a wave from one part of the intestine to the other; the latter, known as *pendulum* movements, exhibit a rhythmic to-and-fro motion of the single coils, which alternately contract and expand—so that the contents are shifted about and thoroughly mixed.

According to van Braam-Houckgeest, the longitudinal fibres play an active part, even in the weakest peristaltic contractions, for the advancing ring of constriction is immediately preceded by a shortening and widening of the intestine which promotes the advance of its contents towards the ileum. The length of the annular wave of peristalsis varies greatly. If it traverses a short distance, it is weak, and is frequently renewed. With stronger

peristaltic movements (which are only seen in the filled and distended jejunum), the ring of constriction travels like a rapidly revolving wheel over long portions of the gut, driving the intestinal contents forward tumultuously in the direction of the caecum. This rapid, vigorous, and extensive wave of peristalsis was termed by van Braam-Houckgeest the *roll movement* (*Rollbewegung*).

Antiperistaltic movements, i.e. movements in the direction of the pylorus, are never observed under normal conditions. They were formerly assumed to exist, as asserted by Engelmann in 1871, owing to the effect of mechanically exciting the intestine, which produces a descending peristaltic and an ascending antiperistaltic wave. In living animals kept under the salt bath, and also in the isolated loop with the Thiry-Vella method, antiperistaltic movements never occur. Fibini (1883) studied the behaviour of a wax bolus introduced into a Vella's loop, and saw that under normal conditions it travelled 1 cm. in 55 min. Retrograde movements, due to the supposed antiperistalsis, never occurred. On the other hand, increase of speed was noted when a faradic stimulus was applied to the proximal end of the loop (velocity = 1 cm. in 10 min.). Psychical influences (fear) also increased the speed of the bolus.

Some clinicians, however, admit the existence of antiperistaltic movements (at least under pathological conditions) to account for faecal vomiting, consequent on stricture of the intestine; but this may also be caused by regurgitation due to the energetic action of abdominal compression, independent of the intestinal contractions, as already affirmed by van Swieten.

The experimental results of excising a more or less extensive segment of gut, and then suturing it in the reverse direction, so that the lower end is joined to the upper part of the intestine, and the upper end to the lower part leading to the ileo-caecal valve, harmonise with the theory that normal peristalsis is descending. These remarkable experiments were first made by Mall, and repeated by Kirstein (1889), then by Kauders (1893), and later by Fasola and Sabbatani (1899). Many of the animals in which this inversion of a loop of intestine was attempted died in the first 2 days after the operation from purulent peritonitis, caused by intestinal perforation owing to laceration at the upper suture, where the intestinal contents accumulate and stagnate. Kirstein, however, succeeded under special conditions in keeping 2 dogs alive. Two cats survived with Kauders for 10-11 weeks. In the first week there was nothing abnormal in their nutrition or defaecation; after that they began to refuse food, and died with every symptom of slow starvation. Out of 20 dogs operated on, Fasola and Sabbatani lost in the first 2 days all in which the greater part of the small intestine was reversed, as well as those in which the inverted

tract was comparatively short, but included the last portion of the ileum. On the other hand, 4 dogs, in which a part of the small intestine of varying lengths (60-110 cm.) had been reversed 15 cm. above the ileo-caecal valve, survived for some time (5, 12, 15, 18 days). At the autopsy all these animals exhibited fusiform distension of the intestine, the centre of which corresponded to the upper suture.

More recently, two German surgeons, Enderlen and Hesse, on repeating the same experiments with 3 dogs, arrived at different results. Two of their dogs lived 73 days; another was killed after 49 days. On faradic stimulation the inverted loop showed peristaltic waves in the bucco-anal direction, *i.e.* in an opposite (antiperistaltic) direction to that normal to the inverted loop. They concluded that although normally there are no antiperistaltic movements in the gut, the reversed loop is capable of adapting itself to the new conditions, and of inverting the direction of its movements.

In Kirstein's 2 dogs (one of which was killed after 7 weeks, the other after 4 months) the important fact was observed of a considerable thickening of the muscles of the intestine, confined to the upper half of the dilated tract, to which the lower end of the reversed loop was sutured. It should also be noted that the dog killed after 4 months (although its nutrition and defaecation were almost normal) was beginning to exhibit emaciation, which might conceivably have continued until, like the other dogs, it perished of marasmus, had Kirstein not been in such haste to make his post-mortem examination.

Further experiments are needed before we can adequately explain these phenomena. It seems to us, however, more than probable that the fusiform dilatation of the intestine, as described above, is the effect of accumulation there of the ingesta, secretions, and intestinal gases, due to the resistance opposed by the reversed loop, with its ascending peristaltic movements, to the passage of the intestinal contents. This resistance (if the inverted part does not adapt itself by reversing the normal direction of its movements) can only be overcome by exaggerated descending peristalsis of the upper part, as shown by the hypertrophy of its muscles, owing to which there is passive dilatation of the first part of the reversed loop, in which hypertrophy of the muscular coat is altogether absent.

It has been attempted, from cases of intestinal fistula in man and dogs, to determine the speed and force of the intestinal-peristaltic movements; but the results were very variable, as we should expect on taking into account the different degrees of repletion, varying character of the ingesta, and dissimilar strength of the several parts of the gut. One important fact alone results from these experiments, and harmonises perfectly with the anatomical

and histological data, *i.e.* that both rate and force of the intestinal movements diminish regularly from duodenum to jejunum, from jejunum to ileum.

The data as regards frequency and amplitude of the intestinal movements in the opposite physiological states of sleep and waking, fasting and digestion, agree fairly well. During sleep the motions, such at least as are peristaltic, are much retarded or entirely suspended. There is little difficulty in demonstrating this fact in persons whose abdominal walls are thin owing to absence of adipose tissue, or better in women who, as the result of previous pregnancy, exhibit the so-called *diastasis recti*, along the linea alba abdominalis. The observations of Busch upon the case above referred to of fistula of the upper part of the jejunum, deserve special consideration, because from the extreme tenuity of the walls and the flattening of the abdomen of the patient, the movements of the intestine were not merely palpable to the touch, but could be seen as a progressive rise and fall of the abdominal wall. During the greater part of the night all intestinal movement ceased. During the day Busch noted periods of repose and periods of intestinal activity, but with no regularity of rhythm or duration. If the intestines were at rest before a meal, no movement appeared immediately after, but there might be a delay of 10 or more minutes. On the other hand, long periods of intestinal motor activity were not infrequently seen in the fasting state, without any obvious reason.

In non-anaesthetised rabbits immersed in a bath of saline at body temperature, the greater part of the intestine usually remained at rest, the duodenum and jejunum alone exhibiting movements with an irregular rhythm. In this connection it should be noted that, according to Pal (1890), the mere fact of opening the abdomen suffices to determine reflex inhibition of the intestinal movements.

These movements apparently become more vigorous and ample during the outpouring of the digestive secretions, and of bile in particular. According to Schüpbach (1907), however, bile has no accelerating influence on a bolus introduced into a Vella's loop by the method indicated by Fubini. Eckhard, too, denies that bile introduced into a coil of intestine in a rabbit immersed in van Braam-Houckgeest's bath has any accelerating effect on the peristaltic motions. At times, however, without any apparent reason, there is, now in one part of the small intestine, now in another, a disappearance or reappearance of peristaltic motion, which may assume the vigour and amplitude of the roll movements described above. Generally speaking, it may be said that the movements are both more frequent and more rapid in the small than in the large intestine, and more lively and ample in the duodenum and jejunum than in the ileum; the former have a more

frequent rhythm (14-22 per minute), the latter a slower rhythm (12-18 per minute).

In dogs with intestinal fistulae near the valve of Bauhin, Radziejeswski observed that the flow of the intestinal contents through the fistula commenced $1\frac{1}{2}$-$2\frac{1}{2}$ hours after a meal: that the first expulsory movements occurred at intervals of 5-30 minutes; the later ones at greater intervals: and that some 6 hours after the meal pauses or rests of many hours could be seen. There are accordingly periods of activity and of repose, although it is not possible to establish fixed data in regard to duration and rhythm of the peristaltic motions. The results of Braun and Lossnitzen differed little.

The movements of the gut can be provoked or modified artificially by mechanical, thermal, electrical, and chemical stimuli; as well as by the effects of hyperaemia and of anaemia; or by chemical agents introduced into the intestine. The most important fact established by direct mechanical or electrical stimulation of the intestine is that the contraction excited at the point of stimulation spreads in both directions along the bowel; in some species of animals, indeed, the curious fact appears that the movement is propagated more extensively upwards than downwards, *i.e.* more in the antiperistaltic than in the peristaltic direction (Engelmann). Nothnagel's experiments, however, show that the effect of excitation varies with the nature of the stimulus. If a crystal of sodium chloride be applied to the outer surface of the intestine, a contraction is produced which is propagated upwards for some centimetres in the direction of the pylorus; a crystal of potassium chloride, on the contrary, produces only a local spasm.

The dissimilar reaction of the longitudinal and the circular muscle fibres to stimulation with the constant current is interesting. Schillbach (1887) first noted that on bringing the kathode into contact with the external surface of a loop of intestine a localised contraction results, while on placing the anode in contact the local contraction is transformed after a few seconds into a peristaltic wave of contraction, which moves from the point stimulated along the loop in both directions. Hillel Jafé (1889) confirmed this observation, and interpreted the primary effect of the anodic closing stimulus as an effect of contraction of the circular muscles of the muscular coat. Biedermann and Sinchovitz (1889) extended these observations, and gave a better explanation of their significance. According to these authors the effect of the unipolar anodic closing stimulus is to produce a ring of constriction by the local contraction of the circular muscles. The effect of the unipolar kathodic closing stimulus, on the contrary, is a slight local contraction of the longitudinal muscles. Luderitz (1891) also confirmed these data and their interpretation.

It is evident that the character of the intestinal movements differs from that of the oesophageal; contraction of the intestine from a local stimulus may spread under certain conditions in both directions, although normally it progresses from the pylorus towards the ileo-caecal valve; the contraction of the oesophagus, on the contrary, is always propagated from above downwards, in the direction of the cardia. Another essential difference between the movements of the oesophagus and those of the intestine appears from the fact that the former continue to spread from above downwards after transverse section of the gullet (Mosso); the latter, on the contrary, are arrested at the edge of the section. These, then, are true *peristaltic* motions, propagated through the continuity of the tissue; the movements of the oesophagus, on the contrary, are (as we have seen) always propagated reflexly by means of the cerebrospinal centres, and may therefore be termed *pseudo-peristaltic*.

Conflicting opinions are held by various experimenters in regard to the influence of the vascular and circulatory conditions, active hyperaemia, venous congestion, ischaemia, and asphyxia, upon the intestinal movements. Nasse, S. Mayer, von Basch contradicted Schiff's statement that obstruction of the aorta evokes or strengthens intestinal contractions; they observed arrest for a time, after which the movements returned with increased vigour. Betz, van Braam-Houckgeest, and Mall, however, found that anaemia inhibited all movements of the intestines. In asphyxia, on the contrary, Mayer and von Basch found increase of the intestinal movements.

The effect of heat on the movements of the gut is also interesting, as shown by Claude Bernard's experiments. He placed the quiescent intestine of a rabbit in a box with glass walls, at a low temperature. As soon as a current of warm air was passed through the box, visceral movements were exhibited, even before the thermometer registered a rise of temperature. Horváth, too, saw that the intestines of dogs, cats, rabbits, frogs, and guinea-pigs remained quiescent between 0° and 19° C., and began to move above that temperature.

Bayliss and Starling (1899), by means of the graphic method, confirmed the statement that obstruction of the aorta arrests the movements of the intestines. They inserted a balloon fastened to a tube, with a recording apparatus, through a small longitudinal incision in the loop, closing the slit with stitches, one of which is taken round the tube. The capsule is distended with air under a pressure of about 10 cm. water, after which the loop is returned to the abdominal cavity. Under these conditions the intestine is seen to be the seat of continuous rhythmic contractions, which are fairly regular, and sweep down the intestine at a low rate. As shown in Fig. 77, instantaneous occlusion of the aorta produces

almost instantaneous arrest of the rhythmic movements, with gradual decrease of muscular tonus. On removing the obstruction, the viscus immediately gives a couple of beats, followed by a pause, after which the rhythmic movements return in beats of growing amplitude, while the volume of the intestine diminishes at the same time, *i.e.* the tone of the muscles increases. This exaggerated return of intestinal activity is probably due to the great vascular dilatation and hyperaemia of the viscus, consequent on the prolonged anaemia which results from the occlusion of the aorta.

VII. The movements of the intestine, like those of the heart,

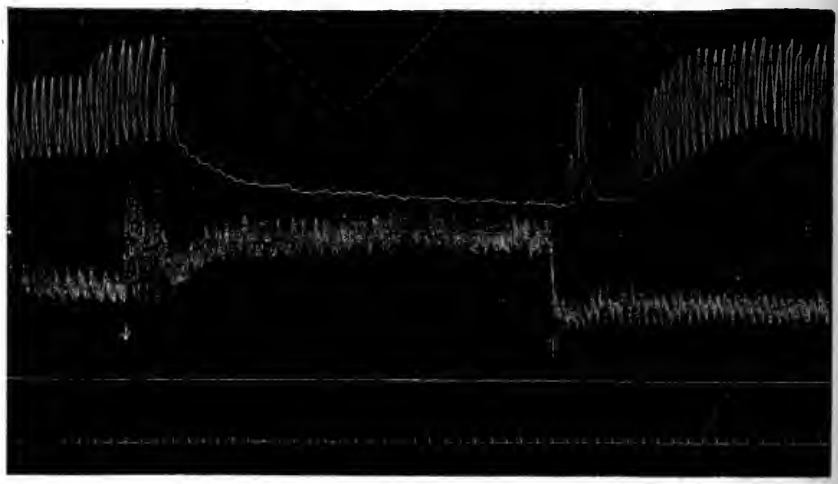

FIG. 77.—Effect on rhythmic (systolic and diastolic) movements of intestine, of obstructing the dog's abdominal aorta. Recorded with balloon method. (Bayliss and Starling.) *CP*, carotid pressure; *I*, contractions of intestine. At ↓ the aorta was blocked; at ↑ it was reopened.

can be carried out independent of the central nervous system. This is proved by the fact that they continue (in a constantly peristaltic form) in excised loops of intestine, under favourable conditions of temperature and moisture (Salvioli). The question whether these movements are *automatic* or *reflex*, and whether they depend on a rhythmic property inherent in the muscle cells, or on the ganglia of Auerbach's plexus with which the muscular coats of the intestine are richly provided, has not been completely solved by the data we possess at present.

The memoir published by Bayliss and Starling (1899) is of great value in this connection. By an ingenious graphic method they succeeded on dogs, anaesthetised principally with morphia, in recording simultaneously the contractions of the circular coat and the longitudinal coat of a loop of small intestine (exposed and

kept in a bath of warm saline). In this way they were able to make a more exact analysis of the rhythmical movements traced in the preceding figure (which probably correspond with the *pendular* movements described by van Braam-Houckgeest) and of the so-called *peristaltic* movements.

The most convenient way of recording the intestinal movements is by the exploring rubber balloon, described above, which has been employed by

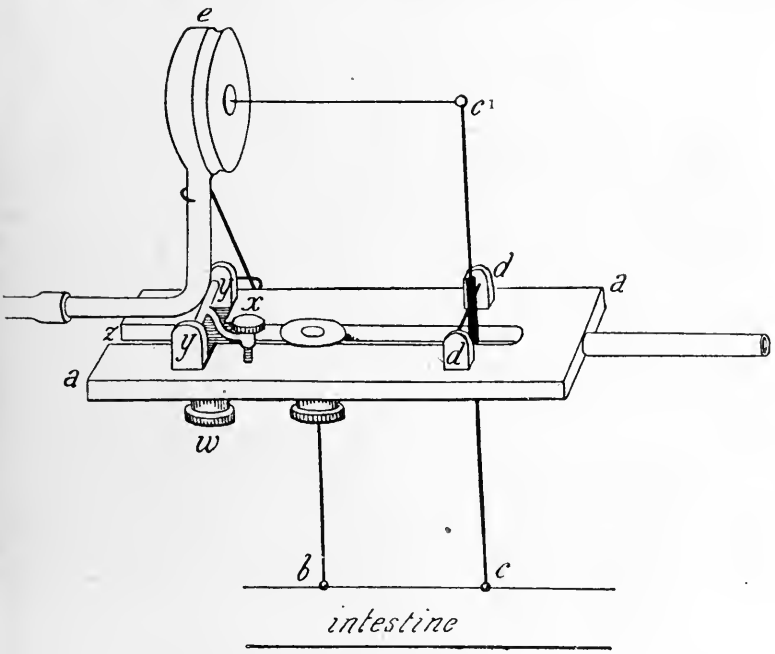

FIG. 78.—Diagram of enterograph. (Bayliss and Starling.) *a, a*, brass plate, in which two steel needles *b, c* are fixed in a slot; *b* can be shifted nearer to or farther from *c* by loosening its fixing screw; *c* is prolonged through the slot, and revolves round the axis *d, d*. The upper end of *c* is fastened by a thread to the disc on the rubber of the tambour *e*, which communicates by a tube *f* with a piston recorder. The lower ends of *b* and *c* are pierced with holes. Through these holes pass fine threads which are carried by a needle through the outer layers of the intestinal wall, and fastened. The muscle fibres running from *b* to *c* can only contract by pulling *c* towards *b*. This causes a movement of the upper end of *c* in the opposite direction, and a consequent pull on the membrane of the tambour, which is registered by the piston recorder. The distance of *e* from *c* and the tension on the muscle fibres between *b* and *c* can be regulated by means of the screw *x*.

various experimenters (Openchowski, Mislawski, Bunch, Courtade and Guyon, etc.). This method, however, can only record the state of activity or rest of the circular coat of the intestine.

In many cases it is advantageous to record the intestinal movements without introducing any foreign body into the gut. With this object Bayliss and Starling invented the instrument called the *enterograph*, as shown in Fig. 78. Two separate enterographs may be fixed at right angles to one another at the same point, so that one lever acts in the longitudinal, the other in the transverse direction, in relation to the intestine, as shown in

the schema of Fig. 79. With this arrangement it is possible to record simultaneous tracings of the circular and the longitudinal coat of the intestine.

The rhythmical (systolic and diastolic) pendular movements are due to synchronous rhythmical contractions and expansions of

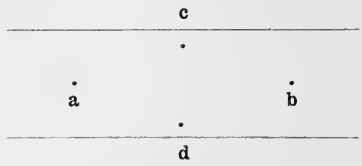

FIG. 79.—Two enterographs placed at right angles on a segment of intestine. *a*, *b*, levers of enterograph recording contractions of longitudinal coat. *c*, *d*, levers of enterograph recording contractions of circular coat. (Bayliss and Starling.)

both longitudinal and circular fibres (Fig. 80). They are more or less visible in the whole coil of intestine, when exposed and immured in the bath. They recur some 10-12 times per minute, and course over the gut from above downwards at a velocity of 2-3 cm. per sec. (Fig. 81). Bayliss and Starling hold that these movements are entirely *myogenic* in origin, *i.e.* due to automatic

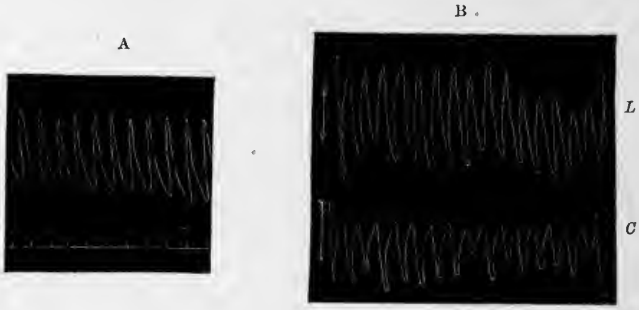

FIG. 80.—Rhythmic contractions of intestine. (Bayliss and Starling.) A, systolic and diastolic movements of intestine. Balloon method. Time marking = 6 seconds. B, same movements as A, recorded by two enterographs, showing synchronous activity of longitudinal (*L*) and circular (*C*) muscle-fibres at same spot. The descending direction of the arrows indicates direction of contraction.[1]

rhythmical activity inherent in the muscle cells, and that they are propagated by muscular conduction, as assumed by Engelmann, Gaskell, and Fano for cardiac rhythm.

In direct contradiction to this thesis we have Yanase's observations on the intestinal movements of embryo rabbits and the human foetus in premature abortion. He found that the period

[1] In all curves recorded by Bayliss and Starling with the *balloon* method, contraction causes an *upward* movement of the lever. In the curves obtained by means of the *enterograph*, contraction is signified by a *downward* movement. Curves to be read from left to right.—TRANSLATOR.

at which the first intestinal movements appeared, both in the guinea-pig (26-27th day) and in man (77th day), is always later than the appearance of nerve cells and nerve fibrils in the muscular coat; hence he upholds the neurogenic interpretation of the intestinal movements.

The peristaltic movements are true co-ordinated reflex acts, which depend on the mechanical (and chemical ?) stimuli operating in the intestine. They are propagated by the local nervous mechanisms (Auerbach's plexus), independent of the central or extra-intestinal nervous system.

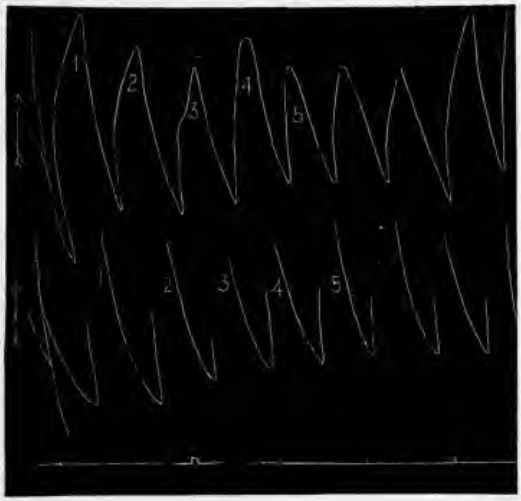

FIG. 81.—To show rate of propagated contractions. (Bayliss and Starling.) Two balloons 10 cm. apart in a loop of intestine, cut at both ends. *UB*=upper and *LB*=lower balloon. Time marking=6 seconds. Rate of propagation=5 cm. per second, as shown by the delay in the systoles 1, 2, 3, 4, 5, of the lower in respect of the upper tracing. (Ascending direction of arrows shows direction of contraction.)

According to Bayliss and Starling, "the production of the true peristaltic wave is dependent on the unvarying response of the intestinal nervous mechanism to local stimulation." They formulated the *law of the intestine* (which might better be termed "law of intestinal peristalsis") as follows: "Local stimulation of the gut produces excitation above and inhibition below the excited spot." This confirms the observations of Colin and van Braam-Houckgeest, from simple inspection, to the effect that intestinal peristalsis always consists in a ring of constriction preceded by a wave of relaxation, which forces the contents of the viscus to pass along the intestine from above downwards. Every point of the intestine is therefore subject to opposing influences transmitted to it along its wall, viz. inhibitory impulses

from above, and augmentor or excitatory influences from below. The activity of the intestinal muscles at any time will depend on the relative influence of these two sets of impulses (Bayliss and Starling).

Exner and his pupil A. Müller made an interesting contribution to our knowledge of the reflex co-ordination of the intestinal movements. Exner observed that when a pin was introduced into a loop of intestine point forwards, it was regularly found after a certain time to be inverted, *i.e.* head forward, point behind. This mechanism of defence is effected by a complicated alternation of relaxation and contraction of the muscle walls; at the point where the mucous membrane is pierced by the pin, the circular coat relaxes, while the longitudinal contracts, so that a tumefaction is formed which surrounds the pointed end of the pin.

At the same time a ring of constriction forms behind the pin, so that it is first turned transversely to the loop, and subsequently reversed, with the head foremost. Müller found that this complicated reflex mechanism acted just as well when the vagi and the solar plexus were divided. It therefore seems as if this mechanism were carried out by the local nervous mechanisms, *i.e.* the plexuses of Meissner and Auerbach.

To illustrate the details of the ingenious theory of intestinal peristalsis formulated by Bayliss and Starling, one of their most important experiments may be quoted. In order to excite peristalsis in an isolated loop of intestine, they insert, about one inch from the upper end, a bolus made of cotton-wool covered with vaseline. Shortly after putting in the bolus, the contractions of the segment of intestine immediately above the bolus undergo increasing augmentation, until the intestine at this point enters into a strong tonic contraction. This presses the bolus onwards, and as the bolus moves the ring of constriction follows it up until it has expelled the bolus through the lower opening of the coil. In some cases, after the bolus has been expelled, a second slow peristaltic wave of contraction may pass from one end of the coil to the other, as if to expel any detached portions of the bolus that may be left behind. This progression occurs only in one direction, from above downwards. If the bolus be inserted from below and pushed up the gut it will be returned by the way it has entered. If, however, the intestine is in good condition, the latter experiment becomes impossible. On attempting to push up the lump of cotton-wool, the intestinal wall contracts strongly above it and resists the upward passage of the bolus.

If two enterographs are placed at right angles to each other at a point about the middle of a coil of intestine, so as to record the contractions of both longitudinal and transverse coats, the synchronous activity of the two coats is seen to be altered by the passage of a bolus introduced from the upper end. Fig. 82 records

this passage. The beginning of the tracings (left) shows the rhythmic synchronous contractions of the longitudinal and circular muscle-fibres. At A a bolus made of cotton-wool coated with vaseline was inserted by an opening into the intestine 4½ inches above the enterographs. The contractions of the circular coat cease instantly, and this inhibition is accompanied by a gradually increasing relaxation. There is some relaxation of the longitudinal coat, but the rhythmic contractions do not altogether cease. At B the bolus had arrived at the upper longitudinal lever, and at C had passed this, and was directly under the transverse enterograph or a little below it. At this point a strong tonic contraction of both coats occurs, expelling the bolus beyond the levers. This strong contraction passes off, to be

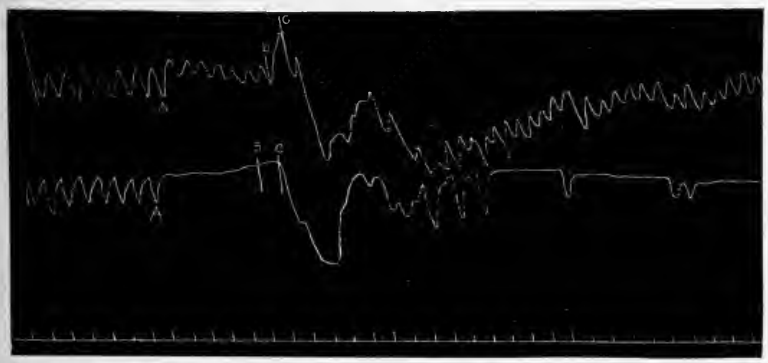

FIG. 82.—Passage of a bolus down the intestine, as recorded synchronously by two enterographs at right angles. Longitudinal (*L*), circular (*C*), coats. (Bayliss and Starling.) (Explanation of letters in text.)

succeeded by another, which like the first is moving down the intestine. In this second tonic wave the rhythmic contractions are evident, superposed on the curve. After the passage of the bolus there is shortening of the gut (increased tone of longitudinal fibres), and the rhythmic contractions of each coat are no longer synchronous.

Other valuable work has recently been carried out upon isolated loops of intestine. Salvioli (1882) had described and successfully applied an admirable technique for studying the functions of parts of the intestine isolated from the animal. He succeeded in nourishing these loops by artificial circulation of blood serum through the superior mesenteric artery. The intestinal movements were recorded by very light levers placed in different positions on the loop, so as to transmit the contractions of both longitudinal and circular muscle-fibres.

This method, with slight modifications of detail, was revived in 1899 by O. Cohnheim, and in 1904 Magnus carried out a

series of experiments which led to interesting although somewhat schematic results. He studied the intestinal movements of an isolated loop, after stripping off (from within outwards) one or more of its coats. He found that when the mucous membrane is removed, the movements persist unaltered, and concluded that they are not *reflex*, excited by stimuli from the mucous coat, but are *automatic* in character. The movements also continue after the submucous coat has been removed, from which he concluded that they are independent of Meissner's plexus. Lastly, on separating the inner (circular) from the outer (longitudinal) muscular coat by a circular incision, so as to sever the inner layer of fibres completely from Auerbach's plexus, he saw that the inner (circular) coat remained motionless, while the outer (longitudinal) coat still contracted rhythmically.

Magnus concluded that the intestinal movements are *neurogenic* not *myogenic*, *automatic* not *reflex*, and that the automatism arises in the peripheral nerve centres of Auerbach's plexus. This is a bold assumption. The violent removal of the mucous or submucous coat cannot (as it seems to us) be equivalent to sequestration from peripheral stimuli, but rather increases them, in consequence of the trauma due to the laceration of so many afferent nerve fibres.

As regards the *neurogenic* character of the intestinal movements, another assertion of Magnus also appears to us to be strained, viz. that the conduction of excitation from one point to another of a loop takes place along the muscular coat, without the co-operation of Auerbach's plexus, nor still less of Meissner's.

Finally, the Röntgen rays, already applied by Guyon to the study of gastric movements, have also been employed on the intestine. Cannon, in particular, has carried out methodical experiments by this method (see p. 194). He fed his experimental animals (cats) on a diet mixed with bismuth sub-nitrate, which intercepts the passage of the X-rays, and thus appears on the photographic screen as a shadow. The animals were kept fasting before the experiment, and the bowels cleared out with castor oil, so that it became possible on living animals to follow the progress of food down the alimentary canal. Cannon found that the food was divided into many little segments in the small intestine, owing to the rhythmic repetition of the pendular movements. This segmentation of the food in a coil is repeated by the fusion and redivision of adjacent segments, in a continuous process, so that the churning-up of the chyme is actively promoted. In the cat the rate of division into segments is about 30 divisions per minute. From time to time a peristaltic wave drives the particles forward, on which the process of segmentation recommences. When the animals are made to react to painful stimuli, the intestinal movements cease. During sleep, on the contrary, they continue.

These elegant experiments have been controlled and confirmed by other workers, particularly by Wolff (1901-2) and Carvallo (1907). The latter, at the Marey Institut in Paris, made some interesting kinematographs of the progress of the food, from the stomach through the intestines, in the frog.

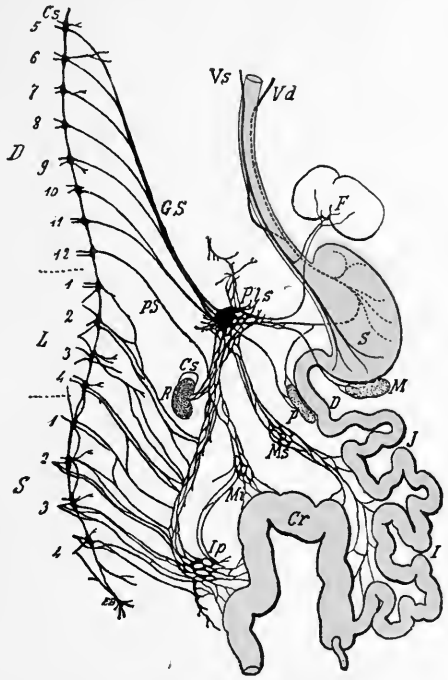

FIG. 83.—Schema to show distribution of sympathetic and vagus in gastro-intestinal tube and adjoining glands, in man; applicable to a large extent to the dog, on which the experiments on the innervation of the intestine were carried out. (Luciani.) *S*, stomach; *D*, duodenum; *J*, jejunum; *T*, ilium; *Cr*, large intestine; *F*, liver; *M*, spleen; *P*, pancreas; *R*, kidney; *Cs*, suprarenal capsule. *Vs*, left vagus, which—after traversing the diaphragm—divides into numerous branches that are distributed to the ventral surface, and along the small curvature of the stomach, giving off an important branch to the liver. *Vd*, right vagus penetrating the dorsal wall of the abdominal cavity, behind the peritoneum, with branches to the posterior surface and great curvature of the stomach, with one or two fibres to the pancreas; these unite at the solar plexus (*Pl.s*), and send branches to the intestine which pass through the superior mesenteric plexus (*Ms*), and follow the course of the sup. mesenteric artery. *Cs*, sympathetic cord, comprising the inferior thoracic tract (*D*), lumbar (*L*), and sacral (*S*). The dorsal rami of the gangliated cord give origin to the great splanchnic (*GS*), and little splanchnic (*PS*), which contain the greater part of the sympathetic nerve to the intestine, after traversing the solar plexus (*Pl.s*), the superior mesenteric plexus (*Ms*), the inferior (*Mi*), and the hypogastric plexus (*Ip*).

The peristaltic movements, which depend on Auerbach's plexus, and are therefore exhibited in excised loops, are also under normal conditions regulated and controlled by the extrinsic nerves which reach the intestine from the cerebrospinal and sympathetic systems. The afferent nerve paths run principally in the great splanchnics and the vagi. The schema of Fig. 83 is intended to illustrate the

relations of these two nerves, by the chain of the sympathetic, the solar plexus, the superior and inferior mesenteric plexus, and the hypogastric plexus, with the various abdominal viscera, more particularly the intestine.

Division of one or the other of these nerves, or even of both, has at first no appreciable effect on the movements of the intestine; in a short time, however, a more or less conspicuous and persistent exaggeration and disturbance ensues, owing to congestion of the blood from the paralysis of the vessels.

Stimulation of the peripheral end of the *splanchnic* by the experiments of Joh. Müller, Ludwig, Nasse, and S. Mayer led to no definite results. Pflüger (1857) first showed that stimulation of these nerves when the intestines were in vigorous motion arrested the movements, in the same way as the vagus causes arrest of the heart, *i.e.* by producing a relaxation. The same effect can be obtained on exciting the spinal cord between the 5th and 11th dorsal vertebrae. This observation (though it is not always to be seen as clearly as could be desired) has been confirmed by all subsequent workers. The phenomenon, as discovered by Pflüger, has, however, received different interpretations. Schiff and Valentin, who saw that weak currents applied to the splanchnic increased the intestinal movements, attributed the arrest with strong currents to the exhaustion of the nerve. S. Mayer and von Basch ascribed the standstill to ischaemia of the intestinal walls, due to the vaso-constrictor fibres of the splanchnic. Van Braam-Houckgeest, who at first adopted this opinion, abandoned it later, on noting that even weak currents, which fail to excite the vaso-constrictor fibres of the splanchnic, do inhibit the movements of the intestine, contrary to the opinion of Schiff and Valentin. Moreover, if the viscera of a rabbit are exposed to the air till they become congested by vaso-motor paralysis, stimulation of the splanchnics has no effect on the blood-vessels, although the intestinal movements are inhibited as in a normal animal. Jacobi stated, in confirmation of Pflüger's theory, that the inhibitory fibres of the splanchnic have a different course from the vaso-constrictor fibres, and that section of the nerves running from the suprarenals to the solar plexus annuls the inhibitory action of the splanchnics, without interfering with their vaso-constrictor effect. As regards excitation from the spinal cord, Pflüger's observation is contrary to that of Cl. Bernard, who found that a transverse section, or the mechanical stimulation (puncture) of the spinal cord above the origin of the splanchnic, is followed by extremely energetic movements of the intestines.

Ludwig and Kupfer, Schiff, Bechterew and Mislawsky, Bunch, observed a motor effect in the intestines on stimulating the splanchnics. The last observer, in 1898, obtained tracings from

the intestine, which show that stimulation of the splanchnics in some animals increases, in others inhibits muscular tonus; in others again there is inhibition with preliminary augmentation of tone. Bunch concludes that the splanchnics contain fibres of opposite functions, and that excitation of the nerves produces one or the other effect, according as the inhibitory or the motor fibres preponderate in the particular animal.

Ehrmann (1885), in work carried out in von Basch's laboratory, suggested crossed innervation by the two kinds of fibres contained in the splanchnics, and assumed that they were motor for the longitudinal and inhibitory for the circular coat.

On the other hand, Courtade and Guyon (1897), in experiments undertaken in François-Franck's laboratory, state that in normal

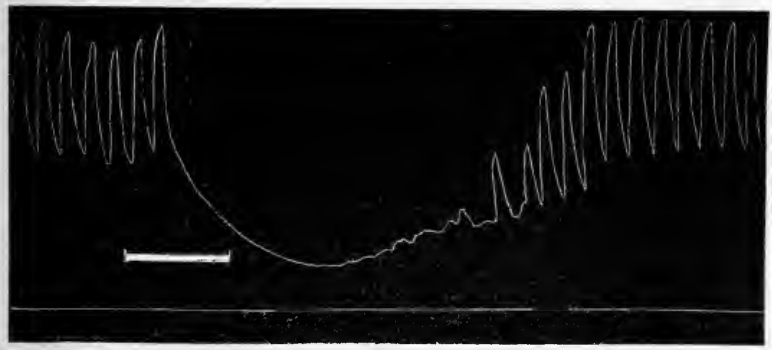

FIG. 84.—Intestinal contractions. Balloon method. Intestine returned to abdomen. Shows inhibitory effect of exciting peripheral end of cut splanchnics. (Bayliss and Starling.) The white mark shows duration of excitation.

conditions of the intestine, excitation of the splanchnic produced exactly the opposite effects, viz. contraction of the circular and inhibition of the longitudinal coat. But they obtained the same results as Ehrmann when the gut was in an abnormal state owing to defective circulation and diminished tone of its walls. The splanchnics must therefore contain motor and inhibitory fibres for both layers of muscle.

Whatever interpretation be given to these conflicting results, it is certain that under really physiological conditions the intestine, on opening the abdomen of a dog in a warm saline bath, with intact splanchnics, is absolutely motionless. Under these conditions Bayliss and Starling (1899) find that division of the splanchnics produces no immediate change in the intestines; but after 15 to 30 minutes they gradually become more active, the previously motionless intestine begins to beat rhythmically, and any contractions which were previously present become stronger and more regular. The vessels become hyperaemic from vascular dilatation

owing to paralysis of the vaso-constrictor fibres. Under normal conditions, therefore, the splanchnics have a restraining influence on the intestinal movements, which ceases after section of these nerves.

This conclusion is strengthened by the result of stimulating the peripheral end of the cut splanchnic immediately below the diaphragm, after inserting a small exploring balloon into a loop of intestine. As shown by Fig. 84, after a somewhat prolonged latent period, there is a complete cessation of the rhythmic movements with marked relaxation of the intestinal wall. When stimulation ceases, there is a long after-effect, followed by gradual return of the rhythmical movements, and increased tone of the wall.

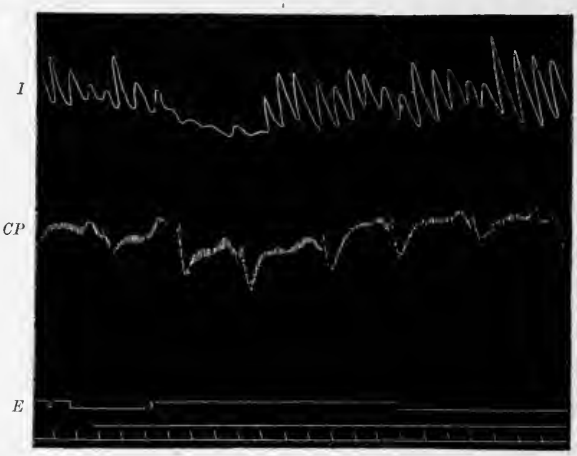

FIG. 85.—Intestinal contractions. Balloon method. (Bayliss and Starling.) Stimulation of right vagus in neck of dog, after atropin. *I*, inhibition; *CP*, carotid pressure; *E*, length of excitation.

The influence of the *vagus nerves* on the movements of the intestines has also been the subject of not a little controversy. E. Weber, Budge, Ludwig and Kupfer, Engelmann with many others, maintained that they have a motor action, and, notwithstanding some differences of detail, it might be concluded from their results that this was the exclusive effect. Bunch, however, observed in certain rare cases out of a large number of experiments, that the stimulation of the vagus may, like that of the splanchnic, produce inhibition. Ott (1904), again, expressly declared that peripheral stimulation of the vagi has an inhibitory effect. This harmonises with the conclusions of Bayliss and Starling, which may be briefly summarised.

According to these authors, no tonic influence on the intestines, such as is apparently exercised by the *splanchnic*, can be attributed to the *vagus*. Generally speaking, division of the vagi has no

perceptible effect, either immediately or remotely, upon the movements of the intestines.

Peripheral stimulation of the vagi (after division of both splanchnics, as recommended by van Braam-Houckgeest and Jacobi, so as to remove the tonic inhibitory impulses passing along these nerves to the intestines) constantly produces temporary diminution or cessation of the intestinal contractions, owing to the cardiac inhibition which causes intestinal anaemia. If the inhibition of cardiac activity is prevented by intravenous injection of atropine, peripheral excitation of either vagus has no effect on the intestine. But if the stimulation is repeated several times an

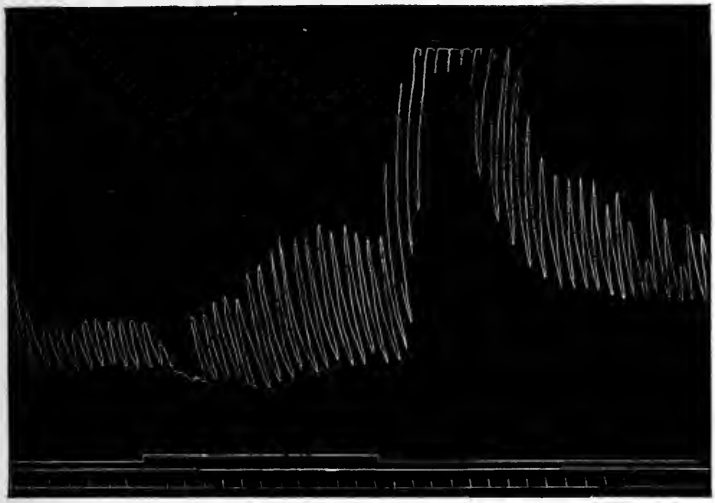

FIG. 86.—Tracing of intestinal rhythm as in Fig. 85, during a later stimulation of right vagus. (Bayliss and Starling.) In this tracing the primary inhibitory effect is scarcely visible, while the subsequent motor effect is strongly marked, and at one point produces a tonic spasm which obliterates the intestine and compresses the balloon.

augmentor effect sets in, which increases with each stimulation. The first *effective* stimulus is expressed in a temporary inhibition which causes the dropping of one or two beats. In the succeeding stimulations there is a double effect, *i.e.* the primary inhibition is followed by an augmented rhythm; the beats increase in amplitude and frequency, and the relaxation is incomplete, so that there is a great increase of muscular tone (Fig. 85). In many cases the excitation is so pronounced that the lumen of the gut and balloon are obliterated altogether by a strong tonic contraction (Fig. 86). There seems to be no relation between the extent of the inhibition and the amount of subsequent augmentation.

Bayliss and Starling concluded that the vagus nerves contain two sets of fibres, *inhibitory* and *augmentor*. The inhibitory fibres

have a short latent period, the augmentor fibres a long latent period. The action of the vagus on the intestines is therefore twofold—an initial inhibition, followed by augmentation which outlasts the excitation of the nerve.

Little is accurately known as to the localisation of the *cerebro-spinal centres* of the nerves which influence the intestinal movements. It is supposed that the spinal centres for the splanchnics lie in the lower part of the cervical cord and the upper part of the dorsal cord. But according to Ott inhibitory effects are also obtained with stimulation of the optic thalami and the cerebral peduncles. According to Budge and Valentin the intestinal movements can also be excited by electrical stimulation of the corpora quadrigemina and corpora striata; according to Schiff, also by that of the medulla oblongata, the annular protuberance, the cerebral and cerebellar peduncles. Bochefontaine in Vulpian's laboratory obtained movements of the intestines from dogs, with faradic stimulation of certain points of the motor zone of the cerebral cortex.

Bechterew and Mislawsky, and Bunch, tried to ascertain which roots of the spinal nerves give off fibres to the intestines, by way of the sympathetic cord. According to Bunch the fibres that run to the splanchnics originate in the anterior roots of the sixth thoracic and succeeding pairs of nerves, down to the second, third, fourth, and fifth lumbar pair. On their way to the small intestine they traverse the ramifications of the solar plexus, in the ganglia of which they have a cell station.

The above discussion shows that the physiological theory of the nerve centres and the central and peripheral, afferent or efferent, nerve paths which regulate the intestinal movements, is still very incomplete, doubtful in places, and fragmentary throughout.

VIII. Having reviewed the chemical phenomena of digestion carried on in the stomach and intestines, we may opportunely consider the physiological question proposed as early as 1772 by Hunter, which has given much food for thought and experiment to physiologists.

Hunter was the first who discovered, by dissection of a number of subjects, the phenomenon of the softening of the wall of the gastric fundus, which may lead to perforation, and the evacuation of the contents of the stomach into the peritoneal cavity. He noted particularly that this condition appeared most frequently, not in persons who had died from disease, but in those who had previously been healthy, and had come to a sudden death. Having confirmed the fact for certain animals some time after they had been killed, he interpreted it as a result of the digestion effected by the gastric juice, which continued after death, and dissolved not only the food-stuffs ingested, but the stomach itself, after it had been deprived of the "vital principle." He

concluded that digestion depends neither on the movements of the stomach, nor on heat, but upon the gastric juices, which represent the solvent for the food-stuffs introduced.

Spallanzani, who had already demonstrated digestion *in vitro* when Hunter's memoir was published, recognised in the post-mortem digestion of the gastric walls a confirmation of his discovery. Accordingly he set himself enthusiastically to repeat and vary the experiments of Hunter, but since he did not know the right conditions of external temperature and the most favourable pre-mortem period of digestion, he never succeeded in obtaining rupture of the stomach, but only a dissolution of the mucous membrane near the fundus. From this he concluded that "the abdominal sheaths of dead animals are less subject to the influence of the gastric juices than the meat introduced into the interior of the stomach." After feeding a fasting dog on some fragments of another dog's stomach, killing it at once by strangulation, and keeping the body in a warm place for nine hours, after which he made the post-mortem, he writes as follows: "The dissolution of these pieces of stomach was very marked, while nothing, on the contrary, was seen in the walls of the stomach in the dog that had been killed, save a slight maceration of the large end of the stomach, owing to which the villous coat when touched with the finger or other body is readily detached and dissolved." He explains this fact on the assumption that the fragments of stomach, "being free and floating in the visceral cavity, were covered at every surface by the gastric juice, while the walls of the stomach were subject to its action on the inner surface alone." Another conclusion is implicit in these words, viz. that the epithelium that clothes the mucous membrane of the stomach is even after death more resistant to the solvent action of the gastric juice than the muscular and serous coats of the gastric walls. He convinced himself by his experiments as a whole of the fact Hunter had discovered, of the *post-mortem auto-digestion of the stomach*, and accepted his explanation. He only protested that the phenomenon could not be independent of heat, "too many facts being cited in this book which point infallibly to the opposite conclusion."

In 1856 Pavy undertook to disprove the interpretation given by Hunter of auto-digestion. Hunter, to support his position, had propounded the following bold proposition: if it were possible to introduce the hand into the stomach of a living animal, it would resist digestion; this would not occur if the hand were severed from the body. Pavy showed this to be a fallacy, for he found that the hind limb of a living frog, and the ear of a live rabbit, introduced into the stomach of a dog by gastric fistula, did not escape the action of the digestive juice. Hence he concluded that "vital force" is incapable of protecting the tissues either of cold-

blooded or of warm-blooded animals from the solvent power of the gastric juice. Pavy's experiments were immediately confirmed by Bernard, and in 1862 by Inzani and Lussana also.

Pavy explained the resistance of the living stomach to the action of the gastric juice as follows. Since this organ is highly vascular, the alkalinity of the blood and lymph neutralises the acidity of the gastric juice in proportion as the mucous membrane is impregnated, and throws the pepsin out of court. The rabbit's ear and the frog's leg, being poor in vessels, are incapable of neutralising the juice, and become digested. In support of his argument, Pavy succeeded in obtaining auto-digestion of certain zones of the dog's stomach, in which he had interrupted the circulation, a fact subsequently confirmed by Virchow, Panum, and Cohnheim. We shall presently see the weak points of this theory.

Bernard explained the phenomenon on the assumption that the gastric mucosa is protected during life by its epithelium, "qui se détruit et se renouvelle avec une grande facilité; de là, quand la vie cesse, sa rapide altérabilité." Next to the epithelium he attached great importance to the layer of mucus that varnishes the stomach walls, so that "le suc gastrique se trouve comme dans une vase de porcelaine." This same view was also adopted by Inzani and Lussana, although, with the object of confirming it, they destroyed or modified the protective epithelium of living animals by various means, without observing any subsequent digestion of the gastric walls.

Schiff's experiments (1868) plainly showed that the epithelium is not indispensable to the integrity of the gastric mucosa. He was unable to produce lesions of the mucous membrane in fistula-dogs, after scratching off the epithelium of the stomach in places with his nail. He kept a dog, in which he had produced an open sore in the mucous membrane, alive for more than six weeks without inducing auto-digestion of the stomach walls. He found, indeed, that dead epithelium is also highly resistant to digestion, for when he repeated Spallanzani's experiment of introducing pieces of ox-stomach into the stomach of a dog, he found that the muscular coat became soft and was partially digested, while the epithelium, under the microscope, remained wholly intact.

Gaglio (1884) took up this interesting question in our laboratory, starting from an acute criticism of Pavy. If living tissues are digested by the gastric juice, on what does the special immunity of the stomach depend? Is it really a universal fact that all living tissues save the stomach are attacked and digested by the gastric juice? Seeing that the pancreas secretes a juice that has a peculiarly solvent action on proteins, which are digested along the entire tract of the small intestine, why did Pavy not ask himself why the pancreas and intestine also escaped

auto-digestion during life? He would at once have perceived the inadequacy of his explanation, which applies to the stomach only, and would have attacked the problem on wider grounds.

In the first place, does post-mortem auto-digestion take place in the pancreas and the bowel? Gaglio demonstrated this by killing dogs 5 to 10 hours after digestion had commenced, by an incision in the medulla oblongata, after which he placed the body in an oven kept at a constant temperature of 39° C. by a d'Arsonval regulator. On making sections, unmistakable signs of auto-digestion appeared throughout the small intestine, the mucous membrane of which was irregularly perforated, and showed between half-digested loops of intestine parts that were more or less intact. In the place of Peyer's patches he noted deep pits with sharply marked walls, which resembled ulcerated plaques. Beyond the lymph follicles of the open or necrosed plaques, he found that the muscular coats were more or less softened according as the digestive process was more or less advanced, which depended on the state of the intestinal loop, *i.e.* as filled with chyme, or empty and distended with gas. The pancreas was softened, reddish-brown in colour, with some parenchymatous effusions of blood. Under the microscope it showed deformed gland cells, in which the inner granular zone was no longer distinct from the outer homogeneous zone, the one bulging out, the other being reduced to detritus. Similar results were obtained from experiments on fowls, guinea-pigs, and rabbits.

When Gaglio had killed the dog and placed it in the warm chamber while the stomach was still full of food, he found that the phenomena of auto-digestion were most marked in the stomach, which might be almost entirely digested, and that the chyme poured into the peritoneal cavity might begin to digest the other viscera. But when the animal was killed 11 hours after an abundant meal, he found the stomach perfectly empty without any clear signs of auto-digestion, save for a more or less extensive softening of the mucous membrane, while the inner wall of the small intestine and pancreas exhibited phenomena of digestive solution as described above.

The problem of auto-digestion cannot therefore be confined to the stomach, but must be extended to the intestine and pancreas also. Accordingly, the cause that prevents auto-digestion during life is not peculiar to the stomach, but is probably common to all organs on which the digestive juices containing proteolytic enzymes take effect, both such as act in an acid medium (pepsin), and such as digest in an alkaline medium (trypsin).

In order to see if the resistance to the action of the digestive juices is common to other living organs as well, in analogy with that of the stomach and intestine, Gaglio introduced active gastric juice, or a very active glycerol extract of pancreas, into

the rabbit's bladder (after ligation of the ureters), into the vagina and uterus of the same animal, and into the throat of the fowl isolated between two oesophageal ligatures, and failed after 5 to 7 hours to detect any manifest sign of digestion in the walls of these organs. He concluded that resistance to the action of the digestive juices is not a property of the alimentary canal alone, but is common to other living organs.

Even if Pavy's theory explained the resistance of these organs to the action of gastric juice, it is wholly inadequate to explain their resistance to that of the pancreatic juice. If we assume, on the contrary, that these organs, which have a copious blood-supply, are the seat of vigorous absorption through the blood and lymph capillaries, it is easy to explain their resistance to the action of the digestive juices, since these are absorbed and removed before they can penetrate and saturate the tissues—a preliminary condition to auto-digestion. That the proteolytic enzymes do not remain and exhaust their activity *in situ*, but are reabsorbed, was demonstrated by Brücke, who found them in the urine, and also in the muscles.

This theory of Gaglio certainly gives a simple and straightforward interpretation of the phenomena which he studied, taking them as a whole; but it is not sufficiently general to account for other phenomena, subsequently brought to light by other workers. None the less, credit is due to Gaglio for having prepared the field for further investigations, by directing the attention of physiologists to the post-mortem auto-digestion of the intestine and pancreas, and proposing the problem of the non-digestion of these and other organs during life, in a more comprehensive and logical form.

In continuation of Gaglio's experiments, Viola and Gaspardi attempted to discover if the living spleen, a highly vascular organ, is also refractory to the solvent action of the gastric juice. With this object they introduced and fixed the spleen, with the whole of its neuro-vascular peduncle, through an aperture made in the stomach of dogs and cats.

The animals thus operated on died or were killed after 12 to 48 hours, and the post-mortem showed complete absence of auto-digestion. It should be noted that the animals after this crucial operation either ate nothing or were fed on milk, which they probably could not digest, since under such conditions the secretion of gastric juice would be *nil* or scanty. No demonstrative value can therefore attach to these results.

Contejean (1894) improved on the ingenious experiments of Gaspardi and Viola by fixing an intestinal loop into the stomach of dogs. In one of his most successful experiments, the dog was killed 12 days after the operation, in which time twenty full meals were digested. On section, it was found that the portion of intestine bathed with gastric juice (4·5 cm. long, 1·5 cm. wide)

showed four small perforations in a longitudinal direction, through which the intestinal mucosa was protruding so that it touched the gastric mucous membrane at several points. From this and other concordant results, Contejean concluded that the blood circulation, by carrying away the digestive enzymes, is able to protect the highly vascular organs from their solvent action; but that this protection is not unlimited, since after a certain time auto-digestion sets in, and is arrested only when the parts exposed to contact with the digestive fluids are once more covered, by regeneration, with a mucous membrane and special epithelium.

The results obtained under admirable experimental conditions by Contejean revived the question whether living protoplasm can or cannot be attacked by enzymes, and in what the protective action of the epithelia that clothe the mucous membrane consists? The new fact adduced by Contejean does not solve this problem, because the tissue of the intestinal walls is digested by the gastric juice in which, besides the ferment, the hydrochloric acid must be reckoned with.

Matthes (1893-94), with the object of clearing up the pathogenesis of gastric ulcers, performed a number of experiments on dogs, and studied with the microscope and the unaided eye the course of cicatrisation after circumscribed or extensive ablations of the gastric mucosa. He found that small losses of tissue were immediately occluded by local muscular contraction, and that ablations of even 6 cm. in diameter fill up promptly to two-thirds their extent, while the exposed part does not increase nor grow deeper by auto-digestion, but heals by a new formation of mucous membrane clothed with epithelium. This was a fact already known to pathologists, who are well aware that round ulcers of the stomach may heal up without necessarily leading to perforation by auto-digestion.

Matthes, by a number of other experiments, arrived at the conclusion that the digestive enzymes are inactive towards living tissues in a healthy state, and are therefore incapable of producing auto-digestion in the body. But the hydrochloric acid of the gastric juice acts as a protoplasmic toxin which first kills the tissue cells, after which they are digested by the pepsin. So that in the experiments of Pavy, Bernard, Lussana and Inzani, Contejean, the phenomenon of the digestion of living tissues *is apparent only*. They are not digested unless they have been previously killed, or at least profoundly modified by the hydrochloric acid. Different animal tissues re-act differently to hydrochloric acid; some are not altered by it at all; some very little; others again are profoundly modified. According to Matthes, this depends on an adaptation of the cells to the external conditions under which they live and function. The resistance of the walls of the stomach to the toxic action of the hydrochloric

acid must primarily be referred to the constitution of its epithelial cells. Yet it seems to us essential to recognise that the sub-epithelial tissues also present a considerable resistance, otherwise we cannot explain why extensive interruptions in the continuity of the mucous coat can be repaired before the tissue is digested.

Even before Matthes, and independent of him, this problem was treated in a yet more general form by Fermi (1890-95), who brought new evidence to support the thesis that *living protoplasm cannot be attacked by the proteolytic enzymes.* He called attention to the bacteria and animal and vegetable parasites that swarm in the alimentary canal, referring to facts that were already partly known, but that no one had thought of invoking in connection with this subject.

Fermi observes that Hyphomycetes and Blastomycetes live and multiply in both natural and artificial gastric juice, and modify its reaction and digestive activity; that trypsin in alkaline solution is inactive *in vitro* to the whole class of Schizomycetes, which, indeed, live and multiply upon it; that Amoebae consisting of naked protoplasm are neither digested by trypsin *in vitro* nor in the intestine; that the seeds of Graminaceae and Leguminosae flourish and germinate well in sterilised solutions of active trypsin; that, lastly, worms and insect larvae immersed in solutions of trypsin are in no way attacked, and that Lumbricidae and Ascaridae find the proper medium for their development and reproduction in the intestines of animals.

Fermi further notes that sterilised active trypsin can be injected in strong and repeated doses (2 grms. per diem for a week) under the skin of living guinea-pigs, without producing any symptom of digestion. It is not absorbed, but is destroyed *in situ* by the living protoplasm of the tissues. Ten minutes after injection in the guinea-pig, and five hours after in the frog, it is no longer possible to find a trace of trypsin anywhere in the body, even with the highly sensitive gelatin method—gelatin, according to Fermi, being liquefied even by the most dilute solutions of trypsin. When mixed with freshly minced organs of newly killed animals, the trypsin disappears completely after 24 hours. This is not the case when the organs have been previously boiled.

The so-called digestion of living tissues is due to the deleterious action of hydrochloric acid, which alters or kills the cells prior to their digestion by pepsin. This action is promoted by temperature. In effect the tissues of a living frog resist the solvent action of the gastric juice *in vitro* at 15-20° C.; while they are digested at the temperature of 38° C. at which Pavy, Bernard, and others experimented. The cells of the gastric mucous membrane are specialised cells, adapted for living in the presence of hydrochloric acid, like the cells of the sulphuric acid glands of certain Gasteropods which tolerate this acid in 4 per cent solutions, like

the cells of Blastomycetes and Hyphomycetes which develop in gastric juice, like the cells of highly acid plant organs which perish in an alkaline medium.

An experimental illustration of the theoretical conclusions of Fermi and Matthes was put forward by one of Fredericq's pupils, Paul Otte, in 1896. He sought to elucidate the comparative value of the epithelium as a protective organ of the subjacent tissue. With this object he isolated a loop of intestine in the dog, washed it with physiological saline, and then introduced active gastric, or equally active pancreatic juice, kept in the cavity by means of two ligatures at the extremities of the loop, and stitched up the abdominal wall. After 5 to 8 hours the animal was killed, and the changes produced by the digestive juices in the loop examined, either by simple inspection or with the microscope. His results briefly described are as follows :—

(*a*) Neither pancreatic nor gastric juice is capable of attacking the normal mucous membrane of the intestine, although this is not, like the gastric mucous membrane, inured to the presence of free hydrochloric acid. This result is identical with that obtained by Gaglio on the bladder, and probably lends itself to the same interpretation.

(*b*) If before introducing one or the other of the digestive juices, the loop of intestine is washed for a short time with 2 per cent silver nitrate solution, and then with 0·6 per cent sodium chloride, no digestive alteration is produced, although the epithelium which covers the tips of the villi is altered and killed by the action of the caustic. Nor does the injection of 0·05 per cent sodium fluoride solution produce any sign of digestion in the loop, although it completely alters the osmotic and absorbent power of the mucosa without destroying the epithelium. These results can be explained neither by the theory of Gaglio nor by that which attributes an exclusively protective function to the epithelium.

(*c*) If before introducing the digestive fluids into the loop, the blood-vessels running to it are tied, auto-digestive phenomena make their appearance rapidly. Since mere ligation of the vessels, without introducing digestive fluids, produces no clear symptoms of necrobiosis in the intestinal epithelium after eight hours, we are forced to conclude that ligation, by altering the nutrition of the mucosa, disposes it to become saturated with the solvent fluids to which it is normally refractory. The auto-digestive lesions common in the stomach and intestine of patients who have died after a long illness, are also due to the bad nutrition and enfeebled resistance of the mucous membrane to the digestive action of the pancreatic juice.

As a whole, the phenomena which we have been discussing show the resistance of the living protoplasm to the attacks of the

intestinal enzymes. This property is not peculiar to the cells of the gastric and intestinal walls, but is probably common to all living cells. Thus after much research (which has certainly not been useless, and is highly suggestive) the old doctrine of Hunter, emphasised by Spallanzani, emerges, rehabilitated, from the attacks of its opponents. Hunter's theory cannot, of course, be taken in its original mystical and allegorical form, which is the habitual disguise of such scientific intuitions as outrun experiment. Fundamentally it amounts to this: the cause of the resistance of living protoplasm to the action of the digestive enzymes must be sought not in *extrinsic* but in *intrinsic* conditions, *i.e.* in its intimate constitution.

More recently Weinland (1902), starting from the fact that the Ascarids find in the intestine the medium best suited to their existence, has attempted to determine the intrinsic conditions that render them refractory to the proteolytic action of trypsin. On rubbing up these intestinal worms into a pulp, with successive alcoholic extractions, he obtained a substance which he termed anti-ferment, because it has the property of protecting the proteins from the proteolytic action of pepsin or trypsin. According to other work of Weinland, there is within the interior of the epithelial cells of the gastric and intestinal mucosa an anti-ferment with similar action to that of the Ascarids. This would explain the special resistance of the epithelium to auto-digestion, not only during life, but also to some extent after death. How then are we to explain the resistance to auto-digestion during life in those tissue cells which are digested after death? It is not enough to assume with Weinland that they probably contain an anti-ferment; it is necessary to prove that the latter is destroyed at the moment life ceases. Such a demonstration is absolutely impossible, because the method of extracting the anti-ferment begins by killing the tissues in reducing them to pulp; and if this pulp contains the anti-ferment, as affirmed by Weinland, this would imply that it is not unstable, but persists after the death of the cells. The true solution of this problem would evidently solve the enigma of life and death!

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CHAPTER V

INTERNAL RESTITUTIVE SECRETIONS

CONTENTS.—1. Gastric absorption. 2. Intestinal absorption. 3. Fate of the different groups of food-stuffs after absorption. 4. Importance of living epithelium to absorption of crystalloid substances (salts and sugars). 5. Absorption of neutral fats in form of soaps; synthetic regeneration by epithelium of intestine. 6. Absorption of proteins, proteoses, and peptone; synthetic regeneration. 7. Mechanism of internal secretion of absorbed and regenerated compensation-products. 8. Formation of glycogen (amylogenesis) and glucose (glycogenesis) by hepatic cells. 9. Hepatic glycogenesis an internal secretion; regulation by nervous system. 10. Derivation of hepatic and muscular glycogen from carbohydrates of food. 11. Derivation of glycogen from decomposition of proteins and fats (*diabetes mellitus* from pathological causes, *experimental diabetes* from phloridzin and removal of pancreas). 12. Accumulation of alimentary fat; adipogenesis. 13. Accumulation and consumption of alimentary protein. 14. Protective function of intestinal epithelium and liver. Bibliography.

IN proportion as the food-stuffs are altered by digestion in their passage through the alimentary canal, and are transformed from insoluble into soluble substances, from such as are not diffusible into such as are readily diffused, they are absorbed by the epithelium of the gastro-intestinal mucous membrane, and are converted into Chyle, which is then poured out by internal secretion into the lymph sinuses of the mucosa. *Chyle* therefore denotes, not the total product of digestion, but rather the sum of such natural or digested food-stuffs as are discharged into the lymph torrent by internal secretion, after their partial regeneration into the constituents of lymph and blood—which is the synthetic or anabolic function of the living cells of the absorbing mucous surface. Hence the concept of "chyle" is purely theoretical. The milky fluid which can be collected during digestion from a fistula of the thoracic duct and from the larger *chyliferae* or lacteal vessels is not really the whole of the chyle. It does not contain all the substances absorbed and transformed by the gastro-intestinal mucous membrane, in their relative proportions, since a large part of these substances are taken up by the blood capillaries of the mucous coat (particularly in the villi of the small intestine) and carried to the liver by the portal system, while another considerable part are absorbed by the solitary

and agminated follicles and by the lymph glands interposed along the lacteals. The chyle poured out (with the lymph) into the left subclavian vein contains a comparatively small proportion of the total of the food-stuffs elaborated by the secreting and absorbing cells of the gastro-intestinal mucous membrane, and destined to compensate the tissues for their losses.

The title *Internal Restitutive Secretions* given to this chapter comprises the study of all those complex processes by which the individual groups of food-stuffs (which may or may not have suffered the chemical metamorphoses of digestion discussed in the two preceding chapters) are absorbed, partially regenerated, secreted into the lymph spaces of the mucosa, carried away by the lacteals and venous portal system, stored up in the various organs, tissues, and cells as reserve materials, and finally poured out or secreted into the blood, to compensate for the losses caused by assimilation and the functional work of the tissues.

I. The Mucous Membrane of the entire tract of the alimentary canal, from mouth to anus, forms, on account of the epithelium which covers it, a single, extended, absorbing surface. But the mouth, pharynx, and oesophagus, owing to the thickness of the stratified epithelium, and to the fact that the food does not remain long enough in them to undergo any important chemical digestive modifications, play no perceptible part in absorption, although certain intoxications prove that they are capable of it.

On the other hand, it is well known that the *stomach* does play an active part in absorption. The simplest demonstration of the fact is the rapidity with which certain poisons take effect, particularly after the introduction of toxic substances in alcoholic solution. Another obvious proof of absorption in the stomach is seen in sections from animals killed during digestion, in which the lymphatics of the stomach are found to be congested.

Von Mering (1893) published results of his accurate observations on the absorptive functions of the gastric mucous membrane, which are important from both a hygienic and a clinical standpoint. His method consisted in establishing a duodenal fistula on dogs, and then introducing into the stomach a given amount of fluids or watery solutions of various foods, after which the outflow from the fistula was collected, measured, and analysed at consecutive intervals.

If the animals were allowed to drink plain water freely, it spurted in a short time from the fistula in jets that recurred 2-6 times per minute; 2-15 c.c. of water were excreted at each jet. Von Mering ascertained by over 100 tests that the quantity of fluid escaping from the fistula was approximately equal to that introduced, and might even be larger, owing perhaps to the saliva that became mixed with it during deglutition. He concluded that water was not absorbed by the stomach in any

perceptible amount. Against this, however, we must set the fact that evacuation of the stomach does not occur as rapidly when the duodenal fistula is obstructed, on which the fluid is prevented from escaping to the outside, and is forced into the intestine. This is due, according to von Mering, to the fact that the fluid on filling the small intestine reflexly delays the flow from the stomach, and increases the tone of the pyloric valve. Under these conditions (which correspond to the normal) it is probable that absorption of water by the gastric walls is considerable.

When, instead of plain water, salt solution is introduced into the dog's stomach by the duodenal fistula, the liquid that flows out of the fistula contains much less salt and much more water. The stomach must, therefore, absorb the salt and excrete the water. After injecting, *e.g.*, 30 grms. of sodium chloride dissolved in 400 c.c. water into the stomach, 6·5 grms. of salt were absorbed, and 787 c.c. of fluid escaped from the fistula. The same fact appears on injecting a solution of glucose into the stomach: part of the sugar is absorbed, and the volume of fluid escaping from the fistula is much increased.

When solutions of proteose and peptone are injected into the stomach of dogs with a duodenal fistula, the quantity absorbed increases with the concentration of the solutions. In this case, moreover, that part of the water which forms the solvent is absorbed as well as part of the dissolved substances. According to von Mering, the gastric mucous membrane can, under the most favourable conditions, absorb 60 per cent peptone, while it can only absorb 20 per cent sugar. Concentration of peptone solution promotes absorption of water, but the contrary takes place for sugar.

Considerable influence is exerted upon gastric absorption by substances that excite the epithelium of the stomach, *e.g.* alcoholic beverages, and the usual condiments and spices.

Alcohol is entirely absorbed, and greatly assists absorption of the substances dissolved in it. Salt, in the amount that is agreeable to the palate and is commonly used as a condiment (about 2 per cent), also favours absorption, as do also mustard, pepper, nutmeg, ginger, etc. These condiments accordingly not only excite gastric secretion (as is commonly stated), but also facilitate absorption of foods which are naturally soluble or have become soluble by digestion in the stomach—either by exciting the absorbing epithelial cells, or by provoking active hyperaemia and improved circulation in the blood and lymph capillaries of the mucous membrane.

II. The tract best adapted to digestion is undoubtedly the Mucous Membrane of the Gut, especially that of the small intestine, more particularly of the duodenum and jejunum, where there

are large valvulae conniventes and the villi are long and very numerous. The visible surface of measurement of the small

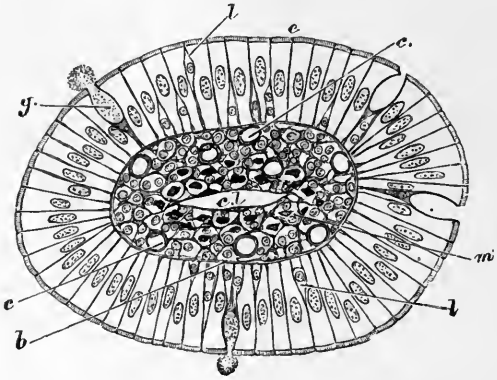

FIG. 87.—Cross-section of a villus of cat's intestine. Highly magnified. (E. A. Schäfer.) *e*, columnar epithelium; *g*, goblet-cell with mucus partly exuded; *l*, lymph-corpuscles between the epithelium cells; *b*, basement-membrane; *c*, blood corpuscles; *m*, section of plain muscular fibres; *cl*, central lacteal.

intestine extends in the adult to some half a square metre. But the many folds of the valvulae conniventes, and extensive inflexions and projections of the mucous coat of the villi, increase the true surface of this part of the mucous membrane to about 10 square metres. The chyme is distributed over this vast absorbing surface, so that *absorption*—the main function of the epithelium that clothes the villi as well as the solitary and agminated glands scattered over the small intestine—is greatly facilitated.

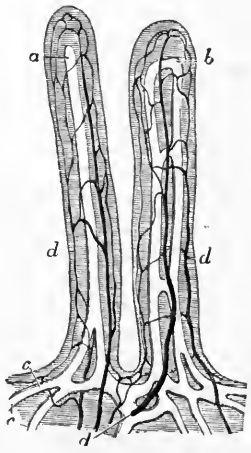

FIG. 88.—Injected lacteal vessels in two villi of human intestine. (Teichmann.) 100 diameters. The lacteals are filled with white substance; the blood-vessels with dark. *a*, *b*, lacteals, single in one villus, double in the other; *c*, horizontal lacteals, communicating with those of the villi; *d*, blood-vessels which consist of small arteries and veins with capillary network between.

The *villi*, as the chief organs of absorption, claim special attention. They vary in length from 0·5-0·7 mm., are larger and more numerous in the duodenum and jejunum, and diminish in size and number in the ileum. According to Krause, each square millimetre of the jejunum contains 10-18, of the ileum 8-14. On the basis of this calculation the total number of villi in the whole of the small intestine may be taken as four to five millions, and each square centimetre of the apparent surface of the intestine gains about twenty-three times in area from the

protrusion of the villi. As shown in Fig. 87, they consist of a special epithelium which encloses a lymphoid tissue: in the centre of this is a lacteal, the wall of which consists of simple epithelioid cells with wavy outlines, which in all probability have little stomata

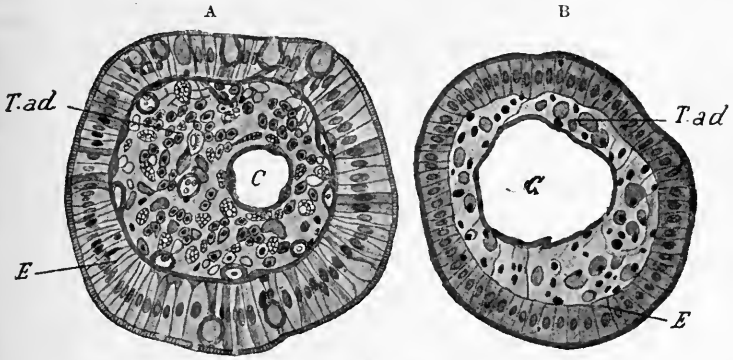

Fig. 89.—Cross-section through villus: A, of dog; B, of rabbit. (Heidenhain.) *C*, central lacteal *T.ad*, adenoid tissue; *E*, epithelium with striated cuticle.

or spaces at the junction of the cement substance. The central lymphatic (which sometimes consists of two vessels joined at the end by a loop, as shown in Fig. 88) communicates with the subjacent intermuscular lymph plexus. The adenoid tissue of the villi is generally more developed in carnivora than in herbivora, in which, on the other hand, the central lymphatic is much wider

Fig. 90.—Magnified blood-vessels of intestinal villi. (Sharpey.) From specimen injected by Lieberkühn. Each villus shows a small artery and vein with capillary network between.

(Fig. 89). The adenoid tissue of the villi is also traversed by a vascular loop consisting of small arteries and veins, united by a capillary network (Fig. 90). The retiform adenoid cells are intermixed with muscular tissue which is a prolongation of the muscularis mucosae (Brücke), and the meshes or lacunae which they form contain numerous lymphocytes, filled with granules, which stain black with osmic acid, but do not consist of fat, since

they are insoluble in ether (Heidenhain). Lastly, according to Ramon y Cajal, the lymphoid tissue of the villi presents a very fine plexus of nerves, the peripheral termination of the coarser plexus of Meissner which is situated in the submucous layer of the intestine (Fig. 91).

The columnar epithelium with a striated border which clothes the villi (see Fig. 43, p. 124) is apparently identical with that of the crypts of Lieberkühn, but the latter stains more intensely with various pigments, and its border is much less plainly striated. Moreover, the nuclei of the latter often exhibit mitotic division, while karyokinetic figures are never seen in the epithelial cells of the villi. These differences probably indicate (as maintained by A. D. Waller) that the normal function of the epithelium in the crypts is the *external secretion* of succus entericus, while the epithelium of the villi is an organ of *absorption* and *internal secretion* of the absorbed substance. This removes the difficulty which some physiologists find in admitting two opposite and simultaneous functions for the same cells, *transudation* and *absorption*. We shall find direct evidence for this theory when we examine the absorption of fats in detail.

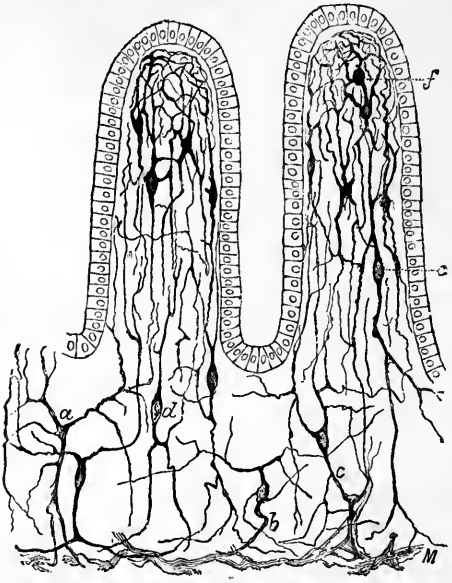

FIG. 91.—Nerve endings from small intestine of guinea-pig. Potassium chromate and silver nitrate method. (Cajal.) *a*, *b*, *c*, *d*, small nerve-cells belonging to the interglandular plexus of the mucous membrane; *e*, *f*, corresponding cells belonging to nerve plexus of villi; *M*, nerve fibres belonging to Meissner's plexus, distributed in muscularis mucosae.

Not only from the great extension of the absorbing surface, but also from the various chemical digestive processes which the chyme undergoes in the small intestine (owing chiefly to the action of the various enzymes of the secretions poured into it), absorption along the whole of this tract is more active than in the stomach. Of this the case of duodenal fistula described by Busch gives plain evidence. Although the patient was abundantly fed by the mouth, she suffered continually from hunger, and in a few weeks her weight went down so much that she was threatened with death from marasmus, which was only averted on feeding her through the lower end of the fistula. In the cases of fistula at the

end of the ileum described by Braun and Ewald, on the contrary, the body-weight was tolerably well maintained on an abundant diet per os, notwithstanding the considerable loss of nutritive substances through the fistula.

The maximal degree of absorption of the food-stuffs from the chyme is effected principally in the duodenum (below the orifices of Wirsung's duct and the common bile duct) and the jejunum. Ruggi's case of extensive resection of the ileum referred to in the last chapter (iv. § 5), in which the faeces did not contain an abnormal excess of proteins, fats, and carbohydrates, is a direct proof that, owing to physiological adaptation, nearly the whole of the intestinal absorption can be performed in the upper part of the small intestine.

Normally, therefore, no absorption of food-stuffs worth noting takes place in the large intestine. The absence of villi (see Fig. 42, p. 123) and of valvulae conniventes, and the superabundance of mucin-secreting crypts, support this conclusion. A physiological argument for the insignificant absorption of food-stuffs which takes place under normal conditions in the large intestine, is shown by the fact that in no cases of fistula of this part of the gut, as described *for man*, was any diminution of weight observed in the individuals affected (Czerny, Marckwald). In *dogs*, on the contrary, according to Albertoni, nutritive absorption is not completed in the small intestine, but continues in the large bowel. These animals, in fact, become emaciated with a fistula of the caecum. Harley's recent researches confirm these observations, and show that dogs with fistula of the large bowel absorb fats and carbohydrates normally, but proteins only imperfectly.

Hardly anything but water is normally absorbed in the large bowel of man. It is, in fact, in this part of the gut that the intestinal contents assume the pasty consistency proper to faecal matter, and the mucin secreted by the crypts of the large intestine (*supra*) lubricates the surface of the faeces, and facilitates their expulsion.

Later on we shall see how under abnormal conditions of alimentation per rectum the large bowel is capable of absorbing not only diffusible substances such as alcohol, salts and glucose, but also colloidal substances, including protein.

III. Before we attack the study of the complex mechanism of intestinal absorption, it will be advisable to obtain some idea of the paths which the food-stuffs take after absorption, this question being simpler and easier of solution, so that it leads up to the other.

From the time of Bartholin, who completed the discoveries of Aselli, Pecquet, and Rudbeck on the so-called *Vasa Lactea*, until a few years ago, there was a tendency to assume that the principal stream of food-stuffs from the intestine to the blood was represented by the *chyle* flowing through the thoracic duct. The work

done in Ludwig's laboratory by his pupils Röhrig (1874), Zawilski (1876), von Mering (1877), Schmidt-Mülheim (1877), and confirmed by I. Munk and Rosenstein (1890), for man in a case of lymphatic fistula, corrected this erroneous assumption, and showed by a great number of observations that it is only the fats (and again only a part of these) which pass by way of the thoracic duct, while all the other foods absorbed travel, for the most part at least, by the blood capillaries of the villi, and pass directly to the liver by the venous portal system.

On introducing a cannula into the thoracic duct of a dog near its opening into the left subclavian vein, it is seen that the flow from the cannula in the time unit is not sensibly augmented during the period of digestion and absorption; but the lymph, which is semi-transparent previous to digestion, turns into chyle, *i.e.* becomes opaque and milky, during digestion, particularly after a meal rich in fatty substances. In fact, comparative analysis of the chemical composition of the lymph and chyle from the thoracic duct shows that the sole difference between the two fluids lies in the preponderance of fat in the chyle, which varies in character according to the nature and amount of the fats ingested. Most of it is present as *emulsified neutral fats*, in the form of the finest droplets visible under the microscope, which dissolve in ether, and stain black with osmic acid. A small part (about $\frac{1}{20}$) is present in the form of *saponified fatty acids*. After a meal rich in fatty substances the chyle collected from man may contain 4·7 per cent fat (I. Munk), and that from the dog 14·6 per cent (Zawilski); while the lymph that flows from the fistula in the fasting state contains only 0·06-0·26 per cent.

This naturally leads to the question whether the whole of the alimentary fat absorbed by the gastro-intestinal mucous membrane passes by the thoracic duct to reach the blood stream, or whether part of it may pass along the portal system or by other paths. On giving a measured quantity of fat to a dog with fistula of the thoracic duct, and subtracting the small amount of fat which leaves by the faeces, we obtain approximately the quantity of fat absorbed, which may be compared with the total amount that escapes by the fistula during the whole time in which the lymph preserves the milky appearance of chyle. On estimating this quantity, it is found to be about 40-50 per cent of the total fat absorbed. There is thus a deficit of 50-60 parts of the fat, which must pass into the blood, not by the thoracic duct, but by some other way. This fat might conceivably pass by the paths that feed the portal system, since some authors have found that the serum separated from the portal blood was also milky during digestion. According to Foster, however, this argument is fallacious, because during the digestion of a meal rich in fats the whole of the blood, including that of the carotid, contains much fat, and the serum of the

latter is more milky than that of the portal vein, showing it to be fat absorbed from the lacteals and not from the blood capillaries of the intestinal villi. This is proved by the fact that during the flow of chyle from the fistula of the thoracic duct the portal blood contains a very small amount of fat. The deficit of absorbed fat can, therefore, only be explained, according to Foster, on the assumption that, as it passes through the lymph glands of the mesentery, part of it escapes from the chyle and the blood torrent by unknown ways, and by a process of which we have as yet no conception.

Foster's view was opposed as long ago as 1901 by Munk and Friedenthal, and in 1907 by D'Errico, who more particularly contested the data on which Foster founded his theory. D'Errico calculated the fat content of the blood collected from the portal and jugular veins, and proved that under normal conditions, after a meal rich in fats, the former contained more fat than the latter (0·412-0·385 per cent in the portal blood, 0·280-0·212 per cent in the blood of the jugular). This difference was not less in the samples of blood collected after deflecting the mouth of the thoracic duct to the exterior (0·412-0·315 per cent of fat in the portal, 0·205-0·208 per cent in the jugular).

If this larger fat content of the portal blood is to be ascribed to the fat absorbed by way of the blood-vessels, we must conclude that absorption by this path is considerable, seeing the large amount of blood that circulates in the portal system during the period of digestion. It must, however, be remembered that the work so far carried out on the fat content of the blood is unreliable because, as Kumagawa and Suto showed (even if they are taken comparatively), the methods employed may lead to grave errors which make any interpretation of the results questionable. It is advisable to regard the subject of the paths of fat absorption as an open question, which has not been decided by Foster's theory.

While the question whether part of the fat is absorbed by the capillaries of the villi, and passes by the venous paths of the portal system, is thus under discussion, it is indisputable that the sugar introduced with the food, as well as that formed during the digestion of carbohydrates, under conditions of normal alimentation traverses the portal system exclusively, and is carried by it to the liver. Von Mering's accurate researches (1877) show that the percentage sugar content of the chyle collected from the thoracic duct is not perceptibly greater than that of the lymph collected before a meal, and that of the arterial blood, which never exceeds 0·06-0·16 per cent. On the other hand, on comparing the percentage amount of sugar from the blood of the portal vein with that of the hepatic veins, it is found that while the difference is negligible in the fasting state, it is increased during digestion in the former (up to 0·4 per cent), and not in the latter. This is no great increment,

and might fall within the limits of experimental error; but if we take into account the enormous quantity of blood that circulates in the portal system during the whole period of digestion, we cannot doubt that sugar can be absorbed by the capillaries of the villi, however insignificant the amount present in 100 c.c. of portal blood may be.

It is only when the amount of sugar introduced into the intestine is abnormally great that part of it is absorbed from the lymphatics, and produces an increase in the sugar of the chyle escaping by the fistula (Ginsberg, 1889). But in view of the slow rate at which the chyle flows along the thoracic duct, it must be remembered that even in this case of excessive dosage with sugar, the quantity that traverses the lacteals is minute in comparison with that absorbed by the blood capillaries and carried to the liver. In the girl with a lymphatic fistula described by I. Munk and Rosenstein, it was noted that at most one-half per cent of the absorbed sugar passed through the lacteals. Since in this case there was excessive absorption of water by the lacteals, it is probable that the current of water carried off a part of the sugar dissolved in it. Since the increased sugar content of the blood during digestion can only be detected in the portal vein and not in the hepatic veins, it follows that the sugar must be fixed and stored up in the cells of the hepatic parenchyma. We shall see the great importance of this fact in discussing the metabolism of the liver.

The experimental data which are to hand in regard to the course of the proteins after absorption are less definite. Schmidt-Mülheim, with Ludwig, found that ligation of the thoracic duct did not hinder protein absorption. More precise observations were made by I. Munk and Rosenstein (1890) in the case of the girl of eighteen with a lymphatic fistula. After a copious flesh meal, the effusion from the fistula showed no perceptible increase either in percentage of proteins or in absolute quantity escaping from the fistula during the twelve hours subsequent to the meal. From this they concluded that no amount of absorbed protein worth noting passes by the lacteals; it must therefore travel by the blood capillaries of the mucous membrane of the intestine.

Wurtz, however, prior to Munk, had observed that the chyle of oxen before rumination contains only 3·97 per cent protein, while after rumination the protein content was raised to 5·96 per cent.

Possibly, as Foster rightly pointed out, all proteins do not take the same path, and are not absorbed under identical conditions by all animals. If in herbivora, where the diet contains little fat, the whole of the carbohydrates and proteins were absorbed by the blood-vessels of the intestinal mucous membrane, little would be left to pass by the lacteals. The structure of the villi shows that the central lacteal of guinea-pigs and rabbits is larger than in

dogs, where, on the other hand, there is more adenoid tissue (see Fig. 89). It is difficult to reconcile this fact with the theory that the central lacteal serves exclusively for absorption of fatty substances.

I. Munk, who upholds this doctrine, himself cites in his *Text-book,* in addition to the data he obtained from man, the results of the comparative analyses of lymph and chyle made by C. Schmidt and Fr. Simon and Rees on various animals, which appear to us to speak in favour of a less exclusive theory. To facilitate comparison we have arranged these data in one table:—

100 parts contain	Man.		Horse.		Ass.		Cow.	Dog.
	Lymph.	Chyle.	Lymph.	Chyle.	Lymph.	Chyle.	Lymph.	Chyle.
Water . .	95·2	92·2	95·8	92·8	96·5	90·2	96·4	91·2
Solids . .	4·8	8·8	4·2	7·2	3·5	9·8	3·6	8·8
Fibrin . .	0·1	1·0	0·1	0·1	0·1	0·4	0·1	1·0
Proteins .	3·5	3·2	2·9	4·0	2·7	3·5	2·8	2·7
Fats . .	Trace	3·3	Trace	1·5	Trace	3·6	Trace	4·9
Extractives .	0·3	0·4	0·1	0·8	0·1	1·6	0·1	0·3
Salts . .	0·9	0·8	1·1	0·8	0·6	0·7	0·6	0·8

IV. The history of physiology has not seldom shown that new achievements in the field of physical science give rise to the illusion that a part of the mystery which veils the subtle mechanism of the vital processes has been cleared away. After Dutrochet's discovery of diffusion through permeable membranes of substances in solution, it was held by many, without direct experimental tests, that Food Absorption in the Intestine was a phenomenon of the same order, easily explicable on the laws of osmosis, and that the sole physiological object of the chemical processes of digestion was to render the ingested foods diffusible through the animal membrane formed by the epithelial layer of the intestine.

But when this doctrine came to be experimentally tested a number of facts were brought to light which showed that intestinal absorption is no such simple phenomenon, and that the living walls of the intestine are not comparable with an inert porous membrane.

As early as 1869, Voit and Bauer observed the absorption of blood serum injected into a loop of intestine, a phenomenon that cannot be explained by a simple process of diffusion: few, however, realised the importance of this fact, and the absorption of fluids from the intestine continued to be regarded as an effect of osmosis. Hoppe-Seyler (1881) criticised this theory, and held that the passage of the intestinal fluids into the circulation was not a simple effect of the chemical differences between fluids separated

by a permeable membrane, but was rather due to the specific activity of the living epithelium that clothes the intestine. This idea was supported by a series of experiments carried out in Heidenhain's laboratory, and published by Leubuscher in 1885. Even after this, however, there remained no little uncertainty as to the point at which the laws of diffusion intervened and favoured the phenomenon of absorption.

Albertoni in 1891 pointed out that the absorption of sugars took place equally, whether the specific gravity of the solution was greater or less than that of the blood. In 1892 his first results were confirmed by new experiments and brought out an important fact, viz. that absorption of sugars (glucose, lactose, maltose) which had been freely administered was most active in the first hour, and much less in the succeeding hours relatively to the quantity that remained in the alimentary canal. The reason of this phenomenon is unknown. It seems not to depend on saturation of the body by glucose, as Albertoni at first assumed, because he afterwards found that the osmotic pressure of the blood alters very little during absorption of sugar. Since his experiments showed that the colloidal content of the blood increases considerably after the first hour of absorption, he thought this fact was probably in causal relation with its subsequent diminution.

In order to solve the problem of absorption, it was necessary to attack it again in the light of more advanced physical methods, particularly in reference to the absorption of those easily diffusible substances which were classed together by Graham under the name of *crystalloids*. Among the alimentary substances that come under this category we find especially the Salts and the Sugars, sodium chloride and glucose in particular.

Heidenhain (1894) was the first who undertook an exhaustive criticism of the Theory of Intestinal Absorption. He found that solutions of sodium chloride with an osmotic pressure greater than, or equal to, blood, were, when injected into an isolated loop of intestine in a fasting dog, absorbed indifferently, although in the first case (according to the laws of osmosis) hardly any water should have passed from the intestine to the blood, and in the second no absorption at all should have taken place. He concluded that the absorption could only be explained as the effect of *specific forces inherent in the living cells of the wall of the intestine*. In his opinion this conclusion was confirmed by the fact that when the intestinal epithelia were *functionally* injured by a moderate poisoning with sodium fluoride without any perceptible *cytological* change, the absorption of the foregoing solutions was modified so as to be in complete agreement with the laws of osmosis.

These results of Heidenhain were confirmed by Hamburger (1895-96). He, too, found that solutions of sodium chloride, sodium nitrate, or sugar, with a greater or less osmotic pressure than the

blood-serum of the animal experimented on, became in the course of absorption *isotonic* with the latter, and were all eventually absorbed. But since he found that the same phenomena of absorption of solutions which were isotonic, and also of such as were hypertonic, with the serum, could be obtained from animals killed some hours previous to experiment, he denied the importance which Heidenhain allotted to the living cells, and invoked the *imbibition* of the colloidal substances of which the epithelia consist as a possible explanation of the facts which were opposed to the laws of diffusion.

Heidenhain at once replied that it is not possible to establish a comparison between the phenomena that can be observed on living animals with circulating fluids that are rapidly renewed, and those observed on dead animals in which the fluids contained in the depth of the intestinal walls stagnate. It is obvious that even if the phenomena are apparently similar in the two cases, they will not bear the same interpretation. It must also be remembered that in the living animal there is simultaneously with the phenomenon of intestinal absorption a secretion of succus entericus, *i.e.* a current opposed to that of absorption, which is absent in the dead animal.

O. Cohnheim (1897), in Kühne's laboratory, repeated Hamburger's experiments on the absorption phenomena in living and in dead dogs, under proper experimental conditions, and his results confirmed and extended the theory of Heidenhain. On circulating a continuous current of 0·94 per cent salt solution heated to 40° C. through the blood-vessels of the dead animal, and introducing a solution of glucose into a loop of intestine tied at the ends, he saw that a double current was set up, so that part of the sodium chloride passed into the intestine, and part of the sugar into the circulating fluid. Each of the dissolved substances diffused independent of the other, according to their respective degree of diffusibility. The salt being three times as diffusible as the sugar, passed much more rapidly from the capillaries into the intestine than the sugar from the intestine to the capillaries. Under these conditions, therefore, the mucous membrane behaves like any inert membrane, and the double current which passes through it conforms perfectly to the laws of diffusion and osmosis. There is never any *diminution* of fluid in the loop; with both hypotonic and hypertonic solutions, there is always an undoubted *increase* of the fluid in the intestine. The possibility of absorption, as it takes place in the small intestine in living animals, is therefore bound up with the *integrity and functional capacity of the intestinal epithelium.* According to the results obtained by Cohnheim, the epithelium of the gut is capable of absorbing, inasmuch as it is the seat of a specific force which favours the passage of the dissolved substances from the intestine into the depths of the villi,

and impedes their passage in the reverse direction. This capacity of the epithelium for letting certain solutions through in one direction only is met with in many other cells, which, so long as they are alive, possess a wall that is impenetrable to certain substances, and lose this property after death, on which an exchange takes place between the materials they contain and those of the environment. Cohnheim reminds us in this connection of the erythrocytes and the muscles, which in many animals are devoid of sodium and rich in potassium, although they may live in a medium rich in soda and poor in potash. Plant cells, again, are colourless so long as they are alive, although surrounded by a coloured juice, which only penetrates their protoplasm when life is extinct. To the same order belongs the fact discussed at length at the end of the last chapter, viz. that the cells which form the intestinal wall never, while living, allow themselves to be penetrated by the digestive enzymes, so that auto-digestion takes place only after death.

In affirming, on the basis of well-established experimental data, that intestinal absorption is not regulated by the physical laws of diffusion, we do not mean that this process is of no importance, and plays no part in absorption. The living cell (as we saw in the first three chapters of Vol. I.) is the seat of a highly complex *metabolism*, which consists of various chemical and physical processes adapted to specific functional tasks. It would be absurd to suppose that diffusion and osmosis do not figure among the physical processes employed by the cell to accomplish absorption. It would then be impossible to understand why non-diffusible become converted into diffusible substances during digestion. But the process of diffusion utilised in absorption is adapted and modified to the service of a special function, so that it differs essentially in its results from the diffusion which takes place through a non-living porous septum. Foster gives a suggestive interpretation of this difference: "The canals or spaces are constant in a non-living septum; but a film of a living cell may be conceived of as a diffusion septum the pores of which are continually varying, and, moreover, as closing up or opening out at the touch of this or that substance; hence the passage of material through the pores of a living cell takes place according to laws quite different from those of ordinary diffusion."

The capacity for *physiological selection* which Spiro (1897) attributes to living cells in general must be understood in the same sense, and is entirely different from the *physical selection* accomplished by dead tissues.

This physiological theory of intestinal absorption is substantially confirmed by the later work of Höber (1898-1903) and Cohnheim (1898-99).

The former made a comparison in dogs between the absorption

of sodium chloride solution in a loop of the gut, and solutions of sodium sulphate and a number of other inorganic neutral salts. Among the most important results of his work may be noted the fact that isotonic solutions of the various salts are absorbed at different rates by the intestinal wall, independent of the molecular weight of their ions, and the different degree of their electrolytic dissociation. This shows that the wall of the intestine does not behave like a more or less permeable homogeneous membrane, but like a membrane with specific properties.

O. Cohnheim's experiments are a continuation of those of Heidenhain upon the changes effected in intestinal absorption by the action of poisons which alter or destroy the vitality of the intestinal epithelium. With this object he compared the absorption in a loop of intestine of sugar solutions at equal concentration, before and after the addition of various poisons (sodium or potassium fluoride, potassium arseniate, etc.) in such small quantities as not to injure the animal. According to the degree of intoxication of the intestinal epithelium, he obtained a decrease or complete cessation of absorption. He noted further that the poisoned mucous membrane gave the same results as in the dead animal, *i.e.* the intestinal wall lost its property of being traversed *in one direction only.* The sugar solution introduced into the loop was found under these conditions to contain a considerable quantity of sodium chloride from the blood and lymph vessels. Normal absorption is thus proved not to be the effect of any merely physical process, since it is so profoundly altered by a few milligrammes of a given substance. Granting this to be the effect of *poisoning*, it follows that absorption must have *a living, organised substrate,* since this alone is capable of intoxication. Cohnheim justly distinguishes two factors in intestinal absorption: the impenetrability of the wall of the gut to the circulating fluids, and its capacity for absorbing solutions from the intestine. Both these factors, and each independently of the other, can be altered or suppressed by intoxication.

If the absorption of *crystalloids* (represented by salts, sugars, and amino-acids) is not governed by the laws of diffusion and osmosis, but depends on the specific physiological activity of the mucous membrane, and particularly of the epithelial cells which cover it, we may assume *a fortiori* that the absorption of *colloids* (represented by proteins, proteoses, and peptones) which provide the essentials of nutrition, must equally be independent of these physical laws, whether they are changed or left unchanged by the digestive processes.

Before leaving the subject of the absorption of salts and sugars, it must be added that they suffer no chemical change through the metabolic activity of the epithelial cells while traversing the wall of the intestine—which, as we shall see, is not the

case for fats and proteins. Of this there can be no doubt, either for salts or sugars. We saw in the last chapter that all the alimentary carbohydrates are converted by the chemical processes of digestion into monosaccharides, *i.e.* into the form of simple sugars, more particularly into glucose, before absorption. They are thus absorbed and carried to the liver by the portal system in that form in which they circulate normally in the blood. The disaccharides, *i.e.* saccharose, maltose, and lactose (which are bimolecular anhydrides of the monosaccharides) are not usually absorbed as such, but are first hydrolysed, with addition of one molecule of water, by the action of the succus entericus. It is only when highly concentrated solutions are introduced that they are partially absorbed unchanged, the proof of this being that when they reach the blood they do not remain there, but are at once excreted by the kidneys. The polysaccharides, *i.e.* dextrin, the starches and gums, and cellulose (which are polymeric anhydrides of the simple sugars) cannot be absorbed without first undergoing the amylolytic action of the saliva and pancreatic juice. Dextrin and amygdalin alone are sometimes held to be absorbed in small amounts, but this fact has not been proved, and is in any case very obscure.

V. The question of the process of Fat Absorption, and the chemical form into which the fats must be converted previous to absorption, is more complicated.

Till recently, the theory that fat was principally absorbed in the form of a fine emulsion of glycerides (or neutral fats), a fraction only being absorbed as soaps (formed by the combination of the fatty acids liberated by the lipolytic action of steapsin and the intestinal bacteria with the alkali of the secretions of the intestine) was uncontested. On this theory the cleavage of the glycerides is not a *digestion*, indispensable to the absorption of the fat: it merely furnishes a small amount of soluble soaps which facilitate the emulsification of the neutral fats—these being mainly absorbed as *an emulsion of microscopic granules.*

This theory was first put forward by Brücke, and was afterwards supported by the physiological and histological observations of several authors. But further advances in research cast grave doubts upon its probability—at least as a general statement.

In order to remove the difficulties encountered in regard to the mechanism by which the fat globules could penetrate into the interior of the epithelial cells, Perewoznikoff (1876) and Will (1879) proposed the hypothesis that the whole of the ingested fats are split into fatty acids; that they are absorbed in this form or as soluble soaps by the epithelium; and that when absorption has taken place, they are regenerated into glycerides or neutral fats by a synthesis performed by the anabolic activity of the epithelial cells. These authors demonstrated that in the frog, after feeding with pure fatty acids or soaps, with or without the addition

of glycerol, and then treating the intestinal epithelium with osmic acid, the same microscopic results were obtained as after feeding with neutral fats. Will observed the same thing, even when the frog is fed with fats of such a high melting-point, that they cannot be liquefied and emulsified in the intestine. Ewald made the same observations on the intestinal epithelium in 1883, after stripping off the mucous coat of the intestine, and setting it to digest at body-temperature in a solution of soaps and glycerol. This shows that synthesis of the fatty acids and glycerol may be effected by the epithelial cells which survive the separation from the body.

On the other hand, we know from countless observations, particularly those of Cash, in Ludwig's laboratory (1881), of I. Munk (1885), and Heidenhain (1888), that the intestinal chyme of the dog is almost always acid from the pylorus to the ileo-caecal valve, and that consequently the fat which it contains is not emulsified, or at any rate only imperfectly so, and exhibits drops of fat many times coarser than those observed under the microscope in a true emulsion. And yet, Munk says expressly, it can be seen in the parts of the small intestine in which the chyme is acid, and in which the non-emulsified fat floats here and there in large drops, that the lymphatics of the mesentery are full of milky chyle, a proof that fat absorption is going on, even when it is not emulsified and when the chyme has an acid reaction. This observation proves that the fat is absorbed under another form, perhaps in that of fatty acids or of soaps. In fact, when soaps or fatty acids are fed to a dog, small fractions only reappear in the faeces, if fatty acids with a low melting-point are taken.

On analysing the chyle resulting from these experiments, it is found to contain a large quantity of neutral fats, while the content of free fatty acids and soaps has hardly increased at all, and is very insignificant. This fact agrees perfectly with the theory which admits that the fats, like all other food-stuffs, are absorbed in the form of *solutions*, *i.e.* after cleavage, and are synthetically regenerated after penetrating the cytoplasm of the epithelial cells.

Other more direct arguments in favour of this theory are furnished by microscopical observations of the intestinal epithelia in successive phases of fat absorption. All who have occupied themselves with this subject (Kölliker, Will, Ewald, Eimer, Ranvier, and others) agree in admitting that certain parts of the columnar cell and the whole of the striated border, in particular, are always quite free of fat-drops.

The results obtained by Altmann (1889) and his pupil Krehl (1890) are more decisive. If osmic preparations of the frog's intestinal epithelium are studied in various stages of fat absorption, the cytoplasm is seen to be full of granules, the size of which

gradually increases (from mere dots to large spherules) in successively longer intervals from the meal. In proportion as they become longer the granules stain more deeply with osmic acid: the least are round particles slightly tinged with grey, the larger

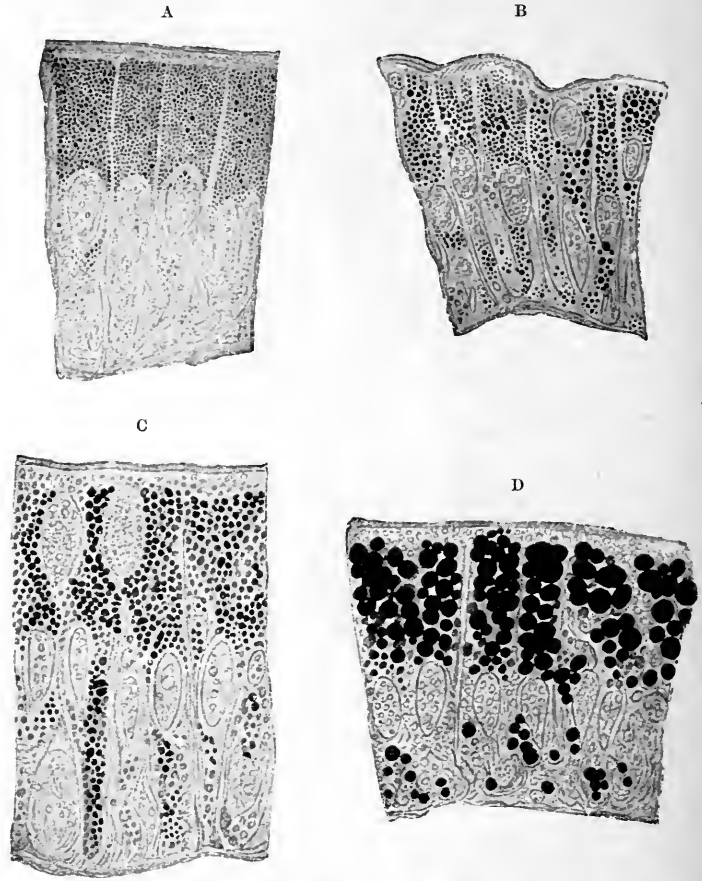

FIG. 92.—Fragments of epithelium from frog's intestine, observed at different periods after fat absorption. (Krehl.) 700 diameters. A, *rana temporaria* in summer, 3 hours after artificial feeding with olive oil; B, *rana temporaria* in summer, 5 hours after same feeding; C, *rana esculenta* in winter, 4th day after feeding with cream; D, *rana temporaria* in summer, 8 hours after feeding with olive oil. The fat droplets are stained more or less black with osmic acid.

are spherules of a distinct black colour (Fig. 92). According to Altmann's theory of the *granular structure* of protoplasm, the punctiform particles, which hardly stain with the osmic acid, would be the elementary granules that subserve the protoplasmic function, surrounded by a layer of fat synthetically regenerated

by the anabolic action of the granules; the black spherules of increasing size observed later on would have nuclei composed of the elementary granules, which are invisible because they are surrounded by a more or less extensive layer of newly formed fat. The credibility of this hypothesis is proved by the observations of Altmann and Krehl on fat absorption in the mammalian intestine. The epithelial cells, in the early stages of absorption, exhibited not grey or black granules, but blackish rings with clear centres (Fig. 93). This appearance can only be interpreted by assuming that the clear centres consist of unstained elementary granules with a layer of fat at their outermost zone, which fat reached the cells in the form of solution, and was regenerated by the anabolic activity of the granules. These important cytological observations

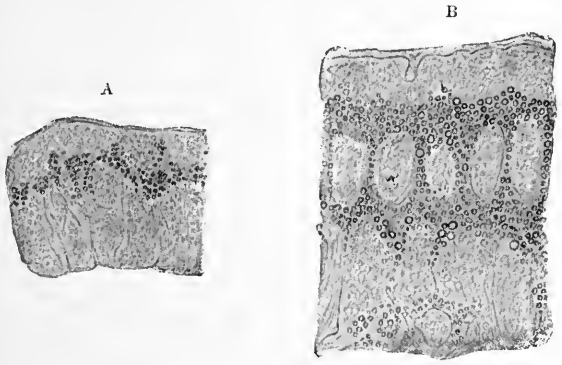

FIG. 93.—Fragments of epithelium from mammalian intestine during fat absorption. (Krehl.) About 700 diameters. A, suckling kitten, 3 hours after artificial feeding with cream; B, white rat, 3 hours after feeding with cream.

seem to us to afford direct evidence for the modern theory of the absorption of fats in the form of *solutions*.

Other physiological arguments in favour of this theory may be deduced from the great importance of the pancreatic juice and the bile in the absorption and utilisation of alimentary fat. We saw in the last chapter that the lipolytic action is due to the pancreatic juice and that the bile has a marked coadjuvant action upon it, as is confirmed by the effects of intestinal acholia (see p. 220 *et seq.*). It is therefore important to consider the effects of extirpation of the pancreas and deviation of the bile from the intestine more closely in regard to fat absorption.

Minkowski's pupil Abelmann (1890) made a great number of experiments on fat digestion and absorption in the animals from which Minkowski had removed the pancreas. He found that after complete extirpation of the pancreas in dogs, the whole of the alimentary fats (butter, lard, olive oil) reappeared in the faeces so that no absorption had taken place. The sole exception was the

emulsified fat of milk, of which 53 per cent could be absorbed. After incomplete extirpation of the pancreas, on the contrary, absorption of about half the ingested fat, and as much as 80 per cent of the fat of milk could be observed.

These conclusions were, however, criticised and corrected by Hédon and Ville (1897), who employed a more perfect method of estimating the fats in the faeces, and further investigated the fat content of the chyle after the complete or incomplete removal of the pancreas. They found that even in perfectly depancreatised dogs there is a certain deficit of eliminated as compared with ingested fat, the missing amount being found in the chyle, which presents a milky aspect and contains a considerable amount of fat.

The work of both Abelmann and of these French investigators shows that cleavage of fats goes on energetically even in the absence of the pancreas (owing to the action of the lipolytic enzyme of the gastric juice, the succus entericus, and the intestinal microbes), since the neutral fat ingested is found in the faeces principally in the form of free fatty acids, much less in the form of neutral fats, and least of all as soaps.

The phenomenon of loss of fat by the faeces in quantities approximately equal to the alimentary fat, after the total extirpation of the pancreas, was confirmed by numerous observers (Harley, Rosenberg, Baldi, Scotti, Hess, Pflüger, etc.). These authors all interpreted it as being due to defective absorption owing to absence of the pancreatic secretion in the intestine.

This explanation is contradicted by the fact that absorption of 80 per cent and more of fat can be seen when a segment of about one-third of the pancreas is left, isolated from the abdominal cavity, and pouring its secretion away outside the body (U. Lombroso, Fleckseder, see p. 101).

It might logically be supposed that on partial removal of the pancreas with deviation of the secretion to the exterior, there would be an increase in the lipolytic and enzymic activity of the other glands which provide for the digestion of the fats and their subsequent absorption. This hypothesis is, however, excluded by the results of Lombroso's experiments on the enzymic activity of the various secretions, before and after the extirpation of the pancreas secreting outside the intestine.

That the loss of fat by the faeces in depancreatised animals cannot be ascribed to deficiency of the lipolytic process, appears from the fact that on administering fatty acids or soaps instead of neutral fats, the amount of fats eliminated by the faeces of depancreatised dogs diminishes very little (Abelmann, Lombroso).

Is it possible that the fat present in the faeces of depancreatised animals does not consist exclusively of non-absorbed alimentary fat, as is generally supposed, but also to a greater or less extent of

the fat previously stored up in the body, which is eliminated by *intestinal excretion* when the *internal secretion* of the pancreas is wanting? Certain observations of Lombroso tend to justify this bold hypothesis.

He noted excess of fat in the faeces of certain depancreatised animals, when fasting or fed with plain egg-albumin. If kept on a mixed diet, the faeces contained more fat than is supplied with the food. A similar phenomenon has previously been recorded by Harley, but to a less extent, so that it came within the limits of experimental error. In some other cases Lombroso observed that the fat present in the faeces of depancreatised dogs, while not in excess of that introduced with the food, had a different melting-point.

These observations (to which we shall return in speaking of the excretory functions of the intestine) show the complex origin of the fat present in the faeces after extirpation of the pancreas. It cannot be taken as an exact expression of defective absorption due to deficiency of the lipolytic enzymes.

Fat absorption in dogs with a complete fistula of the gall-bladder was more particularly studied by Voit (1882), Röhmann (1882), Fr. Müller (1885), I. Munk (1890), Hédon and Ville (1897). The results obtained by these observers agree fairly well together. Those of Munk deserve special attention. He compared the absorption of different kinds of fats in a dog of 23 kilos., operated on 6 months previously by a biliary fistula. He found that 67 per cent pork fat (in a dose of 3·50 grms. to each kilogramme of the animal) was absorbed, while only 36 per cent was absorbed of mutton fat, which has a higher melting-point. Absorption was increased if, instead of these neutral fats, the corresponding fatty acids were administered.

The form in which the fats reappear in the dejecta is chiefly that of free fatty acids (Röhmann, Müller, Munk, Hédon). Voit alone assumes that the form of neutral fat predominates.

It is more important to determine the alterations in the digestion and absorption of fat, when both pancreatic juice and bile are simultaneously excluded from the intestinal canal, the former by extirpation of the pancreas, the latter by fistula of the gall-bladder. The effects of this double operation were studied by Hédon and Ville in their experiments on two dogs, which only survived the operation 12 and 22 days. They found that the digestive disorders, already conspicuous after removal of the pancreas, were accentuated after the bile had been cut off. The two animals became more voracious than when the pancreas alone was extirpated. They speedily exhibited a marked disgust for fat. After some days the faeces showed bloody streaks, and the emaciation and debility became excessive. In the last days of life the dejecta were blackish (*melena*), and death occurred with symptoms of exhaustion.

To us, the most interesting fact is that under such conditions fat absorption should still be possible. Analysis of the faeces showed that non-emulsified fats (diet of bacon and meat) were absorbed to an amount of 10 per cent; finely emulsified fats (milk diet) were absorbed in quantities above 22 per cent. The greater part of the fats eliminated with the faeces (78-90 per cent) appeared in the form of free fatty acids, which were unmixed with soaps, or mixed to a minimal extent only. There was thus a cleavage of fats to an extent not less, but even somewhat greater, than that which took place in dogs with a simple fistula of the gall-bladder, which gives some idea of the fermentative activity of the intestinal bacteria during the fat digestion. The putrefactive phenomena (apparent in the foetid odour of the excrements), which increased during the course of the observations, appear to be in ratio with the cleavage of the fatty substances.

In explanation of the intestinal haemorrhage which hastens the death of animals thus operated on, Hédon holds that bile and pancreatic juice have a beneficent action upon the nutrition of the intestinal mucous membrane; but this is not the place in which to discuss his hypothesis. The important point in his conclusions is that the non-absorbed fats reappear in the faeces mostly in the form of free fatty acids, with few or hardly any soaps. Hédon, with little foundation, considers this fact to be an argument in support of the theory that the cleavage of fats is not a necessary condition of their absorption. We shall see that there is a better interpretation of his significant discovery.

Another fact, which shows plainly that the glycerides in order to be absorbed must first be decomposed, and then reconstituted by synthesis after absorption, appears from the experiments of Otto Frank (1894), which show that on feeding dogs with neutral fats, or with fatty acids which have a higher melting-point than that of the body (45° C.), they can be absorbed, and that a fat is constantly present in the chyle, which melts approximately at body temperature. On the other hand, it was shown by I. Munk that after ingestion of spermaceti (palmitate of cetyl alcohol) palmitin appeared in the chyle. The cetyl-palmitate therefore splits up, and the palmitic acid combines with glycerol to form a neutral glyceride. Nothing, however, is known as to the origin of the glycerol required in this synthesis.

After the doctrine of fat absorption as an emulsion had been overthrown, it still had to be decided whether the fats were absorbed in the form of soaps, or of fatty acids, which, as we know, are readily dissolved in bile, and specially in the bile acids (see p. 220). From a series of exact experiments on the solubility of fatty acids in bile (from ox, sheep, or dog) Moore and Rockwood (1897) concluded that this was sufficient to explain the absorption of alimentary fats in the form of free dissolved fatty acids. But

they denied that the whole of the ingested fat was absorbed in this form. The results of their experiments rather led them to conclude that the form in which fat is absorbed varies in different species of animals; although they maintained that the greater part, if not the whole, of the fat is absorbed in a soluble form by the epithelial cells. In this connection they noticed that when fatty acids are dissolved in bile, the alkaline is transformed into an acid reaction; when dissolved in the filtrate from the intestinal contents of the dog, the acidity increases. If, therefore, the intestinal content has an alkaline reaction, the assumption that it contains dissolved free fatty acids to any non-negligible amount may be excluded. They further observed that the small intestine of white rats was alkaline almost throughout its entire length during fat absorption. In the dog, on the contrary, the lower tract of the ileum only (as a rule) is alkaline, while the larger part of the small intestine gives an acid reaction. In the contents of the latter the dissolved fat is not present exclusively in the form of free fatty acids, but is in the form of soaps as well, showing that it contains more alkali than is required for combination with the inorganic acids, and that this excess of alkali must be combined with the fatty acids. In the last part of the dog's ileum, the contents of which give an alkaline reaction like the whole of the small intestine of the white rat, only soaps are present, in solution. Thus in the white rat, according to Moore and Rockwood, the fat is probably absorbed in the form of soaps; in the dog, part is absorbed as fatty acid and part as soap, in variable proportions.

The importance of the formation of soaps, according to Moore and Rockwood, lies in the fact that they assist the emulsification of the neutral fats. Even if the fats cannot be absorbed in the form of an emulsion it is easy to see how advantageous to digestion and cleavage the emulsification of fat in the intestine must be: it is then reduced to a state of fine division which presents a far larger surface to the action of the lipolytic enzyme. Moore and Rockwood noted emulsification of fats in the intestine in 10 out of 16 experiments on dogs, although never in the degree of fineness and stability characteristic of the milky emulsion present in the chyle.

In view of the experiments above described, on the effects of extirpating the pancreas and diverting the bile, or of the two operations together, as regards fat absorption, it appears to us that other considerations may be added to the conclusions of Moore and Rockwood as to the importance of soap formation. It is evident that the soaps serve not only to emulsify the neutral fats, and thus supplement the function of the lipolytic enzyme and the bacterial ferments, but also to facilitate—probably to render possible—the absorption of the digested fats. The waste fat met with in the dejecta (much or little according to the different conditions of experiment) always consists mainly of free fatty acids

and to a minor degree of soaps. This well-established fact in our opinion authorises the conjecture that, as the epithelium of the stomach is impermeable to hydrochloric acid, so the intestinal epithelium is impermeable to the fatty acids, which can thus be absorbed *only in the form of soaps, i.e.* in the alkaline vehicle of the pancreatic juice, bile, and succus entericus.

Lombroso's observations on the reaction of the mucous membrane stimulated by contact with fatty acids favours the theory that fat is absorbed in the form of soaps.

As shown above (p. 130), he saw that on introducing fatty acids dissolved in bile into a Vella's loop, a copious secretion was induced, and renewed as often as the secretion collected was reintroduced, so long as it contained enough non-absorbed free fatty acid. In view of the quantity of secretion discharged altogether by the loop, and its potential alkalinity, we see that it is approximately what is required to transform the whole of the fatty acid into soap.

Thus the fatty acid, even when completely dissolved, does not appear to be absorbed as such: on the contrary, it evokes an abundant intestinal secretion which tends to transform it into soap. Soaps, however, are only present in very small quantities in the faeces. How is it possible to interpret this phenomenon otherwise than by assuming that the soaps have been absorbed, and thus disappear from the secretion, while the fatty acid is present because the intestinal epithelium refuses to absorb it, probably by a kind of *negative selection.*

VI. The problem of Protein Absorption is no less complex. In the first place, a question presents itself which it will be well to solve as a preliminary. Is peptonisation, or the more or less advanced hydrolytic cleavage of proteins, necessary to their absorption? Are the intestinal epithelia permeable only to *peptones* and *proteoses*, or to the *natural proteins* as well? The first view was sustained by Mulder (1858), and Meissner (1859), and was adopted by many others, particularly by Hermann. Starting from the notion that absorption is a process of diffusion, they held the peptonisation by which proteins are transformed from indiffusible into diffusible bodies to be indispensable for their absorption.

The first critics of this theory, which found much favour, were Brücke (1859-69) and Diatonow (1867-68), who asserted that the natural proteins in solution (colloidal) are with few exceptions capable of traversing the wall of the intestine without alteration by the proteolytic enzymes. Better experimental evidence for this theory was brought forward by C. Voit and Bauer (1869). In a living dog they introduced protein into an intestinal loop (previously washed and isolated by ligatures), in the form of solutions of myosin, syntonin, and egg-albumin, and found them to

be absorbed in 1-4 hours, without showing the least trace of proteose or peptone previous to their disappearance.

In a subsequent study of the absorption of different alimentary substances introduced per rectum into the large intestine (a method that found wide application in clinical medicine) Eichhorst (1871) found that in addition to myosin and syntonin the protein of milk and metaprotein were capable of absorption, without any trace of peptonisation, in the large intestine.

The same fact was observed by Czerny and Latschemberger in man, in a case of fistula of the sigmoid flexure, which allowed perfect washing out and disinfection of the rectum, so as to exclude all intervention of proteolytic enzymes and bacteria. Nencki and his pupils (1891) arrived at the same results, experimenting on man in a similar case of fistula of the large bowel. Their results show that 70 per cent of dissolved metaprotein can be absorbed in a day.

These same proteins, injected directly into the veins, are eliminated in the urine in the form of urea only. They are therefore utilised by the body, and require no digestive alteration to fit them for assimilation. It is otherwise with ovalbumin, caseinogen, haemoglobin, and gluten, which substances, if injected into the blood, are eliminated unchanged in the urine.

Ovalbumin must therefore be transformed into syntonin by the action of the gastric juice, before it can be utilised. In fact, when introduced per rectum in the natural state it is not absorbed (Bauer); ingested by the mouth in large quantities it can be absorbed, but produces *albuminuria* (Brücke). Directly sodium chloride is added, however, it becomes absorbable, though very slowly, and can be utilised (Voit, Bauer, Eichhorst, Huber).

It has not yet been discovered why the addition of sodium chloride renders the mucous membrane of both large and small intestine permeable to egg-albumin, which in itself is inabsorbable. All explanation of the fact is wanting, but it has been positively confirmed and established. Baldi (1896), in a series of very clear and simple comparative experiments, showed that solutions of commercial peptone (which consists principally of proteoses) are also absorbed more rapidly from a Vella's loop, if a little sodium chloride be added.

Caseinogen is normally refractory to absorption owing to the coagulation it undergoes in the stomach from the enzymatic action of the chymosin of the gastric juice; hence it can only be absorbed after decomposition into syntonin and nuclein. Haemoglobin, too, is broken up by the action of the gastric acid into albumin and haematin: the first can be absorbed as such, the second is eliminated for the most part with the faeces, and is only to a minor extent utilised by the liver in the formation of bile-pigments.

This evidence that the greater part of the soluble proteins can be absorbed as such, or after slight changes, radically modifies our ideas as to the importance of the peptonisation effected by the gastric, and still more by the pancreatic, juice in the consumption of alimentary protein. These juices obviously render soluble, and therefore absorbable, the proteins introduced in the solid state, and they also split up non-absorbable protein, and liberate the utilisable protein-groups of the molecules: but *soluble proteins* can be absorbed and utilised as such, without any previous hydrolytic cleavage into proteoses and peptones.

There is, however, no doubt that a considerable part of the soluble proteins do undergo proteolytic cleavage previous to absorption. When we reflect that part of the potential energy of the natural proteins is wasted in their cleavage into proteoses and peptones, the utility of this process is hard to understand. But it should not be forgotten that proteoses and peptones (from their physical and chemical properties), are more easily and promptly absorbed by the intestinal epithelia than are natural or scarcely altered proteins. In this lies the utility of scission and subdivision of the latter, which is carried farther or arrested as required, particularly in proportion as they are introduced in excessive or scanty quantities, and as the proteolytic enzymes are abundant or defective.

The medical use of feeding debilitated persons and invalids on proteoses or peptones may be justified by their ready absorption. But under physiological conditions, such a prescription for utilising the alimentary principles is not only unnecessary, but is neither economical nor advantageous in comparison with a diet of natural proteins, as was clearly proved by Horton-Smith (1891).

The fact that proteoses and peptones are capable of replacing natural protein under all conditions of nutrition was clearly demonstrated by the experiments of Maly and Plosz (1874). The former fed a pigeon, the latter a dog, very satisfactorily for some time upon a diet in which proteoses and peptones replaced the natural proteins. The same successful results were obtained in a striking manner by Zuntz (1885), Pollitzer (1885), Gerlach (1891), and Pfeiffer (1885), the last of whom experimented on himself for ten days in succession.

These results showed the suggestion of some authors (Brücke, Voit, and A. Fick in particular) to the effect that peptones, though absorbable, cannot be assimilated by the tissues, and that natural proteins alone can compensate for tissue waste, to be unfounded. We may conclude that the protein stored up in the tissues comes from two sources: from the dissolved proteins absorbed as such, and from the products of their digestion, *i.e.* proteoses, peptones, and amino-acids. It is difficult to determine how much of the ingested protein is absorbed unchanged, and how much after

undergoing more or less advanced peptonisation and hydrolysis. Schmidt-Mülheim's researches in this direction are not very convincing. It seems probable that the degree of peptonisation and hydrolytic cleavage into amino-acids of the proteins varies considerably within wide physiological limits.

With this question we must associate the effects of total or partial removal of the pancreas, in relation to the absorption and utilisation of alimentary protein. According to Minkowski and Abelmann (1890), a dog wholly deprived of its pancreas may absorb and utilise on an average 44 per cent of the flesh ingested; when the extirpation has been incomplete it may even make use of 54 per cent. When a little pig's pancreas is fed to the animal along with the meat, the amount of protein lost with the faeces is conspicuously diminished. According to Landmeyer's latest experiments (1895), 62-70 per cent of the proteins can be utilised after incomplete ablation of the pancreas. Nothing definite can, however, be concluded from this fact as to the extent under normal conditions of the peptonisation of ingested proteins and their cleavage into amino-acids. It is certain that a considerable portion of them must be subjected to this process not only to accelerate absorption, and thus increase the amount utilised by the body, but also, by means of the molecular aggregates represented by the amino-acid group, to make possible the synthetic constitution of the complex proteins which are *specific* to organisms of different species or genera.

The process by which the proteoses, peptones, and amino-acids are utilised by synthetic processes is very remarkable. They are largely regenerated into *natural protein* (probably into serum-albumin) during their passage through the mucous membrane, by the anabolic activity of the epithelium. The experimental data on which this important conclusion rests are numerous and agree well together.

(*a*) Proteoses and peptone are never found in the blood or lymph, even when these fluids are examined during absorption, after an abundant digestion of proteins. Schmidt-Mülheim and Hofmeister stated that peptone could be detected in blood-serum in a maximum amount of 0·02-0·05 per cent, but more exact experiments subsequently undertaken by Neumeister (1888) excluded even this small amount of peptone. Under the best conditions of experiment, the biuret test is always absolutely negative, both with lymph and with blood-serum.

(*b*) When proteoses and peptone are injected directly into the blood, they immediately disappear from it (Fano), and pass into the urine as bodies foreign to its normal composition (Hofmeister, Neumeister). If a considerable quantity be injected, they induce toxic phenomena and modify the composition of the blood by rendering it incoagulable, which causes an enormous lowering of

arterial blood-pressure, with ecchymosis of various organs (Schmidt-Mülheim, Fano, Kühne and Pollitzer, Neumeister, Shore, Salkowski). It is therefore necessary that the proteoses and peptone absorbed from the intestine shall, before they penetrate into the blood and lymph, be modified until they lose all toxic action.

(*c*) The organ which effects this transformation or regeneration is not the liver, as was formerly supposed, because the portal blood contains no more peptone than the rest of the blood. Moreover, if blood containing peptone be circulated through the vessels of the surviving liver, freshly excised from the animal, the peptone does not disappear nor even sensibly diminish in the circulating blood. The same result is obtained if peptone be injected into a mesenteric vein, *i.e.* in the direction of the liver, in a living animal, the blood of the hepatic vein being then examined (Neumeister). The same appears, again, on injecting peptonised blood by the splenic artery, so that it must pass through the spleen and the liver in succession (Shore). This last experiment shows that the spleen is also incapable of converting peptone into natural protein.

(*d*) It was G. Salvioli (1880) who first, in Ludwig's laboratory, demonstrated that proteoses and peptone are synthetised into natural protein in passing through the intestinal walls. He isolated a loop of intestine from a recently killed dog, closed the ends by ligatures, and introduced a gramme of dissolved peptone. Artificial circulation was then established through the arterial and venous vessels of the loop, by which perfect vitality was maintained, as shown plainly by the peristaltic movements. After four hours' circulation in a glass chamber warmed to 37°-40° C., he found only about half a gramme of coagulable protein, and hardly a trace of peptone in the intestine. No peptone was found in the circulating blood. If it had been added previous to circulation it was found present in the same amount at the close of the experiment. Evidently, therefore, the peptone absorbed from inside the loop disappeared while traversing the intestinal wall, before it could reach the blood. Under the conditions of this experiment, however, a part of the peptone is decomposed into amino-acid previous to absorption.

(*e*) Hofmeister (1885) showed that the mucous membrane of the stomach and intestine is the sole tissue (except the spleen) in which the presence of peptone can be detected during digestion. But the peptone present in the gastro-intestinal mucous membrane rapidly undergoes conversion. If two equal parts of stomach or intestine are taken from a dog killed during digestion, the first part being thrown into boiling water, the second kept for some time at 40° C. before immersing it, peptone will be found in the former, while there is none left in the latter. In this the peptone

disappears, not by decomposition, but by synthetic regeneration into natural protein by the vital activity of the cells of the mucous membrane. The peptone does not in fact disappear from the mucous membrane if this be plunged not into boiling water, which destroys the enzymes also, but into water at 60°, which destroys the vitality of the cells without affecting the enzymes. According to Neumeister (1890) considerable amounts of peptone and proteose can be converted in a short time, when they are mixed with dilute blood and fragments of intestine from a freshly killed animal are thrown in, the blood being then agitated with a gentle current of air, so that every part of it comes into contact with the mucous membrane of the intestine.

Fano (1881) showed that after injecting peptone and proteoses into the blood they disappeared rapidly, while the specific gravity of the erythrocytes increased, which supports the hypothesis that the erythrocytes are the active agents in regenerating the peptones, or some of them at least, the peptone being dehydrated and split up with conversion into globulin, by the potassium salts that predominate in these cells, and by the presence of oxyhaemoglobin. He therefore thinks it probable that the more or less peptonised proteins that penetrate into the blood from the alimentary canal may be partially absorbed and stored up by the erythrocytes, as reserve materials which are subsequently poured into the plasma to compensate for the losses it has sustained.

Hofmeister (1885), on the other hand, supported the hypothesis that the active agents in the regeneration of proteoses and peptones and in their transport in the blood are represented by the leucocytes of the adenoid tissue of the villous mucous membrane, which accumulate there during digestion, and insinuate themselves through the interstices, and perhaps also into the interior of the columnar epithelial cells. He thus attributes to the leucocytes, in the absorption of peptones from the intestine, a function similar to that which the erythrocytes perform in the absorption and transport of oxygen from the lungs to the tissues. Both Fano's and Hofmeister's hypotheses were, however, subsequently contradicted by various facts; notably by the experiments of Shore, who saw that a small quantity of peptone (5 cgrms.) injected into a peripheral lymphatic of one of the posterior limbs reappeared in the lymph collected from the thoracic duct in 30 minutes. On the other hand, we know that peptone does not completely disappear when it is added in small quantities to freshly extracted blood or lymph, although the former contains numerous erythrocytes, the latter numerous leucocytes, which long survive under favourable conditions of temperature.

There can therefore be no doubt that the synthesis of the proteoses and peptones is effected by the vital activity of the epithelial cells of the mucous membrane.

It has been stated that the proteoses and peptones can be synthetised into serum-albumin in the intestine, and also in the stomach, *by simple contact with the living epithelial cells, i.e. previous to absorption.* Von Ott (1883) observed in the abdominal and intestinal cavity of recently killed rabbits, as also in the stomach of living dogs, that serum-albumin can be formed after introducing commercial peptone (which consists largely of proteoses). To prove that this was a true regeneration into serum-albumin he employed not only chemical reagents but also a *physiological* reagent, *i.e.* the frog's heart, excised and attached to Kronecker's apparatus. The heart did not beat when filled with a solution of proteoses or peptone, and recommenced its beat when filled with the same solution regenerated by contact with the gastric or intestinal mucous membrane. Von Ott's results were confirmed and extended by Julia Brinck and N. Popoff in Kronecker's laboratory (1889); they used Vella's loop of intestine for the regeneration of the proteose and peptone.

That the synthetic reconstruction of the coagulable protein is the work of the *living epithelial cells* is proved by the fact that the phenomenon does not occur when proteoses and peptone are brought into contact with the mucous membrane of the intestine or stomach after the death of the cells (20 min. after killing the animal). In this case (if the body is placed in a chamber regulated at 37°-40° C.) auto-digestion of the mucous membrane may take place, but there is no synthesis of the proteoses and peptone introduced. J. Brinck further found in the contents of the intestine a micrococcus capable of the same synthetic function as the epithelial cells, to which she gave the name of *Micrococcus restituens.*

Granting the accuracy of these interesting phenomena, they do not seem to us adequate to prove that proteoses and peptones are regenerated into serum-albumin by simple contact with the living epithelia, *previous to absorption.* If this be admitted, there can be no advantage in the proteolytic process, which facilitates or accelerates absorption. It seems to us more logical and simpler to assume that part of the protein formed synthetically by the cytoplasm of the epithelial cells is poured back into the intestine with the succus entericus or gastric secretion from the glandular crypts of the intestine and stomach respectively. It is now known as a fact that succus entericus always contains a certain amount of protein (0·5 per cent according to Quincke, according to Thiry, Pregl, and others a somewhat larger proportion). And Mme. Schumowa-Simanowskaia demonstrated that pure gastric juice obtained from a gastric fistula with sham feeding always contains a certain amount of protein (0·13-0·18 per cent). We regard it as probable that the coagulable protein found by

Salvioli in the excised loop of intestine into which peptone only had been introduced, has the same secretory origin, *i.e.* it is derived from succus entericus secreted during the absorption and subsequent regeneration of the peptone.

The disappearance of the peptone artificially introduced into the loop of intestine may therefore be the result of a conversion, not into larger complexes, but (at least partially) into simpler crystallisable complexes (amino-acids).

We already know from the work of Kühne (p. 211) that the protracted action of trypsine upon peptone may result in very simple products. Neumeister (1890), who observed the disappearance of peptones from the blood diluted with peptone solution in which he had placed freshly excised fragments of intestine, came to no definite conclusion in regard to the disappearance of peptones by conversion into more complex products; but he brought forward the other possibility, viz. the formation of amino-acids, already suggested by Brücke, by Voit, and particularly by Fick, since he was able to show the presence of leucine and tyrosine, although only in small quantities.

Capparelli (Catania, 1899) suggested the same account of the conversion of peptone in the intestine. He introduced a solution of commercial peptone into an empty loop of intestine in a dog that had fasted 1-3 days, after tying it at the ends and isolating it from the mesentery so as to prevent absorption by the blood, after which it was replaced in the stomach. On testing the fluid after 1-1½ hours the peptone had disappeared. The same occurred *in vitro* on mixing shreds of intestinal mucous membrane with peptone solution, as also with a mixture of various digestive enzymes, or with trypsin alone. In all these cases he found that the products of peptone conversion were highly soluble in water, insoluble in alcohol, dialysible, with a rotary power different from that of the original peptone solution. He concluded that he was dealing with a complex simpler than peptone, which he was, however, unable to identify.

O. Cohnheim has recently formulated more concrete opinions on the same subject. As we saw on pp. 127, 212, he found that the intestinal mucous membrane actually contained a special enzyme which he called *erepsin*, which has this very property of breaking up the proteoses and peptones into smaller complexes (amino-acids). Neumeister and Capparelli may both be regarded as the immediate precursors of the discovery of erepsin.

According to Kühne, Cohnheim, and others, absorption of proteins takes place after their more or less complete conversion into amino-acids. Part of these are synthetised by the mucous membrane of the intestine, part, on the contrary, which are absorbed unchanged, are directly consumed by the tissues, or undergo within their depths the synthetic processes by which

they are fitted to repair the losses that continually occur in the individual cells.

This does not, however, exclude the absorption of protein, as such, more particularly of peptone, *i.e.* before the latter breaks up into amino-acids. In fact, after herbivora (rabbits, guinea-pigs) had been kept for some time on a milk diet, Hamburger observed the presence of the so-called *precipitine* in the blood (*the "biological" reaction*). M. Ascoli, Viganò, and Moreschi employed the same method to determine the fate of the alimentary proteins. It is based on the property by which blood serum is able to precipitate foreign proteins, against which it has been immunised by repeated subcutaneous injections. Raw egg-white or roast chicken was fed to dogs, by means of the sound, the reaction of the blood and lymph (from a thoracic fistula) to rabbit-serum, previously immunised to these proteins, being tested before and after they were introduced (the proteins being precipitated by the serum). In consequence of this diet the lymph (less constantly the blood) of the animal experimented on, was thrown out by serum which had been immunised to the proteins fed. From this Ascoli concluded that the highly complex atomic groups derived from the proteins (if not the proteins themselves, unaltered) which cause the biological reaction of *precipitation*, are able to pass through the gastro-intestinal wall and penetrate to the lymphatic system, without previous reduction to crystallisable products.

VII. From all that has been said of the absorption of the different groups of food-stuffs in the gastro-intestinal canal, and the chemical changes that some of the absorbed products of digestion undergo in consequence of the activity of the epithelial cells, it is clear that the mechanism of these marvellous processes is not essentially different from, certainly not less complex than, that by which each living cell or independent elementary organism draws the alimentary principles required for its nutrition and development from the environment in which it lives, and then gives off the products of its anabolic and katabolic activity.

The special organ of intestinal absorption is the *villus*, which in view of the complex of epithelial cells with which it is clothed, may be regarded as an *extraflected glandular crypt*, in which the epithelia do not absorb the lymph from the end which is attached to the basement membrane, but take up the food-stuffs (whether modified or not by the digestive process) from their free end, at the striated border. The absorbed materials which are partially modified by the metabolic activity of the cells are not poured outwards as in the *intraflected crypts*, but are emptied into the lymph sinuses of the adenoid tissue of the villi, whence they make their way by the blood capillaries through the portal vein to the liver, or by the central lymphatic, which leads to the thoracic duct.

P. Mingazzini (1900) gave new support from the histological

standpoint to this physiological theory, in which the villus of the intestine is regarded as *an inverted glandular organ of internal secretion.* He examined the intestinal villi of various vertebrates, but up to the time of his death had only published his observations on the small intestine of the fowl, which seemed to him the clearest and most important.

When examined in different phases of digestion the villi, he says, may present two entirely different aspects, according as they are in the *resting* or in the *actively absorbing* state. In the first case all the epithelial cells of the villi are regular, and approximately equal in form and height, with nuclei that are always at the same level, *i.e.* toward the middle or inner third of the cell, and protoplasm that stains more intensely towards the external free end, less intensely towards the basal portion beneath the nucleus (Fig. 94).

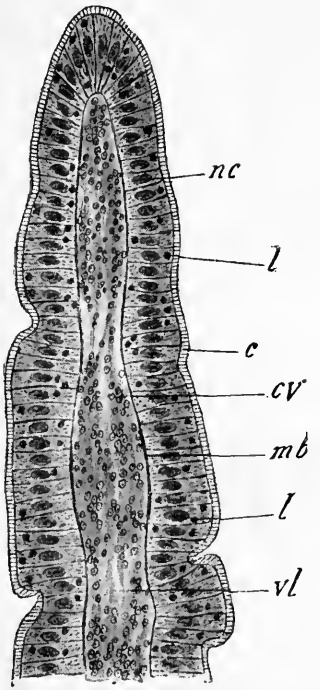

Fig. 94.—Villus of small intestine of fowl. Resting state. (P. Mingazzini.) *c*, striated border of epithelium; *nc*, nuclei of columnar epithelium; *l*, leucocytes scattered in cytoplasm of epithelium; *mb* basement membrane of epithelium; *cv*, adenoid tissue of villus which also contains muscle fibres; *vl*, central lacteal.

During its functional work, the villus looks quite different. While the stroma of adenoid tissue, mingled with bundles of plain muscle cells, preserves the form and dimensions of the resting state, the epithelial covering undergoes profound modifications, which entirely alter the aspect of the villus as a whole (Fig. 95). During the first phase two distinct cellular zones begin to be differentiated: an *outer*, granulated and readily stainable zone, and an *inner*, hyaline, less granulated zone, which stains pale yellow with picric acid. In a more advanced phase of absorption, the inner zone grows out beyond the nucleus, which tends to a conspicuous lengthening of the cells, so that the nucleus is pushed into the outer third of the body of the cell. Finally, in a third phase, the hyaline portion gradually liquefies or vanishes by internal absorption, till at last only the outer zone of the epithelial cells is left, at the base of which the nucleus is found almost in contact with the basement membrane.

As shown in the figure, different parts may be distinguished

in the same villus, showing epithelia in the first, second, or third phase of the process of absorption and internal secretion of the absorbed products. It is usually the epithelia of the apex of the villus which show these changes most conspicuously; along the lateral walls of the villus they are less obvious, and are minimal towards its base.

According to Mingazzini, the stroma of the villi also presents

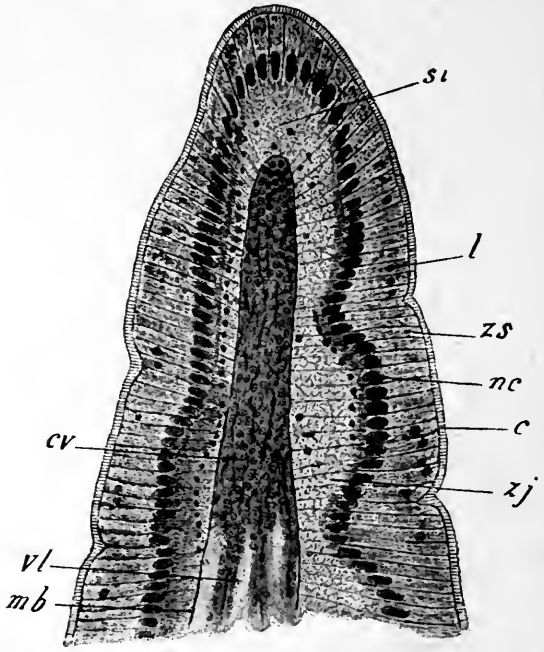

FIG. 95.—Villus of small intestine of fowl during absorption. (P. Mingazzini.) Lettering as in previous figure. In the apex of right side of villus particularly the columnar cells have become elongated and exhibit a zone external to the nucleus (*zs*) that stains deeply, and an internal hyaline zone (*zj*) which contains the absorbed substance. At the apex of the villus the inner epithelial zone is transformed into a granular substance (*si*).

different aspects in different phases. In some cases it seems to consist of a compact tissue; in others, on the contrary, of loose tissue. In the former it is regular in form, and of small dimensions; in the latter the form is not very regular, and the dimensions are larger (Fig. 96). It is possible in the last case that the villi may be swollen owing to the chyle poured out by internal secretion into the lymph spaces of the adenoid tissue, before it reaches the central lacteal. The leucocytes packed between the epithelial cells are perhaps destined to function after the latter have discharged their internal secretion.

These observations of Mingazzini gave rise to much discussion

both in Italy and abroad: some authors (as Drago, 1900; Reuter, 1901; Rina Monti, 1903) agreed with his conclusions. Many, however, hold the opposite opinion (Bezzola, 1901; Arcangeli, 1905; Demjanenko, 1909); so that on the whole the theory of *absorption, considered as an internal secretion,* is not, however well established physiologically, sanctioned by histological evidence, as is the case for other secretions.

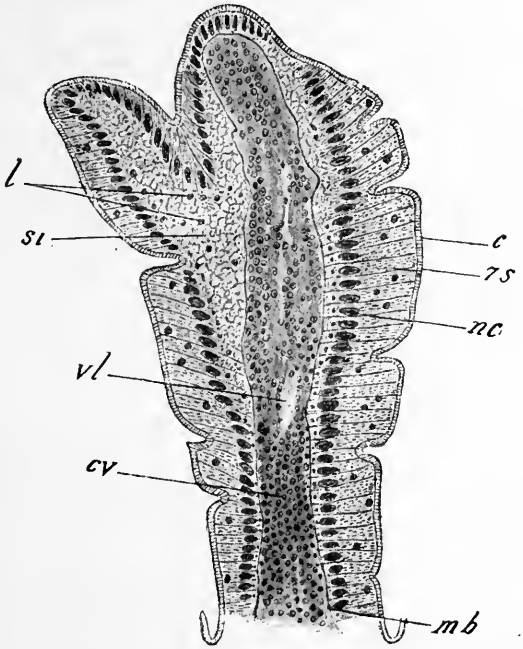

FIG. 96.—Villus of small intestine of fowl in a more advanced stage of absorption and internal secretion. (P. Mingazzini.) Lettering as in previous figure. At the apex of the villus the internal secretion of absorbed substances has already taken place, so that the epithelial cells are reduced to their minimal size. To the left, a sort of lobe projects, in which there is a maximal accumulation of the granular substance secreted by the epithelia. The stroma or adenoid tissue of the villus is compact below, and looser above, and swollen by the penetration of chyle between its fibres. Here the nuclei appear to be farther apart than below.

The fats secreted by the columnar epithelial cells must pass from the labyrinthine spaces of the adenoid tissue of the villus into the central lacteal, and the carbohydrates and proteins mainly into the interior of the capillary network of the villus. The mechanism of this penetration has not been cleared up by direct experiment, and we can only reconstruct this important process by analogy.

In regard to the passage of fat from the labyrinthine spaces to the interior of the central lacteal, we may assume that the epithelioid cells which form the wall of the latter leave lacunae

or stomata, or permit the occasional formation of clefts in the lines of junction, through which the minute fat droplets can pass easily. It must, however, be stated that in chyle the fat is found in a highly fractional form (sometimes known as the *molecular basis*), while in the cytoplasm of the columnar cells, and also in the adenoid reticulum that surrounds the central lacteal, it appears in the form of globules of various sizes. We are ignorant of the mechanism by which this extremely fine division and conversion of the fat emulsion into the molecular basis of chyle takes place, but it seems reasonable to suppose that it occurs at the moment of passing into the lacteal, *i.e.* that the fat globules are altered and broken up in penetrating through the very fine pores that exist or are formed between the junctions of the epithelioid cells.

Hofmeister's notion that the leucocytes which accumulate in the villi during absorption convey the fat into the lacteal must, as already stated, be abandoned. Two facts in particular tell against it. After administration of magnesium sulphate, which produces a cathartic effect, *i.e.* opposed to absorption, an extraordinary number of leucocytes accumulate in the villi, although there is not and cannot be any fat absorption. On the other hand, they are entirely absent from the villi of a sucking puppy, although there is a marked passage of fat into the chyle (Foster).

It is evident that great importance in the penetration of fat into the lacteals attaches both to the passive compression of the villi due to the peristaltic movements of the intestine (Hamburger), and to the active movements of the villi induced by the (probably rhythmic) contraction of the muscle cells, with which the areolar tissue of the villi is well provided. According to Brücke, the muscles of the villi act during contraction like a pressure pump, which empties the contents of the lymph spaces of the stroma into the central lacteal, and the latter into the subjacent lymphatics, which are provided with valves. The valves hinder a reflux during the subsequent relaxation or expansion of the muscles, and thus indirectly allow the lymph sinuses to refill with new material absorbed and secreted by the columnar epithelial cells. Since the muscle bundles have a direction predominatingly parallel to the long axis of the villi, Brücke supposes that during contraction the villi shorten and empty by positive pressure, while during relaxation they lengthen and expand by negative pressure. But it is possible to conceive the mechanism differently. According to Heidenhain the villi shorten and thicken during contraction, so that the central lacteal dilates. During relaxation the villi lengthen and become thinner, in consequence of which the central lacteal is constricted by compression, and evacuated. However we conceive of the phenomenon, it is certain that a rhythmical contraction and expansion of the villi must favour (if it does not absolutely initiate) the movement of the regenerated products

absorbed from the intestine, both into the lacteals and the blood-vessels.

As regards the penetration of sugar and protein, we cannot tell why these substances should under ordinary conditions be absorbed, if not exclusively at least to a predominating extent, by the blood capillaries of the villus. The mechanism of this penetration also is unknown to us by direct experiment. It is probably a process of *transudation* identical with that which gives rise to the formation of lymph (see Vol. I. p. 523 *et seq.*). The difference is that while in the formation of lymph, transudation takes place from the interior of the capillaries into the lymph sinuses, in the absorption of chyle it occurs from the lymph sinuses to the interior of the blood capillaries of the villi. We have seen that transudation consists of two well-known physical processes, *diffusion* and *filtration*. The greater concentration of the food-stuffs of the chyle collected in the meshes of the reticuli of the villi, as compared with that of the constituents of the blood that incessantly courses through the capillary network, certainly presents a condition favourable to endosmosis. On the other hand, the pressure due to the contraction of the muscles of the villi must favour filtration through the blood capillaries from without inwards.

VIII. We have seen that while the products of the proteolytic and lipolytic processes are regenerated during absorption into natural proteins and neutral fats by the synthetic activity of the columnar epithelium of the intestine, the digestive products of the carbohydrates which pass through the intestinal wall penetrate almost entirely by the blood vessels of the villi to the portal system, and are, almost without exception, carried to the liver in the form of *grape sugar* or *glucose*. According to Pflüger, part of the glucose that penetrates into the blood may, instead of remaining there in the free state, enter into chemical combination with the proteins, or the lecithin with which it forms *jecorin*. We have seen elsewhere (Vol. I. p. 130) that the amount of glucose normally present in blood plasma varies, according to Otto, from 0·10-0·15 per cent, and only exceptionally rises to 0·30 per cent, or a little over. This proportion of glucose in the blood is wholly independent of the nature of the food. Two facts may, however, now be considered well established, from the results of numerous analyses of the blood, arrived at by different observers :—

(*a*) After a meal rich in starchy and saccharine substances, the sugar content of the portal blood reaches its maximum, while in the blood of the hepatic veins it remains normal.

(*b*) During fasting, the sugar content of the blood in the hepatic veins is somewhat higher than that of the portal blood, which is minimal.

The first fact leads us to admit that the sugar absorbed from

the intestine after digestion is stored up in the liver: the second that the liver returns the accumulated sugar to the blood by internal secretion.

Thus we are brought back to *the Liver*, that giant gland which we considered in the last chapter merely as the organ of bile secretion, while admitting this to be neither the principal nor the most important of its functions.

Magendie (1816) was the first who demonstrated experimentally that the system of intestinal veins which form the roots of the portal system, and to which Bichat drew the attention of physiologists, is capable of absorbing the substances introduced into the intestine—a fact denied by John Hunter. One of Magendie's crucial experiments was as follows:—

He tied all the lymphatics of a loop of intestine isolated between two ligatures; next, he tied all the arteries and veins with the exception of one artery and vein, of which he removed the adventitia for a certain distance to make sure that no lymph vessel had been left; lastly, he injected a decoction of nux vomica into the loop. After 6 minutes, strychnine poisoning set in with great intensity, showing that absorption had taken place through the roots of the only intestinal vein remaining. The later experiments of Ségalas and of Tiedemann and Gmelin, confirmed Magendie's results, and established the importance of the intestinal veins in intestinal absorption.

But it was Claude Bernard who fully vindicated the claims of the liver, which Bartholin had disallowed. In 1849 he announced that animals, like plants, have the power of forming sugar independent of the nature of the food, and that this new function resides in the liver, which is therefore the seat of a double secretion; the one *external*, of bile; the other *internal*, of sugar.

In studying the course of the ingested sugar, as it passes through the body, Bernard sought for it in the venous blood coming from the right heart and the arterial blood coming from the left carotid, on the assumption that it was decomposed by the lungs. He observed that the blood of the right heart contained sugar, not only when it was extracted from a dog fed on sugar, but also when the animal was kept on a flesh diet. From this he concluded that there must be an organ in the body capable of forming sugar, independent of what was ingested, and that this organ was the liver, because extract of liver was able to reduce Bareswill's reagent and gave rise to alcoholic fermentation, which did not occur with extracts of the other organs.

In order to demonstrate that the liver really manufactures sugar during its life, it was necessary to prove that the blood flowing from the liver contained more sugar than the blood which entered it. In 1850 Schiff, who found a certain amount of sugar in human blood, and in that of animals from the slaughter-house,

argued that this substance must be generally diffused in the body like urea, and that its production could not be localised in a single organ.

In continuation of these researches Bernard (1850) demonstrated the presence of sugar in the liver of mammals, birds, reptiles, fishes, and molluscs. He further proved that the blood of the hepatic veins invariably contained sugar during digestion; that it contained less when digestion was completed; hardly any after a long fast. After prolonged feeding of dogs with flesh, he estimated the sugar content of the intestine and the portal blood, and found none perceptible to reagents; on the other hand, there was a considerable amount in the blood of the hepatic veins and the liver.

In order, however, to establish Bernard's theory of *hepatic glycogenesis* (to which objections were raised by Figuier, Sanson and Colin) upon a solid basis, it was necessary to exclude the possibility that the sugar had been carried by the portal blood, the liver merely having the task of storing it up and accumulating it, as it does with other substances (arsenic, antimony, mercury, etc.). The fundamental experiment which Bernard devised in 1855 for this purpose, consisted in extracting the liver from the abdominal cavity and irrigating it by the portal vein with a continuous current of water. After 40 minutes' irrigation, he excised a bit of the liver, boiled it, and found no sugar in the extract. After 24 hours the remainder of the liver was extracted, and was found to contain much sugar. From this Bernard concluded that the liver contains a material from which sugar is formed. He further concluded that contact with the air is favourable to the formation of new sugar, while it is on the other hand checked by boiling. Since sugar can be formed in the liver of animals fed exclusively on a flesh diet, Bernard concluded that it is manufactured in the liver at the expense of the nitrogenous protein, by a process of fermentation.

Soon after, however, and almost simultaneously, Hensen (December 1856) and Bernard (March and June 1857) extracted from the liver *glycogen* or *animal starch*, a substance similar to vegetable starch or rather to dextrin, which is readily converted into sugar by the influence of the salivary or pancreatic enzyme, as the starch of barley is converted into sugar during germination by the action of diastase. To separate glycogen, the liver of a well-fed animal must be excised, chopped up, and steeped in boiling water. After boiling, the fragments of liver are pounded in a mortar to a paste, which is then extracted, neutralised, filtered, and boiled again to get rid of the proteins, when an opalescent extract is obtained, which is milky in appearance, and remains unchanged by repeated filtration. On adding iodine the extract stains red like erythrodextrin; on heating the colour disappears, to reappear on subsequent cooling. Trommer's test

shows that the solution contains very little sugar. On adding saliva or pancreatic extract, as also on boiling with dilute mineral acids, the opalescence and the iodine reaction disappear, while Trommer's test shows the presence of much sugar.

Brücke obtained glycogen in the pure state by perfecting this method.

Estimation of Glycogen (Pflüger).—The liver of an animal is minced and boiled for 2-3 hours in the water-bath with 30 per cent caustic potash. The solution is then cooled, with the addition of 2 parts water and 4 parts alcohol (96 per cent). The mixture is allowed to settle, filtered in a porcelain filter, washed with a mixture of one volume 15 per cent potash and alcohol at 96°, and then with alcohol alone at 96°. The precipitate is dissolved in boiling water. The filtrate is boiled separately to extract the residue of glycogen. The solution is then neutralised, and refiltered, after which hydrochloric acid is added till the concentration is 2·2 per cent. It is then boiled for 3 hours; when cooled the liquid is neutralised and filtered. The glucose is then estimated: 1 grm. glucose corresponds to 0·927 glycogen.

After the discovery of glycogen, Bernard modified his original view of the direct formation of sugar in the liver. The glycogenesis is *indirect, i.e.* is a function consisting of two quite distinct processes, the first being the formation of the glycogenic substance in the living hepatic tissue (*amylogenesis*), the second the conversion of glycogen into sugar by a ferment, which is probably contained in the blood (*glycogenesis proper*).

To Bernard's statement that the liver normally, *i.e.* during life, manufactures sugar from glycogen, and discharges it by internal secretion into the hepatic veins, Pavy (1861) objected that glycogenesis is not a normal function of the liver, but a post-mortem phenomenon. On drawing off the blood of a living animal from the right heart with a catheter, he found that it contained hardly a trace of sugar, while the same blood, collected after the death of the animal, usually contained a considerable amount. On excising fragments of liver from a live dog, and plunging them directly into boiling water, he found mere traces of sugar in the extracts.

Ritter, MacDonell, Schiff, Lussana (1862-66) repeated Pavy's experiments with variations, but always obtained the same results. The living normal liver either contains no sugar or a small quantity only. They concluded that the liver only forms sugar when the hepatic cells are injured by neuroparalytic hyperaemia, by heterogeneous substances injected into the vessels, post-mortem decomposition, etc. The formation of glycogen is an essentially physiological process; its conversion into glucose is an abnormal or dissimulatory post-mortem phenomenon.

As against this conclusion and in favour of Bernard's theory are the conclusions of Dalton (1871), who found that the living liver contains 0·2-0·4 per cent sugar, a quantity in excess of that usually found in the blood. Recent analyses, moreover, have

demonstrated indisputably that there is a marked difference between the sugar content of the blood from the portal and that from the hepatic veins, without even temporary arrest of the circulation through the liver. While the portal blood on an average contains 0·1 per cent sugar, that of the hepatic vein contains on an average 0·2 per cent. This fact seems to us to decide the controversy in favour of sugar production in the normal living liver.

When we consider the large amount of blood that passes through the liver every day and hour, we see that the marked difference in the sugar content of the blood flowing to and from the liver, while apparently small, must really indicate the production of a very considerable amount of sugar. Seegen estimates that in a dog of 40 kilos. weight, 400 litres of blood pass through the liver in 24 hours, from which we must assume a production of 400 grms. sugar, supposing the blood flowing from the liver to contain 0·1 per cent more sugar than the blood flowing to that organ.

Seegen, however, raised another objection to Bernard's theory. In 1876 he (and soon afterwards Nasse) determined the nature of the sugar produced from glycogen by the liver, and that formed artificially by the action of amylolytic enzymes, and found that the liver manufactures *glucose* or *dextrose*, while artificial digestions of glycogen with saliva, pancreatic extract, or succus entericus yield *maltose*. This fact caused Seegen to question whether Bernard was right in assuming the intervention of a specific enzyme in the phenomenon of glycogenesis, and whether the glucose formed by the liver might not be derived from some substance other than glycogen.

He accordingly undertook a series of experiments to estimate the glycogen and glucose of the liver at different intervals after death, to see whether as the former disappeared the latter is manufactured in a corresponding ratio. In collaboration with Kratschmer (1880) he obtained results unfavourable to Bernard's hypothesis, since the quantity of sugar augments rapidly, directly after death, while the glycogen does not perceptibly diminish, whence he concluded that the sugar is not formed at the expense of the glycogen.

Seegen supposed that the peptones and fats are capable of forming the sugar of the liver, and asserted in support of his views that fragments of liver excised from the living animal produce a larger amount of sugar when kept for 5-6 hours at a temperature of 38° in a solution of peptones, or defibrinated blood, or are plunged into an emulsion of fat and gum, while a current of air is passed through the mixture.

Seegen's results were contradicted by Delprat (1881), Chittenden and Lambert (1885), Girard (1887), Neumeister (1890), Noël

Paton (1894-95), who brought forward other experimental data agreeing with the theory that hepatic sugar is exclusively derived from glycogen. The simplest and most direct proof of this theory is given by Montuori (1895). He excised the liver of a newly killed animal; threw part into boiling water to arrest the production of sugar, and kept another part for some time (24 hours) at ordinary temperature, to allow the sugar to form freely. The weight of the first and second parts of the liver was known. Both parts were then boiled separately in a 1 per cent solution of hydrochloric acid, so as to convert the whole of the contained glycogen into sugar. On careful estimation of the amount of sugar formed, he repeatedly found them to be approximately equal in both parts of the liver. This shows that under these conditions the glucose of the liver is formed exclusively from the glycogen; since if it were also formed from the proteins and fats, more sugar would be produced in the portion of liver left to itself for 24 hours.

Montuori's results were confirmed by E. Cavazzani in Zuntz's laboratory. He also found that the quantity of sugar that can be collected from the excised liver did not increase on the addition of peptones or glycerol (after Seegen's method). Weiss (1898), on the other hand, with Bunge, confirmed Seegen's results on repeating the experiments with an emulsion of gum and fat. This induced Montuori (1899) to undertake new experiments to ascertain whether fat added to the excised liver in a suitable form would be partially converted into sugar. His results were entirely negative. Hesse, Abderhalden, and Rona (1904), under identical conditions with Weiss and Seegen, did not obtain the positive results of these authors, but confirmed the negative conclusions of Cavazzani and Montuori. It may therefore be concluded that there is at present no evidence that the liver when excised from the body is able to form sugar from any material other than glycogen.

IX. The fact that on steeping freshly excised liver from a living animal in boiling water, the conversion of glycogen into sugar is arrested, made Bernard refer this conversion to the work of an enzyme, a kind of *hepatic diastase*. But his attempts to isolate this enzyme, which were repeated by Hensen, led to no conclusive results.

In 1873 Wittich succeeded in extracting a highly active ferment from the liver (when completely bloodless, washed and pounded) by means of alcohol.

Pavy (1894), by a method of extraction analogous to Wittich's, confirmed his results, and isolated from the liver a specific enzyme which determined the conversion of glycogen into glucose *in vitro* with various intermediary products (dextrin, isomaltose, and maltose).

These results were subsequently confirmed by Musculus, v. Mering, Külz, Pregl, and others.

Theoretically the amylolytic enzyme of the liver may be derived from a special *zymogen* contained in the protoplasm of the hepatic cell, which is destroyed along with the enzyme when a freshly excised liver is thrown into boiling water.

Noël Paton (1893) observed that chloroform or sodium fluoride retarded the first phase of sugar-formation in the excised liver, during the period in which it is most active owing to survival of the hepatic cells. Since Pavy and Salkowski showed that chloroform does not modify the activity of the amylolytic enzyme extracted from the liver, it appears to us that the delay in glycogenesis observed by Paton must be due to alteration of the protoplasm of the hepatic cells. This would retard the formation of the zymogen on which the development of diastase in the excised liver depends.

In a recent series of experiments E. Cavazzani brings forward the following facts:—

(*a*) Formation of glucose in the liver is increased by stimulation of the caeliac plexus, but the amount and activity of the haemodiastase in the blood circulating through the liver is not increased. Equal quantities of hepatic blood collected before and after stimulation of the caeliac plexus convert an equal quantity of starch into sugar in the time unit and under the same experimental conditions.

(*b*) In a mixture of blood and glycogen solution the conversion of the glycogen into sugar by the haemodiastase is very slow, whereas post-mortem glycogenesis is a very rapid process.

(*c*) Methyl violet, which does not affect the saccharifying action of haemodiastase, when injected into the circulation, becomes mainly fixed in the liver, and in suitable doses checks the hyperglycaemia of asphyxia, and greatly reduces post-mortem glycogenesis. Methyl violet (as was previously known, and confirmed by Cavazzani) exerts a markedly paralysing action on protoplasm.

(*d*) Sulphate of quinine, again, which is indifferent to enzymes and toxic for protoplasm, acts like methyl violet on the formation of sugar in the liver.

Cavazzani's observations do not, however, prove that hepatic glycogenesis is not due to an amylolytic enzyme formed by the liver. At most they support the thesis that the diastase of the blood does not depend on that of the liver, and that methyl violet and salts of quinine reduce post-mortem glycogenesis because, by paralysing the protoplasm of the hepatic cells, they obstruct the formation of the zymogen, and its conversion into the diastatic enzyme.

Cl. Bernard regards hepatic glycogenesis as a process of

internal secretion. He founded this doctrine solely on the fact that the formation of sugar in the liver is controlled by the nervous system. In 1858 he saw that on puncturing the floor of the rhomboidal sinus near the apex of the calamus scriptorius, such a marked increase of sugar occurs in the blood (*hyperglycaemia*) that it is eliminated after about an hour, by the kidneys (*glycosuria*). He also found that reflex excitation of the bulbar centre suffices to produce the same phenomenon. In fact, stimulation of the central end of the vagus divided between the lung and the head will produce glycosuria. The proof that glycosuria is determined by hyperglycaemia from excessive sugar formation in the liver lies in the fact that diabetic puncture does not produce glycosuria in animals in which the glycogen of the liver has disappeared (by fasting, various intoxications, etc.).

But the importance at first attributed to the diabetic puncture as discovered by Cl. Bernard gradually diminished, as new data came to light. These showed that injury, destruction, or irritation of other parts of the central and peripheral nervous system could produce a more or less transitory glycosuria. Eckhard found that in rabbits lesion of the vermis of the cerebellum induced glycosuria. Schiff recognised the same phenomenon with lesions of various parts of the brain (division of optic thalami, lesions of cerebral or cerebellar peduncles, or of the pons Varolii, complete section of the posterior columns of the cervico-dorsal tract of the cord). Pavy saw that glycosuria appeared after section of the bulb and the protracted use of artificial respiration. Lustig and Oddi obtained glycosuria after excision of the caeliac plexus. In our own numerous experiments on the extirpation of more or less extensive and variously localised tracts of the brain or cerebellum, and the total or partial section of the cord at different levels, we have invariably, when the urine was examined, found sugar in the first days after the operation. The same thing occurs (according to Eckhard, Külz, Schiff, and others) with the stimulation or simple section of many nerves (particularly the vagi, splanchnics, sciatics). There is thus no circumscribed *diabetogenic centre*; but it may be said that the abnormal excitation of any important part of the central and peripheral nervous system may directly or indirectly provoke glycosuria.

Both Bernard and Schiff referred the phenomenon of glycosuria consequent on nerve lesions, or the direct or reflex excitation of parts of the nervous system, to the vasomotor disturbances, and resulting active or passive hyperaemia of the liver. This increases the development of hepatic diastase, and therewith the saccharification of the glycogen contained in the hepatic cells. It is also an admissible hypothesis that the liver contains, besides the vasomotor nerves, others which directly influence the metabolic activity of the hepatic cells (and thus regulate the formation of

hepatic diastase), and that the direct or indirect excitation of these produces the exaggerated glycogenesis and consequent glycosuria observed as the effect of various nerve lesions.

In support of this hypothesis A. and E. Cavazzani brought forward experimental results which appear to us of considerable value. In 1892 they found that stimulation of the caeliac plexus with an induced current, lasting for a few minutes, augments the sugar content of the blood flowing from the liver. In 1894 it occurred to them to use this means of increasing hepatic glycogenesis, both in living and in recently killed animals, not merely to confirm the fact that increase of sugar in the liver coincides with a diminution of glycogen, but also to see if the phenomenon changes in correspondence with the activity or arrest of the circulation in the liver. They extirpated a hepatic lobe from live and from recently killed dogs, and then stimulated the caeliac plexus for about 15 minutes. A second lobe was then excised, after which they estimated the glucose and glycogen in both lobes, after weighing and boiling them. The results of their experiments are briefly as follows:—In living animals stimulation of the caeliac plexus produces a marked increase of glucose in the liver and a comparatively greater diminution of glycogen, because part of the sugar is carried away as fast as it is formed by the blood current. In freshly killed animals in which the circulation is at a standstill, the same stimulation still produces increased glycogenesis, and the correspondence between the glucose formed and the glycogen that disappears is absolute or nearly so. From this we may conclude: (*a*) that stimulation of the nerve fibres which run from the caeliac plexus to the liver increases the hepatic glycogenesis; (*b*) that the sugar formed comes from conversion of the glycogen; (*c*) that this conversion is up to a certain point independent of the external circulatory conditions, so that it is improbable that the influence of the nervous system on hepatic glycogenesis consists in a simple vasomotor action leading to increased irrigation of the liver with blood.

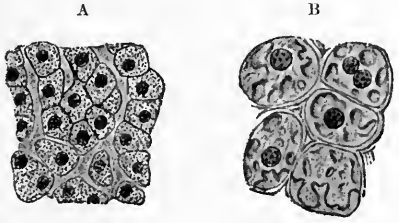

Fig. 97.—Hepatic cells of dog after fasting 36 hours (A); and 14 hours after an abundant meal (B). (Heidenhain.) In A the cells are small and finely granular; at B they are much magnified by the accumulation of glycogen, a hyaline substance that obscures the granulations of the cytoplasm.

E. Cavazzani further demonstrated that the glycogenesis promoted by excitation of the caeliac plexus is accompanied by cytological changes in the hepatic cells, similar to those which Afanasiew and others detected in the liver of fed and fasting animals (Fig. 97).

Lastly, he made important observations on the exothermal phenomena in the liver under all experimental conditions in which an increase of hepatic glycogenesis takes place:—(*a*) In asphyxia, according to Morat and Dufour, so soon as there is hyperglycaemia, the temperature of the liver rises. (*b*) The same is found during stimulation of the vagi when, according to Butte, hepatic glycogenesis is exaggerated. (*c*) When, after cardiac paralysis and suspension of circulation, the formation of sugar becomes more active, while all other organs are cooling more or less rapidly, the liver exhibits a post-mortem rise of temperature, lasting 10-20 minutes, of half a degree or even more. (*d*) In fasting or very emaciated animals the asphyxial and post-mortem rise is almost or entirely absent, since, as we have seen, glycogenesis is limited by scarcity of glycogen. The opposite occurs with well-nourished animals. (*e*) In animals into which curari or atropine, or methyl violet in suitable doses, is injected intravenously, neither asphyxial hyperthermia nor hyperglycaemia is perceptible. With injection of methyl violet, post-mortem glycogenesis is also suspended, in correspondence with which fact the temperature of the liver falls rapidly like that of the other organs.

From these facts, as a whole, it is evident that the hepatic glycogenesis by which glucose is formed from the glycogen and poured into the blood, is accompanied by phenomena highly similar to those observed during the secretion of other glandular organs.

X. It now remains to see from what constituents the glycogen which serves for the secretion of glucose originates, and whether other tissues besides the liver are capable of forming or storing up glycogen as a reserve material.

In the first place, it must be observed that the amount of glycogen accumulated in the liver varies considerably with different animals, and also in the same animal under different conditions of nutrition and diet. Pavy, in dogs which had been fed for a long time on bread and potato, found 15 per cent glycogen in the liver. In rabbits fed on starchy foods and beetroot it amounted to a maximum of 27 per cent. Supposing the human liver to be capable of accumulating 10 per cent of glycogen, and the weight of the liver to be 1500 grms., we should have 150 grms. glycogen stored up in this organ.

That the glycogen content of the liver depends essentially on diet has been convincingly proved by the fact that during an absolute fast the glycogen wholly or almost entirely disappears from the liver, in rabbits after 5 days, in dogs after 2-3 weeks. According to Pflüger, the glycogen never disappears completely, even in rabbits; in dogs a certain amount remains even after a fast protracted for weeks.

When an animal that has been almost entirely deprived of its

hepatic glycogen by fasting is fed on a diet rich in carbohydrates, the glycogen of the liver is rapidly formed again, and may be present in a considerable quantity a few hours after the meal.

It is certain that the chief part of the hepatic glycogen is derived from the alimentary carbohydrates. Voit saw that the readily fermentable monosaccharides, both dextrose and laevulose, are converted into glycogen in the liver, either when introduced into the intestine of a rabbit that has fasted for 4 days (and is thus almost destitute of glycogen), or when injected directly but slowly into the circulation. The disaccharides, saccharose and maltose, which ferment less readily, only form glycogen when they are introduced into the intestine, where they are converted into monosaccharides previous to absorption.

The sugar absorbed from the intestine, carried to the liver, and there converted into glycogen by a process of dehydration and cleavage, prevents hyperglycaemia, or the abnormal increase of blood-sugar which produces glycosuria, *i.e.* its useless elimination by the kidneys. Pavy noted (1867-69) that slow injection of sugar by one of the veins leading to the portal does not produce glycosuria; while sugar injected with the same precautions and in the same dose into the jugular vein is partially excreted with the urine. This fact, subsequently confirmed by others, shows that sugar when it goes direct to the liver becomes fixed there in the form of glycogen as a reserve material. Luchsinger (1875) gave direct evidence of this, when he succeeded in increasing the amount of glycogen in a liver recently excised from the body, by irrigating it artificially with blood containing 2 per cent glucose.

When the amount of sugar introduced with the food is excessive, the liver is no longer able to fix and store it all up in the form of glycogen, so that a certain quantity passes through, and is eliminated by the kidneys (*alimentary glycosuria*). According to Hofmeister, the limit of assimilation of glucose oscillates in the dog between 0·5 and 2 grms. for each kilo. body-weight; the limit for saccharose is higher, for lactose lower. For man, according to von Noorden, the limit of assimilation for cane sugar is on an average 200-250 grammes. Unlike sugars, starchy substances never, under normal conditions, produce alimentary glycosuria, either in man or animals, probably because they undergo comparatively slow digestion in the intestine, so that absorption of the sugar formed, and its passage into the blood, are delayed and take place very gradually.

Not the whole of the sugar absorbed by the intestine after a diet rich in carbohydrates can be fixed and stored up in the liver. This is evident if we consider the comparatively scanty quantity of glycogen contained in the liver, and reflect that previous to each meal the liver already contains a good store of glycogen, which does not entirely disappear even after several days of fasting.

It is therefore necessary to admit that other organs besides the liver are capable of fixing the sugar in the form of glycogen, since we know that an excess of absorbed sugar cannot circulate in the blood without being eliminated by the kidneys. We know in fact that almost every animal organ contains small quantities of glycogen; particularly so *the muscles*, as first shown by Bernard for the muscles of the foetus (1859), and later by Nasse (1869) for the muscles of the adult. The percentage glycogen content of adult muscle is much lower than that of the liver, and seems to vary considerably not only in different animals, but also in different muscles of the same animal. According to E. Voit the glycogen content of the whole of the muscles is slightly in excess of that stored up in the liver. In muscular work, by analogy with what occurs in fasting, the glycogen is consumed until it entirely disappears, not merely from the liver but from the muscles also. According to Külz and Aldehoff the glycogen of the liver disappears more rapidly than that of the muscles, as if the liver supplied it to the muscles in proportion as they use it up. In muscles paralysed by section of the nerves that supply them, increase of glycogen has been found accumulated in consequence of the muscular immobility. In experimental strychnine tetanus, on the other hand, the glycogen can be made to disappear from the muscles and also from the liver. When the muscles enter into *rigor mortis* the glycogen is converted into glucose and lactic acid.

All *embryonic tissues*, as Bernard already recognised, contain a considerable amount of glycogen (particularly the muscles and the placenta), so long as the liver is little developed, and contains only traces of glycogen. Later on the muscles gradually lose their glycogen, while the liver accumulates more and more of it.

It is not certain that the glycogen of the muscles is identical with that of the liver. Hepatic glycogen is certainly conveyed to the muscles in the form of glucose, since Külz demonstrated that the muscles also are capable of fixing the sugar and converting it into glycogen. In fact, the glycogen content of the muscles can be increased in a frog deprived of its liver, by subcutaneous injection of sugar. On the other hand, the presence of glycogen in the blood plasma has not been demonstrated, and where traces are found, these are due to the disintegrated leucocytes which, like all other tissue-cells, contain glycogen (Frerichs).

The glycogen of the liver, as also of the muscles, is rapidly consumed when the animal is made to develop much heat to keep its temperature constant. If a rabbit be cooled in a cold bath, or kept in an atmosphere below zero, all the glycogen accumulated in the liver disappears (Külz). The same occurs with white rats (Zätsch). Cold-blooded animals exhibit the opposite phenomenon. If the temperature is raised, their glycogen disappears, owing to accelerated metabolism. When a hibernating frog, whose cells

are surcharged with glycogen, is brought into an atmosphere of 20° C. or more, the glycogen entirely disappears after a certain time (Foster).

From all these facts we see that (*a*) glycogen arises principally from the carbohydrates of the food; (*b*) it is formed (by a synthetic regeneration and dehydration) from the sugar absorbed by the intestine, not merely from the liver, but also from the muscles and other tissues; (*c*) it functions as a reserve material, in analogy with vegetable starch, which plant tissues use as a source of energy.

XI. Although the larger part of the glycogen stored in the tissues of the body comes from the carbohydrates of the food (owing to a synthetic chemical process due to the anabolic activity of living cells in general, but particularly those of the liver and of striated and plain muscle), it is certain that part at least of the glycogen and glucose normally found in the body are formed by an analytic chemical process from the *proteins*, and also by *decomposition of the fats*—a process effected by the katabolic activity of the tissues.

Cl. Bernard always insisted that part of the hepatic glycogen came from the alimentary proteins, in view of the constant presence of glycogen in the liver of dogs fed for a long time on an exclusively flesh diet. This argument does not, however, settle the question, since the muscles (as we have seen) always contain a certain amount of glycogen or the sugar formed from it. But protracted experiments with a diet of pure proteins,—albumin, fibrin, caseinogen,—according to v. Mering, Külz and others, do cause the reappearance of glycogen, although in small quantities, in animals deprived of it by fasting.

The experimental evidence which Seegen and Weiss brought forward in support of this theory (p. 303) was contradicted by other workers (Montuori, E. Cavazzani, Hesse, Abderhalden).

Pflüger is among those who deny that glycogen is partly formed from alimentary protein. In his classical monograph *Glycogen* (1905) he reviews all his experiments on various animals kept fasting for a longer or shorter time, and then fed up again either with meat, or with special proteins destitute of glycogen and glucoprotein.

He demonstrates that the percentage of glycogen found in the animals experimented on, came within the limits of that in the fasting control-animals, *plus* that amount of glycogen due to the carbohydrate present in the flesh diet. So that if, after feeding-up again, glycogen appears in excess of that in the fasting control, this does not, according to Pflüger, prove it to be formed from the alimentary protein. The latter may stimulate the production of glycogen by utilising the fat, without actually participating in such production. According to Pflüger, this

theory is substantiated by the fact that on feeding urea mixed with alimentary protein, the formation of glycogen increases, although the urea is eliminated again, and cannot play any part in the formation of the glycogen. His argument does not, however, carry conviction, because he gives no direct proof of his thesis.

Other undeniable facts can be mustered in support of Seegen's position. Voit noticed that even after 80 days' torpor the liver of the marmot contains a large amount of glycogen, which can, he says, only be explained on the assumption that the liver during hibernation goes on forming glycogen at the expense of the proteins which the animal has at its disposal. Külz, however, denies this interpretation, and maintains that the glycogen found by Voit is the residue of that formed in previous feeding, the consumption of which is arrested during hibernation. He killed four marmots at different intervals after the commencement of torpor, and found approximately the same amount of glycogen in the liver. In our opinion this fact does not, however, preclude the possibility that glycogen is slowly formed during hibernation, in quantities approximately equal to what is simultaneously consumed. The argument of Külz may be met by another apparently enigmatical fact, which Aducco noticed in 1889 on pigeons that were kept in the dark and starved. The glycogen regularly disappeared from the liver in the first days of fasting, but reappeared in the succeeding days in considerable amount. There seems but one rational interpretation of this phenomenon. In the first days of inanition, when tissue metabolism is still fairly active, the amount of glycogen consumed much exceeds that simultaneously formed, so that the reserve of this material is entirely exhausted. In the subsequent days of starvation, on the other hand, when general metabolism is greatly retarded, the quantity of glycogen formed is greater than that simultaneously consumed, so that a new store accumulates in the liver.

By an identical process the hepatic cells of the frog accumulate a large amount of glycogen during the winter, while in summer, when metabolism is very active, they contain hardly any, since it is consumed as fast as it is formed (Langley). As the intensity of general metabolism in the frog (and in cold-blooded animals generally) depends on the external temperature, it is easy to reduce or entirely abolish the glycogen accumulated in the liver of a hibernating frog, by exposing it for some time to a temperature of 20-22° C. Conversely, it is possible to obtain a certain amount of glycogen from the liver of a summer frog after exposing it for several days (Fig. 98) to a very low temperature.

It is evident that the accumulation of glycogen in the hepatic cells during natural or artificial torpor does not depend on

alimentation, since the hibernating frog entirely abstains from food. Under these conditions, therefore, the glycogen cannot be formed at the expense of the carbohydrates; in all probability it is formed by cleavage of the protein molecule, on which the carbohydrate groups are liberated from the nitrogenous groups.

It is, further, not impossible that under these or similar conditions, in which glycogen and sugar are formed independent of the alimentary carbohydrates, part at least of these products may arise from cleavage of the fat molecule with absorption of oxygen. According to Bunge, this hypothesis is supported by the fact that the blood of animals in protracted inanition (when the glycogen store is exhausted) always contains a small and almost

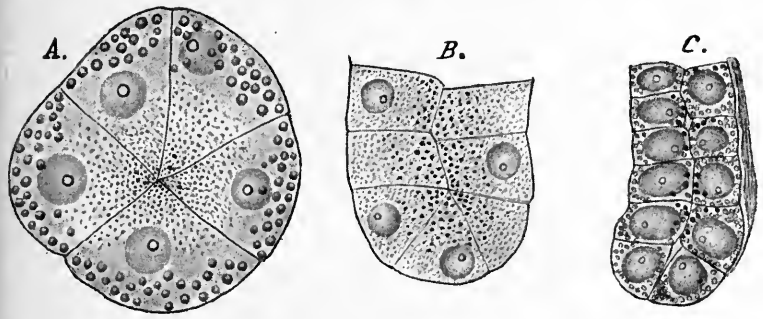

FIG. 98.—Hepatic cells of frog, fixed with 1 per cent osmic acid in three different phases. *A*, during hibernation; *B*, after keeping the frog in winter for 10 days at a temperature of 22° C.; *C*, after keeping it a long time in summer without food. (Langley.) In *A* the cells are very large, with much homogeneous substance which consists of glycogen, diffused throughout the cytoplasm. The protein granules are collected in the inner zone, particularly round the bile canaliculi; the outer hyaline zone, on the contrary, contains a number of fat-globules. In *B* the cells are smaller and contain little glycogen, while the protein granules are diffused throughout the cytoplasm. The hepatic cells of a well-nourished summer frog present a similar aspect. In *C* the cells are much smaller, the cytoplasm is reduced to a minimum, and is almost free of glycogen, with protein granules diffusely distributed; the nuclei, on the other hand, are larger.

constant quantity of sugar, and that under these conditions the consumption of nitrogenous substances is minimal, while the fat reserves are being rapidly exhausted.

In support of the possible derivation of sugar from *fat*, Bunge brings forward the argument that this origin has long been familiar in plant physiology. In 1859 Sachs demonstrated that the fat disappears from oily seeds set in the dark to germinate, in proportion as starch, gum, sugar, and cellulose were formed. Wiesner further demonstrated that absorption of oxygen accompanies and is a necessary condition of this conversion of fat into carbohydrates.

Chauveau adduced the following evidence to the same effect:—(*a*) injection of glycerol into the intestine causes increase of hepatic glycogen, as demonstrated by van Deen. (*b*) During the metamorphosis of the chrysalis of *Bombyx mori*, fat diminishes

while glycogen increases. (*c*) During hibernation the fat of marmots disappears gradually, while the glycogen, as we have seen, remains almost constant.

The possibility of the formation of sugar from glycerol was chemically demonstrated by Emil Fischer. Cremer and A. Lüthje further observed that when glycerol was administered to depancreatised dogs, glycosuria increased approximately in proportion to the dose. They concluded that a similar conversion took place within the body.

Other cogent arguments in favour of the theory which derives a part of the sugar normally formed in the body from the decomposition of proteins or of fat can be adduced from the well-known disease of *diabetes mellitus*, the chief symptom of which is the constant presence of a large amount of sugar in the urine, identical with that formed in the liver from the glycogen (*glucose* or *dextrose*). In its milder forms, the diabetes ceases with the absolute exclusion of carbohydrate from the diet; in the graver forms, the sugar is decreased, but does not entirely disappear from the urine, even with an exclusively flesh diet. Innumerable investigations have been devoted to the study of this disease, and if all that has been published on the subject were collected it would, as Bunge remarked, furnish a library.

Our task is to define the fundamental points of this complicated problem. Does diabetes depend on an alteration of the kidneys, by which the epithelia of the urinary canal allow the glucose constantly present in the blood to filter through more readily? No; for diabetes is constantly associated with *hyperglycaemia, i.e.* increase of sugar in the blood, rising from 0·05-0·15 per cent to 0·22-0·44 per cent. Does it depend on increased hepatic glycogenesis? No; because the liver of persons who have died of diabetes show in not a few cases a definite, sometimes a considerable, amount of glycogen in the liver (Külz, v. Mering), although as a rule it contains but little, as shown by Fig. 99, which gives the iodine reaction of the liver cells of a normal person and of one who has died of diabetes. Glycogen has, moreover, been found in the hepatic cells extracted during life in severe diabetes, by puncture of the liver with a trocar (Frerichs). On the other hand, it is interesting to note in diffuse diseases of the liver (hepatic cirrhosis, acute fatty degeneration, phosphorus poisoning) that there is no sugar in the urine, since both glycogen and sugar have entirely disappeared from the liver. In 17 cases of phosphorus poisoning Frerichs found no trace of sugar in the urine; after administration of 100-200 grms. glucose he only saw it appear in minute amounts in two cases. It is thus impossible to account for diabetes on the assumption that the hepatic cells have become less able to store up sugar.

All the evidence makes it probable that the hyperglycaemia

and glycosuria which represent the main symptoms of diabetes depend on *a lowered glycolysis, i.e.* on the fact that the diabetic organism does not possess the normal capacity for splitting up the sugar as it is formed. This capacity is not entirely lost, but it is much diminished. Külz, indeed, noted that in severe cases of diabetes the amount of sugar in the urine is always lower than the total of carbohydrates ingested, and absorbed from the intestine in the form of sugar.

Another very important observation of Külz is that diabetics are capable of breaking up *laevulose* or fruit sugar, which turns

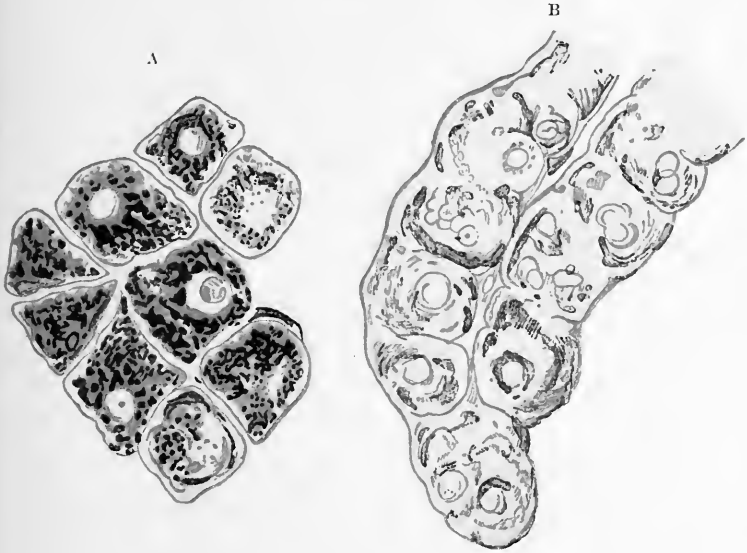

FIG. 99.—Hepatic cells of man under normal conditions (A), and in a diabetic subject (B) treated with gum iodide. (Frerichs.) At A the colour is strongly reddish-brown from the glycogen present; at B the colour is pale, from small amount of glycogen.

the plane of polarised light to the left. They can also use *inulin*, which is converted into laevulose as starch is converted into dextrose. Lastly, he observed that *saccharose* (which splits half into laevulose and half into dextrose), when given in severe cases of diabetes, increased the sugar in the urine by about half the amount of sugar (in the form of dextrose) administered as saccharose. The repetition of this experiment by several other observers yielded results which were not always in agreement with those of Külz. This proves that different diabetics behave differently. Generally speaking, however, the ingested laevulose either does not appear or appears only in very small quantities in the urine. Sometimes part of the laevulose is converted into dextrose, and appears as such in the urine. On the strength of

these data we may conclude that diabetics have to a large extent lost the power of utilising dextrose and glucose.

Since the greater part of the sugar formed in the body is consumed by the muscles, which function under the influence of the nervous system, it is natural to conjecture that the pathogenesis of diabetes is to be found in a specific alteration of the nervous system, more or less diffused in the centres.

Bernard's so-called *diabetic puncture*, of which we have already spoken, seemed at first sight to clear up the obscure pathogenesis of *diabetes mellitus*. But the glycosuria due to puncture of the fourth ventricle is quite transitory; it ceases after a few hours, and the liver remains almost free of glycogen. Puncture does not produce glycosuria in an animal deprived of its glycogen by fasting. If glucose be injected into the mesenteric vein of an animal in which the glycogen store in the liver has been exhausted by fasting, but little sugar escapes with the urine, viz. only that which the liver is unable to fix in the form of glycogen. If, on the contrary, the glucose be injected into the mesenteric vein of an animal that has suffered Bernard's puncture, almost the whole of the sugar is eliminated by the kidneys (Naunyn). It is therefore clear that Bernard's so-called *experimental diabetes* is a process fundamentally distinct from the true *diabetes mellitus*, which, as we have seen, does not depend on incapacity of the liver to form or to retain glycogen.

Another form of temporary glycosuria is that which v. Mering obtained in 1886 by means of *phloridzin*. This glucoside (which is extracted from the root-bark of apple and cherry trees) on boiling with acid breaks up into phloretin and dextrose. When introduced into the stomach of dogs in a quantity of 1 grm. per kilo. body-weight, a glycosuria lasting 2-3 days is produced after a few hours. If the animal be killed after glycosuria has ceased, the glycogen accumulated in both the liver and the muscles is found to have entirely disappeared. So far the process seems to be identical with that which ensues on Bernard's puncture: but it differs essentially in that a second dose of phloridzin administered to the animal after the effect of the first has worn off, regularly reproduces the glycosuria. It is evident that the sugar produced and eliminated after this second poisoning cannot originate in dextrose formed by phloridzin decomposition nor from glycogen, which no longer exists, but that it must come from other materials present in the body, possibly from either the proteins or the fats. The action of the liver does not seem to be necessary to the production of phloridzin diabetes. It can in fact be produced in the frog after removal of the liver.

Minkowski maintains the hypothesis of the *renal origin* of phloridzin diabetes, and assumes that the drug breaks up in the kidneys into phloretin and glucose; that the latter is eliminated,

while the phloretin unites once more with the circulating glucose, the new phloridzin being again decomposed in its passage through the renal tubules.

Other intoxications are capable of producing glycosuria or transitory diabetes, *e.g.* poisoning with curare, with a strong dose of morphine, with amyl nitrite, carbon monoxide, and many other poisons. These analogies and the differences between the various processes which give rise to common symptoms of glycosuria have not been sufficiently investigated.

Another form of experimental diabetes presents a more striking analogy with spontaneous diabetes; this was first discovered by De Dominicis in Italy (1889), and simultaneously by v. Mering and Minkowski in Germany. When the pancreas is entirely removed in a dog (as also in other animals of different classes of vertebrates), all collateral lesions being as far as possible avoided, so that the animal is able to survive this grave operation, a severe form of diabetes invariably sets in with all the characteristic symptoms of spontaneous diabetes—abnormal hunger and thirst, polyuria, depression of muscular energy, etc. The elimination of sugar does not usually begin immediately after the operation, but in 4 to 6 hours, or even later, usually on the second day. It rapidly increases in intensity, and reaches its maximum 24 to 48 hours after the operation with about 8 to 10 per cent of sugar in the urine. If food is cut off, the elimination of sugar decreases, but does not absolutely disappear till after 7 days' absolute fast. With abundant food, the sugar eliminated by the kidneys may amount to 10 to 12 per cent, and even more. With an exclusively flesh diet, a dog of 15 kgrms. may excrete 102 grms. sugar per diem. If bread be added to the meat, the absolute quantity of sugar eliminated may be even greater, *e.g.* a dog of 8 kgrms. excreted 70 to 80 grms. daily for a considerable period. As in spontaneous diabetes, considerable quantities of acetone, acetic acid, and oxybutyric acid are given off with the sugar. As in spontaneous diabetes, there is conspicuous hyperglycaemia, *e.g.* in a dog operated on six days previously there was 0·3 per cent, in another, 27 days after operation, 0·46 per cent sugar in the blood. The glycogen almost entirely disappears from the liver and muscles after the operation; but these organs do not lose their power of forming it by synthesis, and also of accumulating it to some extent. In fact new glycogen can be found in both liver and muscles, after feeding with laevulose, which, as in spontaneous diabetes, can be utilised and only partially escapes into the urine, and that after its conversion into dextrose. Dextrose, however, if administered as a food, reappears entirely in the urine. These facts have been generally confirmed by many observers, both in Italy and elsewhere. Glycosuria has rarely been found absent after complete extirpation of the pancreas (Cavazzani and others); sometimes after total

excision intermittent instead of persistent glycosuria has been observed (Padèri); sometimes severe glycosuria occurs even with partial excision (Sandmeyer).

Many and various have been the hypotheses put forward to explain the relation between loss of pancreas and diabetes. Some of these can at once be set aside, on the strength of experimental data.

As we saw in considering the internal function of the pancreas (see pp. 98-102), the genesis of pancreatic diabetes was at first explained by the serious disorder of the intestinal processes that occur after loss of the digestive functions of the pancreatic enzymes. De Dominicis ascribed the pancreatic diabetes to an auto-intoxication due to the absorption of abnormal substances developed in the intestine, after suppression of the various functions of the pancreatic juice. Gaglio, in support of this notion, added that the toxin which causes the diabetes penetrated from the intestine to the blood, by the lymphatics.

This hypothesis was, however, contradicted by the fact that a segment of pancreas isolated from the intestine and from the abdominal cavity (Minkowski, Hédon, U. Lombroso), or excreting outside the body (Minkowski, Burkhardt, U. Lombroso), sufficed to check the development of diabetes. It is thus necessary to admit that the pancreas, besides its office of secreting digestive juice, is the seat of an *internal* function, by which the formation or consumption of glucose is regulated (see pp. 98-102).

Others suppose that a toxic substance capable of producing diabetes is continually formed in the body, and is normally destroyed by the pancreas as fast as it is formed. After removal of the pancreas, diabetes would develop by a kind of auto-intoxication, analogous to that which occurs after thyroidectomy. But this hypothesis has been experimentally proved fallacious. It was demonstrated first by von Mering and Minkowski, and subsequently by Hédon, that intravenous injection of blood from a diabetic dog neither produces glycosuria in a normal animal, nor increases it if present after loss of the pancreas.

A. and E. Cavazzani, who, as we have seen, discovered nerve fibres to the liver in the caeliac plexus, which, on excitation, promote hepatic glycogenesis, suggested that the diabetes consequent on excision of the pancreas is due to the operative act in which these nerves, which regulate the production of glucose in the liver, are injured. In fact, they described lesions both of certain cells in the caeliac plexus and of the hepatic cells in depancreatised animals. They were thus led to assume an analogy between pancreatic diabetes and Bernard's paralytic secretion of saliva, taking both to be the effect of a degenerative irritation of the secretory nerves. Several data, however, tell against this hypothesis. It is possible to excise a large part of the pancreas without inducing true

diabetes, which is only seen when the organ is completely removed. On the other hand (see p. 99), the whole of the solar plexus can be excised without producing permanent diabetes, transitory glycosuria with acetonuria only being manifested.

According to Lépine and his pupils, pancreatic diabetes depends on the absence from the blood of a glycolytic ferment of pancreatic origin, which normally oxidises the circulating sugar (see Vol. I. p. 127). According to O. Cohnheim, again, this ferment of pancreatic origin acts normally not only on the blood, but also on the various tissues of the body. Pflüger contests both these opinions. As against Lépine he points out that researches *in vitro* show too small a decrease in the sugar content of the blood (4 to 6 per cent) in one hour, to explain the combustion of the carbohydrates. This objection does not, however, meet Cohnheim's position. If we take into consideration the combustion not only of the blood-sugar but that of all the sugar contained in the body, the combustion of 6 per cent in one hour would, under normal conditions, account for the total combustion of sugar in the course of the day. Further research is needed to clear up this important question.

Montuori asserted the importance of *the liver* in the genesis of pancreatic diabetes (1895). He found by ingenious experiments that when pancreatic extract was added by various means to excised liver, less sugar was found after some time than in other portions of the same liver not submitted to similar treatment. According to him this depends, not on the *glycolytic* action of a specific enzyme, as assumed by Lépine and Sympson for the pancreas, but on an *inhibitory* action on hepatic glycogenesis by the pancreas, as was also held by Kaufmann. But in addition to certain theoretical objections, which might be made against the view of Montuori, his experimental results are contradicted by numerous experiments of Pariset (1904-5).

Marcuse found a proof of the importance of the liver to pancreatic diabetes, in the fact that while diabetes always appears in the depancreatised frog (as shown by Aldehoff) it does not occur in frogs deprived of both pancreas and liver. Montuori experimented to see if the same result could be obtained in dogs also. Instead of excising the pancreas he tied all its veins, and instead of excising the liver he tied the portal vein and hepatic artery simultaneously; instead of examining the sugar content of the urine after these successive operations, he estimated the sugar content of the carotid blood. Half an hour after ligation of the pancreatic veins he found a marked augmentation of the percentage of sugar in the blood; about an hour after ligation of the portal and the hepatic artery he found a diminution in the sugar of the blood, which sometimes fell below normal. Montuori correctly interpreted these results as showing that when the

hepatic circulation was cut out, the principal source of sugar in the blood was wanting; the sugar was locked up in the liver, and the hyperglycaemia and diabetes consequent on the lost inhibitory action of the pancreas on sugar production were not developed.

To explain the hyperglycaemia consequent on removal of the pancreas, another hypothesis was invoked, to the effect that the sugar formed in the body undergoes, in passing through the pancreas in the blood, a conversion which facilitates its consumption. This theory, however, seems improbable, when we reflect (*a*) that only a small amount of the total mass of the blood traverses the pancreas; (*b*) that a tenth part of the pancreas left *in situ* is sufficient to impede the production of glycosuria; (*c*) that (according to observations of Capparelli) in cases in which fragments of pancreas are left adhering to the mesentery, or free in the abdominal cavity, glycosuria is delayed, and appears only when these fragments are destroyed by necrotic processes; (*d*) that the glycosuria consequent on complete excision of the pancreas (also according to Capparelli) is temporarily suspended when extremely fresh pancreatic juice or pulp from the pancreas of an animal recently killed during digestion, and diluted with physiological saline, is injected into the abdominal cavity; (*e*) that, lastly, the content of glucose does not differ perceptibly (according to Pal's work in Stricker's laboratory) in the blood flowing to and from the pancreas.

All these facts, on the other hand, agree with the hypothesis of an *internal secretion* of the pancreas, a hypothesis admitted to-day by almost all who have occupied themselves with this difficult subject (see pp. 98-102).

The next point is to determine the nature and mode of action of this internal secretion of the pancreas. Does it exert an *inhibitory action on glycogenesis*, as believed by Montuori, or a *glycolytic action*, as many others hold? The data invoked in aid of the first opinion appear to us to be uncertain. On the other hand, facts are not wanting which speak decisively in favour of the second hypothesis. Among the latter must be emphasised the important phenomenon observed by Colasanti and Bonanni (1897) in their investigation of metabolism in two dogs before and after removal of the pancreas. They saw that the carbonic acid excreted by these animals after complete ablation of the pancreas was less by $\frac{1}{3}$-$\frac{2}{3}$ than that excreted normally, *i.e.* before the operation. While under normal conditions dog A eliminated 640 c.c. carbonic acid, and dog B 636 c.c. carbonic acid, per hour and per kilo. body-weight; after depancreatisation, under the same conditions, the first eliminated 494 c.c., the second 230 c.c. The difference is a loss of $\frac{1}{3}$-$\frac{2}{3}$. This result, which agrees with the observations of Schmidt, Livierato, Boecker and Bartels, on diabetics, can only be due to a diminished

consumption of the sugar which forms the principal source of carbonic acid production. The glycolytic processes are thus considerably reduced in intensity in pancreatic diabetes.

Pflüger, in his important monograph on *Glycogen* (1902-3), maintained the exact opposite, and held that the hyperglycaemia and glycosuria consequent on ablation of the pancreas depend not on *decreased glycolysis* but on *increased glycogenesis*, in excess of the limits within which the body is able to burn up the sugar introduced into it, or which it forms.

How this hyperglycogenesis takes place in depancreatised animals is not very clear from Pflüger's many publications on the subject. For a long time he maintained that the amount of sugar present in the urine of depancreatised dogs is never in excess of that furnished by the glycogen stored up in the body, and derived from alimentary carbohydrates. But after fresh experiments undertaken in a controversy with Lüthje, he convinced himself of the necessity of admitting that glucose may arise from other sources, particularly from the fats accumulated in the liver, while on the other hand he excluded the alimentary proteins, for which Lüthje argued. Gerhardt had observed that much fat could be extracted from the blood and liver of the dog during pancreatic diabetes; Pflüger, after 16 days' pancreatic diabetes in a fasting dog, observed an increase of weight in the liver owing to an enormous amount of fat. It is thus probable, according to Pflüger, that in pancreatic diabetes the fat co-operates in sugar formation to an amount so much in excess of that normally formed as to produce elimination of the excess by the kidneys.

In 1903, to explain the hyperglycogenesis in pancreatic diabetes, Pflüger invoked the existence in the pancreas of an *anti-diastase* which normally moderates the action of the *diastases* of the liver cells; in ablation of the pancreas the increase in glycogenesis would result from the deficiency of anti-diastase. In 1905, on the contrary, he supported the theory of the *nervous origin* of pancreatic diabetes, which he regards as a *nerve reflex*.

In order to demonstrate that the oxidative processes are not diminished in diabetics, Pflüger cites the observations of certain authors, according to which the elimination of CO_2 in diabetics is equal to the amount normally eliminated (contrary to the positive results of Colasanti and Bonanni on depancreatised dogs). This argument does not, however, seem to us conclusive. The normal animal is capable of burning up an enormous amount of alimentary carbohydrate before glycosuria from insufficient glycolysis makes its appearance. Depancreatised animals, on the contrary, do not cease to eliminate sugar even during a prolonged fast until they die from starvation. Obviously, therefore, the contention that pancreatic diabetes is due to increased glycogenesis rather than to decreased glycolysis has no value. Increased glycogenesis can only

be invoked in such transitory forms of glycosuria as are observed in experimental nerve lesions (Bernard's puncture, ablation of caeliac plexus, extirpations or lesions of different segments of the central nervous system, etc.). In all these cases there is a rapid glycogenesis of the glycogen of the liver, and in the absence of glycogen, glycosuria (as we have seen) does not make its appearance. This shows the possibility of its being due to the sudden hyperglycaemia induced by the entry into the circulation of the glucose stored in the liver in the form of glycogen.

The final conclusion which stands out from the mass of facts we have been reviewing is that in pancreatic diabetes *glycolytic* processes are reduced, although *glycogenic* processes are not augmented.

While not a few important questions remain wholly unsolved, it is undeniable that experimental investigation of pancreatic diabetes has thrown much light on the pathogenesis of spontaneous diabetes, in which a more or less evident alteration of the pancreatic parenchyma has been detected in all recent researches.

XII. The Fats, absorbed in the form of soaps, regenerated by the synthetic activity of the intestinal epithelia, and broken up into minute droplets in passing through the walls of the central lacteal of the villi, are (as we have seen) poured out by the thoracic duct into the blood torrent, where they give a more or less milky aspect to the blood plasma according as the diet has been more or less rich in fats.

After a short time, however, the fat content of the blood, which may immediately after absorption amount to 1 per cent of the total mass of the blood (and even exceed it, up to a maximum of 6 per cent according to Bleibtreu) becomes much diminished, till shortly before a meal, and in a prolonged fast, traces only of fat are left in the blood plasma (Vol. I. p. 130). When but little fat is given with the food, it is evidently consumed during the day, perhaps within the blood, either by direct oxidation, or in consequence of the katabolic activity of the leucocytes of the blood and lymph. These always contain a certain amount of fat globules ingested by the phagocytes, which can be distinguished from the protoplasmatic granules by the fact that they discolour in ether and stain black with osmic acid. After a plentiful meal of fat, however, the fat escapes to a great extent from the blood, and is stored up in the tissues as a reserve material, as we found to be the case with the carbohydrates.

We are wholly ignorant of the mechanism by which the fats leave the blood, and penetrate to the interior of the tissue cells. Since fat must be decomposed and saponified before it can be absorbed by the epithelium of the intestine, it is probable, according to Altmann, that cleavage is again required before it can leave the blood and penetrate into the tissues, which must be followed

by a further synthetic reconstruction within the cytoplasm. However this may be, it is certain that fat almost entirely disappears from the blood plasma, and passes into the areolar connective tissue (probably by means of the leucocytes), where it is incorporated and stored up in the connective tissue corpuscles to be utilised as the body requires it.

The first experimental demonstration of this fact was given by Fr. Hofmann (1872). He caused the whole of the fat to disappear from a dog by a thirty days' fast. As the index of the complete consumption of fat, he took the rapid increase of nitrogen in the urine which immediately precedes death from inanition. When this occurred, he began to feed the dog with much fat and little meat, of which he estimated the exact protein and fat content. After five days he killed the animal, and estimated the total amount of fat present in the whole body, exclusive of that left in the intestine. He found that in five days the animal had accumulated 1353 grms. fat. Since it was impossible that the whole of this fat should be derived from the few proteins ingested (which would have yielded a total of 131 grms. fat), the alimentary fat must be assumed to have accumulated in the tissues.

Pettenkofer and Voit (1873) took another way of demonstrating the same fact. They determined the total intake and output of dogs fed copiously with fat and scantily with meat. They saw that the whole of the nitrogen introduced was excreted with the urine and faeces, while a large amount of the ingested carbon was retained in the body. Thus the organism had accumulated a large amount of a non-nitrogenous substance rich in carbon, which substance could only be *fat*.

Many tissues besides the adipose connective tissue are able to accumulate fat. After a meal rich in fats, fat-globules of various sizes are seen in the plain and striated muscle fibres, in the nerve cells, gland cells, and especially in the hepatic cells. The chief storehouse of fat is certainly the adipose connective tissue which forms the *panniculus adiposus* beneath the skin, and covers or fills the spaces in many internal organs, in a variable amount and form adapted to the different localities. It should be noted that adipose tissue is more variable in volume than any of the other tissues, that it increases or diminishes in a comparatively short time, according as the individual takes an excess or insufficient amount of food. The fattening of stock is due principally to abundant diet, and to limited muscular work.

In examining a lobule of subcutaneous adipose tissue, under the microscope, with a low power, it appears (as shown in Fig. 100) to be a collection of round globules which are highly refractive and crowded together. These stain black with osmic acid, and consist of irregular lobules, united by a scanty amount of fibrillar connective tissue, which follows the course of the blood-vessels.

On examining a portion of a fatty lobule with the high power (Fig. 101), the fat globules are seen to be enclosed within round or

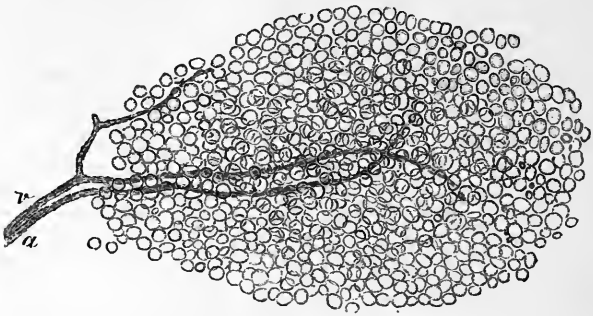

FIG. 100.—Small lobule of fat from the subcutaneous tissue of guinea-pig. (Schäfer.) Magnified about 20 diameters. *a*, small artery to lobule; *v*, small vein. The capillaries within the lobules are not visible.

oval bladders of different sizes (80-40 μ) which are the residuum of the original protoplasm of the connective tissue cells, the nuclei of these being still present, though often hard to see, since they are

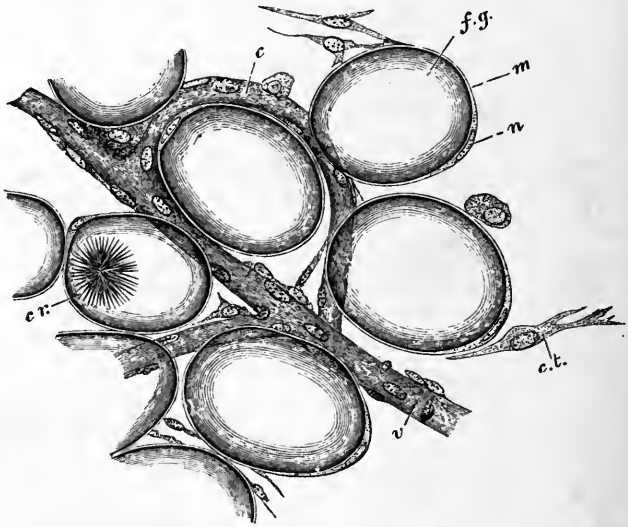

FIG. 101.—A few cells from the margin of the fat-lobule represented by the preceding figure. (Schäfer.) Highly magnified. *f.g*, fat-globule distending fat-cell; *n*, nucleus; *m*, membranous envelope of fat-cell; *c r*, bunch of crystals within a fat-cell; *c*, capillary vessel; *v*, venule; *c.t*, connective tissue-cell; the fibres of the connective tissue are not represented.

displaced and compressed by the fat-drops which distend the bladder. The fat-cell is thus only a connective tissue corpuscle reduced by the accumulation of fat in its cytoplasm to a vesicle

surrounding the fat, which is a little denser at the point where the displaced nucleus lies. After the fat has been removed by a proper solvent, the fat-cell appears as a connective tissue corpuscle of which the cytoplasm is converted into a large vacuole.

The analogy between fat-cell and gland-cell, *e.g.* hepatic cells, is obvious. As the one stores up sugar in the form of glycogen, so the other collects fat. The sole difference is that in the liver-cell the glycogen is arranged as a hyaline mass between the granules and the network of cytoplasm; in the fat-cells, on the contrary, the fat flows together in a single mass, forming a large vacuole in the midst of the cytoplasm and pushing the nucleus of the cell to the periphery.

The analogy between the liver-cells and fat-cells is more striking when we reflect that both have, respectively, the power, not only of storing up the carbohydrates, or the fats, of alimentary origin, but also of forming these substances by their specific metabolic activity from other materials.

The ordinary plan of fattening stock-animals, *e.g.* pigs and geese, with an excess of carbohydrate food, in which there is little fat, shows plainly enough that not the whole of the fat accumulated in the body, but only a small fraction of it, is derived from the fat given in the diet. Moreover, we must take into account that the fat accumulated in different animals differs somewhat in its composition. It consists mainly of olein, palmitin, and stearin, in variable proportions, with small amounts of the glycerides of butyric, capronic, caprylic, and other fatty acids, united with a little phosphorated substance (lecithin and jecorin) and also cholesterol, which, while it has some of the properties of the fats, belongs by its constitution to the alcohol group.

Owing to the different proportion in which olein, palmitin, and stearin are present, the body fat of different animals is distinguished by different melting-points. Thus the subcutaneous fat of man melts at 15-20° C., that which surrounds the kidneys only at 25°; the fat of dogs at 22°; of ducks at about 28°; of the ox at about 40°; of the sheep at 50°: olein, which melts most readily, predominates in the first; stearin, which is least fusible, in the last. This different constitution of the fats depends, not on differences of diet, but on the differences of metabolic activity in the living cells by which it is formed. The diet can in fact be considerably varied, without perceptibly affecting the composition of the fat reserves in different animals. Owing to this fact, *i.e.* that the fat of each species of animal has a definite melting-point, it was long held that alimentary fat did not give rise directly to the fat of the body. This, however, was proved by subsequent researches to be erroneous.

Kühne suggested as a decisive experiment in regard to the origin of tissue fat from alimentary fat, that it might be possible to get some fat extraneous to the body stored up by alimentation.

Lebedeff and I. Munk, and still more G. Rosenfeld (1899), successfully performed this experiment, which others had attempted with doubtful results. Lebedeff succeeded in making two dogs which had previously fasted for some time store up linseed oil in the one case, mutton fat in the other. In the same way I. Munk found rape oil and mutton suet in the fat of dogs after feeding them with these substances. In man, too, he succeeded in showing that extraneous fatty acids could be stored up in the form of neutral fats. Rosenfeld not merely noted in dogs an abundant storing up of mutton fat and cocoa butter, but was able, even after a month in which these fats had not been administered, to demonstrate mutton fat almost in the pure state in the animal's body.

The greater part of the fat stored up as reserve material in the body, with the exception of the little derived immediately from the alimentary fats, may be referred to the carbohydrates or the proteins. Liebig, on the strength of a number of observations, particularly that bees fed on honey only, in which there is very little protein, produce large quantities of wax, proposed the theory that the greater part of the fat stored up in the body is derived from carbohydrates. On the other hand, many other observations to hand show that fats may arise from cleavage of the complex protein molecule, when the nitrogenous group gives rise to formation of urea, and the non-nitrogenous group to the formation of fatty acid. The so-called fatty degeneration of the tissues, in which the cytoplasm is converted into fat granules, is a sufficiently cogent proof of this theory. The "maceration" of cheese due to *Penicillium glaucum* is known to consist in a process in which calcium paracasein decomposes with formation of fats, ammonia, and other nitrogenous substances, which are found in macerated cheese.

A more direct proof of the derivation of fat from protein was adduced by Bauer (1878) from slow phosphorus poisoning, which produces fatty degeneration of all the tissues in different degrees. When a dog had lost the whole of its nitrogen and carbon by fasting, he began to inoculate it subcutaneously with minute doses of phosphorus dissolved in oil. After several consecutive days, the daily amount of nitrogen excreted with the urine was doubled, while the elimination of carbon and absorption of oxygen were diminished by half. Phosphorus poisoning, therefore, doubled the consumption of protein, while the non-nitrogenous groups of the protein molecule were stored up as fat. In fact, the post-mortem showed fatty degeneration of all the organs. Bauer found 42·4 per cent fat in the dry substance of muscle, 30 per cent in dry liver, while normally the first contains only 16·7 per cent, and the second only 10·4 per cent fat. We may, therefore, conclude that fat is formed from protein in phosphorus poisoning.

These results were, however, submitted to more rigorous examination by other workers (Klaus, Legert, Athanasiu, Lebedeff, Rosenfeld). They have proved that in so-called fatty degeneration, particularly from phosphorus, there is at first not an increase, but a diminution of the total amount of fat in the body. In the majority of organs the amount of fat has not increased, and where it has augmented (liver) this occurs by migration of fat from the adipose tissues. In fact, if a dog has previously been fattened up with mutton suet, the fat extracted from the liver degenerated by phosphorus shows the characteristics of mutton fat.

That fat can be formed from protein under normal conditions was shown by Pettenkofer and Voit (1862, 1870, 1871), by experiments on dogs kept on a full flesh diet. They estimated the total intake and output of nitrogen and carbon, using as a criterion of the carbohydrate metabolism the carbonic acid exhaled by the animal into the large respiratory apparatus, invented by these authors, of which we shall speak in treating of general metabolism. They found that the whole of the nitrogen from the flesh of the diet is excreted with the urine; on the other hand, a considerable amount of carbon remains in the body, either in the form of fat (as supposed by the two Munich workers) or in the form of glycogen (as others more correctly assumed).

Pflüger, however, who did not admit the derivation of fat from natural protein, succeeded in showing that the carbon of the body was not derived from the proteins introduced, but from the glycogen and fat simultaneously administered. The quotient C/N was calculated too high by Pettenkofer and Voit. This was explicitly recognised in subsequent work by E. Voit, Cremer, Kumagawa.

Liebig's theory of the derivation of fat from carbohydrates remained unshaken till Voit proposed to explain the fattening of animals by hyperalimentation with carbohydrates, on the theory of "sparers," *i.e.* by assuming that carbohydrates diminish the normal consumption of fats, which therefore accumulate in the body.

Later work has, however, shown the earlier theory to be correct, *i.e.* that the larger part of the fat stored up in the body originates in the carbohydrates. I. Munk (1885) repeated on a dog the experiment of Fr. Hofmann, causing it to consume all its fat in a 31 days' fast, and then nourishing it on a minute amount of flesh and with increasing quantities of starch and sugar. After 24 days the animal was killed, when he found that it contained 960 grms. fat, only 172 grms. of which could be derived from the flesh ingested; the other 788 grms. could only be formed from the carbohydrates, of which, according to Munk's calculations, 8·3 per cent had been converted into fat.

N. Tscherwinsky (1883) performed a more rigorous experiment

on two young pigs of ten weeks, born in the same litter and of equal weight. One was killed to determine the amount of fat and nitrogenous substances contained in its whole body. The second was kept alive four months, and constantly fed on barley, which was chemically analysed. The total amount of fat and nitrogenous substances were then estimated in this pig also, and it was found that in four months, at most, 1560 grms. protein and 8560 grms. fat had been formed. Taking into account the whole amount of protein and carbohydrate absorbed from the gastro-intestinal canal, it was found that the animal had consumed 5930 grms. protein and had formed 7900 grms. new fat. Since only the least part of this large amount of fat could derive from the alimentary proteins consumed, it followed that the greater part of it came from the carbohydrates.

Another definite proof of the direct formation of fats from carbohydrates was furnished by Meissl and Strohmer (1883), who experimented on a pig one year old, which they fed for a week on rice, with simultaneous estimations of the intake and output of nitrogen and carbon. Other similar proofs were given by Rubner (1886), who experimented on a dog fed after two days' fast on cane sugar and starch. Thus not only herbivora but carnivora also are able to form fat directly out of carbohydrates.

From the chemical point of view—as was remarked by Bunge—the formation of fat from carbohydrates is an enigma. The fact is, however, well established experimentally, and is one of the clearest examples that the cells of animal tissues are capable, no less than those of plant tissues, of very complex synthetic processes.

XIII. We have seen that the synthetic reconstitution and polymerisation of the principal digestive products of protein, *the proteoses and peptones*, is the function of the columnar epithelium which lines the gastro-intestinal canal. These substances, therefore (which are the true compensation products for the losses suffered by the living protoplasm in the performance of its functions), penetrate into the circulating fluids of the tissues in the same form as that in which they are found in the plasma of the blood and lymph. Although not experimentally demonstrated, it is highly probable that the greater part, if not the whole, of the proteins introduced with the food reach the circulation in the form of *serum albumin*.

Owing to the marked tendency of the body to maintain the constitution of the circulating fluids almost constant, the sum of the protein absorbed after each meal does not accumulate in the blood, but is at once stored up in the various tissues, where it undergoes further transformations, either by forming more complex syntheses and entering into the living protoplasm, or by undergoing a series of retrograde changes in which the whole of its potential energy is utilised under different forms by the body.

Unlike carbohydrate and fat, the protein of alimentary origin cannot, outside very restricted limits, be stored up in the body in a stable form. In fact, under normal conditions, and with a regular diet, the adult organism excretes during the day (in the form of urea and other nitrogenous waste products) approximately the same amount of nitrogen as is introduced with the food, apart from that which leaves with the faeces. The slight up and down variations of the absorbed as compared with the excreted nitrogen, the *plus* or *minus* that can be noted from day to day on a sufficient diet, do not accumulate but tend towards compensation, so that an almost perfect equilibrium of metabolism is obtained, on comparing the sum total of the nitrogen introduced and that given off in the space of a few days. Elsewhere we shall discuss fully the modifications of the organic balance in regard to the different individual conditions and the varying nature and quantity of the food.

Here we must confine ourselves to insisting on the fact that while there is normally present in the tissues of the body a certain provision of non-living protein, which constitutes a reserve of nitrogenous material which can be utilised during a fast, and readily replaced on the ordinary diet, this provision is invariably confined within strict limits, so that it is not possible to increase it (as can be done for fats, and to a certain extent for carbohydrates) by an exuberant or *luxus* diet of nitrogenous substances. Within physiological limits we constantly see that as the protein introduced in the diet increases, so the amount of nitrogenous waste products eliminated by the kidneys rises in proportion.

This practically complete independence from the daily supply of nitrogenous foods of the reserve protein stored up in the tissues, shows clearly that only a minimal part of the total amount of alimentary protein reaching the circulation is converted by the anabolic activity of the cells into living matter, to repair the perpetual losses suffered by the cytoplasm in its intimate structure —the greater part (which fluctuates enormously according to the poverty or excess of the habitual diet) being consumed by the katabolic activity of the tissues before it can become part of the bioplasm. So that the nitrogen of the waste products daily excreted comes to a large extent directly from the nitrogen of alimentary protein.

The process by which the consumption of alimentary protein takes place within the tissues is quite unknown to us. We can only state that it differs essentially from that by which protein is broken up in the gastro-intestinal canal by the action of the digestive enzymes. According to Neumeister (1890), living tissues never convert protein into proteoses and peptone. We have seen that the protein in the liver gives rise to the nitrogenous and sulphur-containing constituents of the bile, which

are eliminated by external secretion, also perhaps to a simultaneous production of glycogen, which accumulates in the cytoplasm and is slowly elaborated and poured out into the blood in the form of glucose. Protein undergoes a different conversion in each glandular organ that has a specific function. We are more or less acquainted with the end-products of these hidden processes, but of the intermediate links forged within the cytoplasm we know nothing.

We do not know definitely whether the reserve protein of alimentary origin is equally distributed throughout the whole of the cytoplasm, or whether (as for fat and glycogen) there are organs and tissues which store it up in larger amount, and may be regarded as special reserves. It seems probable that the lymph organs serve as such a storehouse, since, as Fredericq noted, they shrink in volume more than the other organs during fasting—the liver excepted, which in starvation consumes the whole of its stored-up glycogen, and is greatly reduced in weight and volume.

We know that vegetable protoplasm, either with or without chlorophyll, is able to nourish itself and to develop, at the expense of the materials which it draws from the inorganic world. Plants, in other words, are capable of manufacturing by synthesis from the elements, or the very simple compounds which they obtain from the earth, air, and water, the whole of the organic substances —*carbohydrates, fats, and proteins*—which enter into the composition of their tissues. Is it possible that the same phenomenon, in a minor degree and starting from less simple compounds, takes place in the animal organism also? We have seen that *animal amylogenesis* and *adipogenesis* can occur either by synthetic processes, which start from the glucose, or by analytic processes, *i.e.* cleavage of the protein molecule. Is animal protoplasm also able to effect synthesis of the *protein molecule* from the nitrogenous (amino-acids) and non-nitrogenous groups into which it has been broken up?

The whole of the protein stored up in the animal body is usually held to be of alimentary origin, the total nitrogen eliminated in the urine being taken as the measure of its consumption. But although this theory has been uncontested, it is founded on no direct experimental evidence. It is not so much a true scientific theory as a physiological dogma, deduced from the ancient doctrine of the antagonism between plant and animal organisms—which is no longer tenable to-day. When we discuss the metabolism which underlies muscular activity and muscular work, we shall have to examine a fact which seems to give countenance to this doubt, and to admit the possibility of *animal proteinogenesis.*

O. Loewi (1902) succeeded in giving a direct experimental

foundation to this theory of proteinogenesis. On feeding dogs with starch and cane sugar, together with the soluble nitrogenous substances of the pancreas—digested until the biuret reaction completely disappears—he found that the animals were not only capable of maintaining their nitrogenous equilibrium, but were also able to store up a considerable amount of nitrogenous substance.

This process of the reconstruction of proteins by the combining together of amino-acids with loss of water (polymerisation) is made more intelligible by the recent work of Emil Fischer, who (as stated in Vol. I. p. 28) succeeded by the synthesis of different amino-acids in obtaining much more complex compounds, which he termed *polypeptides*. In some of their properties these resemble the proteins.

XIV. To complete this chapter we must draw attention to certain important experimental data, which show that the epithelial cells that line the gastro-intestinal canal have (like the hepatic cells), besides the *secretory* function we have discussed, a *protective* function. By this they are able to diminish or inhibit the effects of toxic substances, whether introduced from without or formed within the body, especially in the intestinal canal, owing to the processes of digestion and putrefaction which take place there. This protective function is more particularly built up on that capacity for *physiological selection* by which the epithelia of the intestine, while they absorb certain substances (in defiance of the laws of osmosis) that diffuse with difficulty, do not, on the other hand, permit others to pass which are more diffusible. This selective capacity, of course, has a limit, otherwise intoxication by gastro-intestinal paths could not take place,—which is an obvious absurdity. It is certain that many poisons of the category of alkaloids produce a greater toxic effect when injected under the skin than when administered by the mouth. It is often found that the lowest lethal dose, as given hypodermically, is innocuous or far less harmful when swallowed. M. Schiff (1861) and F. Lussana (1864) were the first to demonstrate this point.

The phenomenon depends not merely upon the slow rate at which alkaloids and other toxic substances are absorbed by the intestinal epithelium, but also on the fact that after absorption they pass by the roots of the portal system to the liver, where they are arrested by the hepatic cells, which store up the alkaloids in their cytoplasm, partly destroying them, partly restoring them to the intestine with the bile, and partly discharging them by the hepatic veins to be eliminated by the kidneys. Schiff actually found the fatal dose of narcotic poisons to be much lower when they were introduced hypodermically, than when they were injected directly by the portal vein. He further found that a frog, in which the vessels to the liver had been tied, died after the

subcutaneous injection of $\frac{1}{80}$ of a drop of nicotine, while a normal frog survived this dose without exhibiting the characteristic symptoms of poisoning. Lastly, he saw that if the hepatic parenchyma were triturated with alkaloids (nicotine or hyoscyamine) the resulting extract had no toxic action on dogs. This power of the liver to destroy or diminish the toxic action of alkaloids does not hold for other organs. On triturating the substance of the kidneys, *e.g.*, with alkaloids, the latter keep their toxic efficacy intact.

Mineral poisons, again, can be partially absorbed and retained in the liver cells, whence they are slowly turned out into the intestine by means of the bile. Orfila was the first who drew attention to this fact, subsequently confirmed by all toxicologists. Compounds of lead, copper, arsenic, iron accumulate in the liver in preference to any other organ. Special physiological importance attaches to the absorption and storage of iron in the liver, a fact correctly interpreted by Lussana in relation to the haematogenic or haemoglobinogenic action of medicinal preparations of iron. In confirmation of this statement, Marfori (1893), in Schmiedeberg's laboratory, found a special iron-protein compound in the liver, to which he gave the name of *ferratin*, analogous with the *haematogen* which Bunge discovered in the yolk of egg, neither of which gives a direct iron reaction, when treated with ammonium sulphate.

Heger (1873-77) demonstrated the antitoxic action of the liver by artificial circulation in the excised organ of defibrinated blood, to which nicotine had been added. He observed that this blood lost its characteristic odour after passing through the liver, the alkaloid being partly retained by the liver cells. In subsequent experiments he found that the liver was capable of absorbing and retaining 25-50 per cent of the alkaloids passed through it (strychnine, quinine, morphine, and nicotine), while none were retained by the lungs, and very little by the muscles.

In accordance with Schiff's observations, Lautenbach stated that one drop of nicotine sufficed to kill a large dog, with manifestations of tetanus, when the injection was made into the general circulation, while two drops could be injected into the mesenteric veins without inducing death or symptoms of tetanus, simple phenomena of narcotic poisoning only being manifested. From this Lautenbach concluded that nicotine contains two toxic groups, one of which alone (*i.e.* that which produces tetanus) is retained by the liver. René opposed these conclusions on the strength of new experiments.

More extended researches with a larger number of alkaloids were made by Jacques, and particularly by Roger (1886, 1887, 1889, 1892), in support of the theory that the liver stored up and partially transformed the poisons that reached it from the digestive canal

by the portal system. The following only of Roger's conclusions need be cited:—

(*a*) Dogs in which the portal vein has been tied, die after injection of 3 mgrms. nicotine per kilo. body-weight, while normal dogs exhibit only transitory disturbances after injection of 5 mgrms.

(*b*) Solutions of salts of quinine, morphine, atropine, curare, alcoholic extracts of putrid fluids, when freed from potassium salts and injected into the intestinal veins of rabbits, show a toxicity less by half than on injection into the peripheral veins.

(*c*) The liver retains ethylic alcohol, but not glycerol, acetone, or inorganic substances in general. Ammonium carbonate is, however, no less toxic when it passes through the liver.

(*d*) The venous blood from the systemic system and from the hepatic veins of dogs is much less toxic, when defibrinated and injected into the veins of rabbits, than the blood from the dogs' portal vein. This higher toxicity of the portal blood seems due to the products of intestinal putrefaction, since it disappears after repeated disinfection of the intestine with napthaline and iodoform.

(*e*) The liver is capable of partially converting toxins. If fresh hepatic tissue be pounded up with nicotine and then extracted with dilute, boiling sulphuric acid, only a part of the poison is recovered.

(*f*) The liver degenerated by phosphorus poisoning, or cirrhotic from ligation of the bile-duct, is no longer capable of exercising any protective action against poisons. The same is true of the liver of animals which have lost their glycogen after fasting. In foetal development also the appearance of the protective action of the liver coincides with accumulation there of glycogen.

Verhoogen (1893) arrived at other new data which show that the depurating action of the liver does not depend solely upon its position, and is not merely exercised upon the toxic substances formed in the digestive apparatus. He found that on injecting strong doses of morphine (5 to 6 grms. hydrochlorate) into the jugular vein of dogs, and killing them at different times, the alkaloid accumulated preferentially in the liver, bone marrow, and spleen, whatever the interval from the diffusion of the poison. This preferential accumulation of the alkaloids in these organs does not depend on their content of blood, because the percentage of toxin is less in the blood.

Verhoogen obtained the same results with sodium iodide, and with small amounts of other substances, within physiological limits.

To prove that the liver has the property of modifying certain alkaloids, he mixed solutions of hyoscyamine with extract of frogs' liver, and found that this substance lost all or almost all its property of dilating the pupil. Bile has not the same property,

which is due to an unknown capacity of conversion by the hepatic cells.

F. Schupfer, under Colasanti's directions, made equally interesting observations on dehepatised as compared with normal frogs, in regard to the toxicity of alkaloids inoculated beneath the skin of the back. He was able to demonstrate that the liver reduces the toxicity of cocaine hydrochlorate by $\frac{2}{3}$; of neutral sulphate of atropine by about $\frac{1}{2}$; of apomorphine hydrochlorate by $\frac{2}{5}$; of pilocarpine hydrochlorate by $\frac{1}{2}$.

Many other experiments were made by other workers, with the object of discovering whether, under conditions in which the liver is unable to function properly, either in pathological states or after operations, the toxicity of the urine increases abnormally. The results of Roger (1886), Surmont (1892), Bellati (1893), Villetti (1893), Bisso (1895), tend to show that the toxicity of urine is more or less proportional to the gravity of the anatomical and functional lesions of the liver.

Bisso's work, under the direction of Colasanti, seems the most definite. He operated on dogs by gradual occlusion of the portal system (Bernard-Oré method), collected the urine, and determined its toxicity by Bouchard's method of injection into the veins of rabbits.

He found that the toxicity of the urine varies in normal dogs with the diet. It is maximal with a flesh diet, minimal with a milk diet, intermediate on a diet rich in fats. After occlusion of the portal vein, urinary toxicity is tripled, while the original ratio between the several diets persists. The liver accordingly functions as a protective organ in the body, by arresting and destroying the toxic substances formed during the secretory, digestive, and putrefactive processes of the alimentary canal. A strict functional relation between the liver and kidneys must also be admitted, since, when the protective function of the liver is in abeyance owing to occlusion of the portal vein, the kidneys function more actively, and expel the toxic substances accumulated in the body.

In order to define the nature of the protective function normally exercised by the liver against the toxic products that enter through the portal roots, Schröder and Salomon established an artificial circulation in the liver, and made a chemical analysis of the blood before and after it passed through this organ. They saw that on adding ammonium carbonate to the blood, it was converted into urea after circulating through the liver. This conversion is due to a synthetic process effected by the hepatic cells, in which the ammonium carbonate loses water and is converted into urea. This conversion does not take place if the blood is circulated through the kidneys or muscles.

After excision or ligation of the liver in geese, Minkowski

observed a marked increase of ammonia in the urine, associated with a considerable diminution of *uric acid*, which (as we shall see elsewhere) takes the place in birds of the *urea* of mammals.

These data show that the depurative action of the liver upon the ammoniacal compounds developed in the digestive apparatus of mammals and birds, consists in their synthetic conversion into urea or uric acid, respectively.

Hahn, Massen, Nencki and Pawlow (1892) deflected the portal circulation from the liver by joining the portal vein, which had previously been tied near the hilum of the liver, with the inferior vena cava. This ingenious experiment was first carried out by Eck in 1877, and afterwards repeated by Stolnikow, when some of the operated dogs survived. Those which survived the experiments of the Russian investigators exhibited phenomena of auto-intoxication towards the tenth day from the operation—consisting in sensory and motor disturbances, which developed into clonic and tetanic convulsions, recurring in spasms. The excitatory phenomena were succeeded by a comatose period in which some animals died, while others recovered comparative health. Careful observation showed that these attacks of auto-intoxication were exhibited by the dogs that had eaten most meat. Pawlow and Massen induced similar attacks in operated dogs by forced feeding with an excessive quantity of nitrogenous foods.

When Nencki and Hahn (who took charge of the chemical part of the work) discovered a large amount of carbamic acid in the urine of the operated dogs, it occurred to Pawlow and Massen to see whether the phenomena of intoxication were due to this abnormal product, which would under natural conditions be converted by the liver. On injecting carbamate of sodium or calcium, to an amount of 0·25 grm. per kilo. body-weight into the veins of a normal dog, they noted nervous disturbances similar to those seen in dogs with Eck's fistula, while the same salt introduced into the alimentary canal was innocuous, even in larger doses. They noted, further, that the administration of sodium carbamate by the mouth, even in smaller doses, in dogs with Eck's fistula, produced a similar poisoning to that obtained with a flesh diet. From this they concluded that the toxic agent which produces the spasms of auto-intoxication in the operated dogs is represented by the carbamic acid, which is normally neutralised by the hepatic cells, and gives rise to the formation of urea, carbonic acid and water, according to Drechsel's theory. The Russian experimenters confirmed this conclusion by excising a large part of the liver in dogs with Eck's fistula, and tying the hepatic artery, when a comatose state was at once produced, followed by strong convulsions which led to death after 6-12 hours.

The liver in animals with Eck's fistula was found to be atrophied, with partial fatty degeneration. The kidneys showed

albuminoid degeneration of the epithelia, due to accumulation in the blood of toxic waste-products.

The urine of operated as compared with normal dogs proved to contain carbamic acid, which was either entirely absent in normal urine (Drechsel and Abel) or occasionally present in minute quantities (Hahn and Nencki). The urine of the operated dogs further showed a distinct reduction in the urea content, associated with a constant increase of uric acid and ammonia. These facts, which agree with the theory that the greater part of the urea is formed in the liver, show that in all probability a considerable part, if not the whole, of the carbamic acid is a product of the conversion of nitrogenous substances effected by the spleen, pancreas, and walls of the intestinal tract, which, when normally conveyed to the liver by the portal system, gives rise to the formation of urea.

Nencki, Pawlow, and Zaleski (1896) arrived at very important results in a series of observations on the ammonia content of the blood and other organs, and the formation of urea in mammals. They found that the portal blood in dogs fed on flesh contains five times as much ammonia as arterial blood, twice as much as venous blood. On the other hand, the ammonia content of the blood of the hepatic veins is approximately equal to that of arterial blood. They further showed that the amount of ammonia varies in the blood of the different roots of the portal system; it is maximal in the gastric mucous membrane, and largely exceeds the quantity found in the contents of the stomach. On the other hand, the ammonia content of the intestinal mucous membrane and of the intestinal contents is approximately the same. It diminishes in starvation, and still more on a mixed non-flesh diet of bread and milk. Ammonia seems to be a metabolite of the digestive glands, because the same quantity is found in the gastric mucosa of a dog fed abundantly on flesh, and of another dog, with a gastric and oesophageal fistula, subjected to "sham feeding." Lastly, these experimenters found in a dog with Eck's fistula that the ammonia content of the blood increases to a marked extent during a flesh diet (as compared with a diet of bread and milk), this increase becoming larger in proportion as the symptoms of auto-intoxication are aggravated.

From their results as a whole these authors concluded that owing to the function of the gastric and intestinal glands (including the pancreas), an enormous amount of ammonia is produced, which is stored up in the liver, where it is converted into urea. According to them, the larger part, if not the whole, of the urea originates in the metabolism of the glands, which differs from that of the muscles, the liver being thus the most efficient defence of the body against intoxication due to ammonia and carbamic acid.

De Filippi's latest experiments (1899) on dogs with Eck's fistula partially confirm the results of the Russian school. De Filippi states that with a mixed diet dogs are able to live for months in good condition, and even to put on weight. When fed with raw meat, they suffer after 2-3 days from vomiting, and refuse their food. If forced to swallow it, the phenomena of auto-intoxication described by the Russian observers set in on the third or fourth day. But as compared with these cases, he noted others in which even a protracted flesh diet produced no disorder, or at most a general progressive emaciation. The season apparently has great influence on the acute or chronic effects of an Eck's fistula. In winter acute intoxication never fails, and may even appear with a mixed diet; while in summer some cases are refractory to poisoning, even with a continuous flesh diet. The intoxication produced by raw meat does not depend, according to De Filippi, on the amount of nitrogenous constituents, because a vegetable diet rich in proteins, as well as meat extracted with hot or cold water, produces no sign of poisoning. On the other hand, concentrated aqueous solutions of meat produce toxic symptoms after 4-5 days, which are fatal in a short time.

De Filippi's experiments on the metabolism of a number of dogs with Eck's fistula led to very irregular results, which differed considerably in different animals. The most remarkable phenomena are as follows:—

(*a*) The total nitrogen eliminated with the urine is as a rule much less than the nitrogen introduced with the food, even taking into consideration that eliminated with the faeces. We do not know the form in which this nitrogen is retained; it does not seem to be eliminated by the lungs in the form of ammonia.

(*b*) A marked diminution in the urea eliminated by the kidneys corresponds with the retention of nitrogen, while the ammoniacal nitrogen increases, and the uric acid is doubled or even trebled.

(*c*) The nitrogenous extractives of the urine increase in dogs fed on aqueous extract of meat, as compared with normal dogs, a proof that they are either not converted into urea, or to a minimal extent only.

(*d*) In all fasting dogs provided with Eck's fistula, De Filippi observed that the administration of 100 grms. glucose, lactose, or saccharose is followed by glycosuria, which is not the case in normal dogs. It appears half an hour after ingestion, and lasts 3-4 hours. With ingestion of glucose the glycosuria is less persistent and less intense (0·2-1 per cent). Sometimes it is entirely absent, which may be explained as meaning that the glucose can be converted into glycogen and stored up by the muscles as well as the liver, to which it is conveyed by the blood of the hepatic artery.

Post-mortem examination of operated dogs that have perished from auto-intoxication show in addition to advanced atrophy of the liver, a grave alteration of the renal parenchyma, probably different in character from that of ordinary nephritis. This renal alteration, however serious, is not accompanied by albuminuria. Once only De Filippi found in the urine of a dog 0·05 grm. per cent of albumin. Complete anuria may appear in the extreme period of intoxication that precedes death.

This special renal alteration explains the whole of the irregularities in the toxic phenomena presented by the different animals operated on, which vary greatly in the different periods following the operation. According to De Filippi the deflection of the portal system from the liver includes the principal paths by which the injurious metabolites absorbed by the intestine are rendered innocuous by the liver. So long as the kidneys function normally, the toxic circulating substances can be removed from the blood by an excess of work of the kidneys. But this excess of work and the constant passage of toxic substances finally affect the renal parenchyma, so that compensation fails, and intoxication sets in. The choice of diet is very important in delaying this renal alteration; a diet of raw meat is harmful, owing to the extractives which it contains, since these produce rapid alterations of the renal epithelia, and cause an accumulation of toxic substances in the blood. Hence the importance of a milk diet in the treatment of hepatic cirrhoses and nephritis.

The above data show that while many highly important problems are still unsolved, the theory of the protective functions of the liver is firmly based upon innumerable experiments, which are of great interest, from both the physiological and the clinical point of view.

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CHAPTER VI

THE INTESTINE AS AN ORGAN OF EXCRETION

CONTENTS. — 1. Physical characters and chemical composition of faeces and intestinal gases. 2. Alimentary residues and waste products in faeces, while taking food and in fasting. 3. Formation of faecal masses a function almost exclusively confined to small intestine. 4. Theory of normal human faeces. 5. Toxicity of faeces. 6. Mechanical and chemical functions of caecum. 7. Mechanism of defaecation. 8. Innervation. Bibliography.

WE have seen (in Chapters III. and IV.) that the character common to all the chemical processes carried on in the alimentary canal is the hydrolytic cleavage of the larger molecules of the food-stuffs, by which these are reduced to smaller groups of atoms, and become more soluble and diffusible. They are thus converted into suitable material for the *anabolic chemical* activity of the living protoplasm, and the synchronous and homologous (*constructive* or *reintegrative*) changes within its cells.

In the last chapter, in discussing what is known of these hidden processes, we followed the three different groups of organic food-stuffs from the alimentary canal to the blood, and from the blood to the liver, as well as to the other tissues and organs. We found that the *anabolic* processes (both chemical and cytological) precede or succeed—or in any case are intimately connected and associated with—processes of the opposite or *katabolic* nature. In these the nutrient substances, on penetrating into the protoplasm, or before entering the structure of the living matter, for the most part undergo a succession of retrograde chemical transformations, by which they are ultimately reduced to waste products, destined to be eliminated from the body as useless or injurious. This disintegrative work of the tissues, in which the potential energy of the restitutive substances of alimentary origin is liberated under various forms, necessarily involves a certain consumption and expenditure of living matter, which increases the sum of the katabolic products.

The ultimate and simplest waste products of the animal economy are:—

(*a*) *Urea*, which is derived entirely from the consumption of proteins, and is formed chiefly, if not exclusively, by the liver.

(*b*) *Carbonic acid and water*, which are produced by oxidation of all three groups of organic food-stuffs, and are formed in every living tissue-cell;

(*c*) *Salts*, particularly phosphates and sulphates, which are formed by oxidation of the sulphur of the proteins and the phosphorus of the nuclein, lecithin, and other phosphorated substances.

These final products of metabolism, together with many other intermediate products of oxidation, are expelled from the body as fast as they are formed, by the various organs of excretion—the intestines, kidneys, lungs and skin.

The kidneys are the principal organs for the elimination of waste products. They secrete urine, which contains the greater part of the urea and other nitrogenous products, the greater part of the salts, a very large amount of water, and a little carbonic acid. The lungs (as we saw in Vol. I. Chapter XI.) eliminate most of the carbonic acid formed in the tissues, along with a considerable amount of water in the form of vapour. The intestine and skin, although their excretory functions present some specific characters, may undoubtedly be regarded as vicarious excreting organs, which are complementary to the lungs and kidneys.

Intestinal excretion must be treated first, since it is a necessary complement to the study in the three preceding chapters of the functions of the digestive canal.

I. We have already considered the Intestine as an organ for the digestion of foods, and absorption of the digestive products. We now have to consider it as an organ for *excretion, i.e.* a canal which collects a certain quantity of waste matter destined to be periodically cast out of the body, in the form of the *faeces* or *excrements*.

The investigation of the faeces—with as exact a determination as is possible of their chemical constitution, their origin, and the process by which the several products contained in them are formed, together with the quantitative and qualitative variations of the latter in relation to various forms of diet—is a subject of great scientific interest, which has not hitherto received adequate treatment.

The amount, physical characters, and composition of the excreta differ widely in the different classes of animals, principally in relation to the nature of their diet. Herbivora excrete a much larger amount of faeces than carnivora, because vegetable foods (in comparison with those of animal origin) are much richer in substances which are indigestible or difficult of digestion, so that larger quantities have to be taken in to satisfy the needs of the body, and a larger residue is left in the intestine. Man, who is omnivorous, produces a variable daily quantity of faeces, according as his diet is mainly vegetable or animal: with the first he normally excretes a larger amount, with the second, a less.

Apart from the nature of the diet, the daily amount ingested, in excess of certain physiological limits, alters the amount of the faeces. A superabundant meal, although it may consist wholly of digestible substances, gives rise to more excreta, because a more or less considerable portion escapes the action of the digestive enzymes, and fails to come in contact with the absorbing surface of the intestine. In a mixed diet of normal amount, the weight of the human faeces is about $\frac{1}{7}$-$\frac{1}{8}$ that of the ingested food (Liebig), *i.e.* 120-150 grms. with 30-37 grms. solid substances (C. Voit).

The consistency of the faeces varies with their water content, which generally fluctuates between 68 and 82 per cent, within physiological limits, *i.e.* excluding cases of diarrhoea, in which there is much more water. It depends less on the quantity of water drunk than on the vigour of intestinal peristalsis, the tone of the intestinal vessels, and the state of the epithelium by which intestinal absorption is regulated.

The chemical reaction of the faeces varies greatly with the scope and activity of the fermentative and putrefactive processes in the different parts of the intestine, conditions which are not easy to determine for individual cases. In the last part of the ileum the reaction may be alkaline, neutral, or slightly acid; in the large intestine it is usually distinctly acid. This depends, not on acidity of the secretion from the mucous membrane (which is alkaline, both in the small and in the large intestine), but on acid fermentations in the faecal content due to the intestinal bacteria which decompose the carbohydrates. This is proved by the fact that the acidity of the faeces is greatest when the diet is rich in starchy and saccharine substances.

The acidity of the faecal masses is mainly due to the presence of lactic acid, derived from the lactic fermentation of sugar, the vigour of which probably varies with the amount of carbohydrates ingested and with other conditions of the intestinal tract, which have not been exactly determined.

The neutral or alkaline reaction sometimes exhibited by the faeces depends essentially on the putrefactive processes of the proteins, which give rise to a development of ammonia.

The abundant secretion of mucus in the large intestine also favours the neutral or alkaline reaction of the faeces.

The colour of the faeces varies considerably according to the nature of the food. Contrary to the general opinion, the bile pigments and their decomposition products have little influence on the normal colour of the dejecta.

On an exclusive flesh diet the faeces, independent of the bile, are blackish, owing to the presence of haematin and ferrous sulphide. On an exclusive diet of brown or wholemeal bread they are lighter in colour. On a diet rich in fat they are yellowish or clay-coloured. In infants the greenish-yellow colour of the excreta

is partly due to biliverdin and bilirubin (Lesage), which are normally reduced in adults.

The obnoxious odour of the faeces increases with the putrefactive processes of the intestine, and depends principally on the development of scatole (Brieger). With a flesh diet the faecal odour is more pronounced than with a vegetable diet.

The chemical and morphological composition of the faeces are so variable that it would be tedious to quote the analysis given for individual cases. Halliburton distinguishes the following groups of materials:—

(*a*) *Undigested Food-stuffs.*—Neutral fats, carbohydrates, and also proteins with a superabundant protein diet. It should be noted that unaltered protein is never found in the faeces with a moderate diet (Hoppe-Seyler).

(*b*) *Indigestible Food-stuffs.*—Cellulose, keratin, mucin, nuclein, chlorophyll, gum, resin, cholesterol, phosphates and other bases, particularly calcium.

(*c*) *Food-stuffs difficult of Digestion.*—Granules of raw starch, fragments of elastic tissue, tendon, cartilage and (especially with a superabundant flesh diet) more or less unaltered muscle fibres.

(*d*) *Waste Products of Food-stuffs.*—Groups of aromatic substances (scatole, indole, phenol, etc.) formed by putrefactive processes and probably tending, when formed, to check or arrest these processes; groups of fatty acids, (formic, acetic, butyric, isobutyric, valerianic, capronic acid, with others such as lactic, malic, succinic, etc., in a free state or combined with ammonia and other bases); haematin from decomposition of haemoglobin; insoluble and non-absorbable soaps of calcium and magnesium; stercorin, which according to Flint, is a decomposition product of cholesterol; excretin, as described by Marcet for human faeces, the composition of which is wholly unknown. All these products originate not in the activity of the digestive enzymes, but in the fermentative and putrefactive processes effected by the intestinal bacteria.

(*e*) *Substances converted and not reabsorbed, of the Bile and other Intestinal Secretions.*— Mucin, cholalic acid, cholesterol, lecithin, which partly come from the foods, hydrobilirubin and stercobilin, which are reduction products of the bile pigments, and no longer give Gmelin's reaction. The co-operation of the pancreatic juice seems necessary in the formation of these pigments, since in two cases of obstruction of Wirsung's Duct, Walker found no stercobilin in the excreta, which had the clay colour characteristic of the faeces in jaundice, although the liver was healthy and the bile flowed freely into the intestine.

(*f*) *Bacteria of different Kinds, Epithelial Cells and Detritus.*— Great quantities of bacteria are present, *Bacterium coli commune* (as we have seen) largely predominating. The epithelial cells shed by the mucous membrane are sometimes almost intact, the

striated border being still visible; more often, however, they are imperfect, or reduced to the bare nuclei.

This completes our definite knowledge of the composition of human faeces, under normal conditions.

The development of gases in the digestive canal, which mix with the air swallowed with the food and the saliva, is largely associated with the complex process of formation of the faeces. This development of gases arises from the fermentative and putrefactive processes of the intestinal bacteria. It is therefore entirely absent during intra-uterine life, when the contents of the intestine are destitute of microbes. Since the development of gases is due to decomposition of the various food-stuffs, it follows that the gaseous mixture must vary in composition according to the nature of the diet.

The oxygen of the swallowed air is entirely or almost entirely absent in the intestinal canal, no doubt because it is rapidly absorbed by the blood, through the mucous membrane which functions as the respiratory surface. This absorption of oxygen with simultaneous excretion of carbonic acid takes place almost exclusively in the gastric cavity, where the presence of the hydrochloric acid of the gastric juice normally checks any fermentation of the chyme, with ebullition of gases. The gaseous mixture in the stomach, therefore, consists of the air swallowed with the food and the saliva, and to a less extent of the duodenal gases, which may penetrate the pyloric orifice, or diffuse through it. Planer found in the gases of the dog's stomach 66-68 per cent nitrogen, 23-33 per cent carbonic acid, and only 0·8-6·1 per cent oxygen. These data show that a respiratory exchange takes place in the stomach, the oxygen of the air swallowed being absorbed by the blood circulating in the capillaries of the mucous membrane, while the carbonic acid of the blood passes into the air of the stomach, and partially mixes with that which comes from the duodenal gases.

The gases of the intestinal contents were analysed by Planer in the dog. They vary in composition in the small and large intestine with a flesh and a vegetable diet, as shown by the following table of volumetric percentages:—

Gas.	Small Intestine.			Large Intestine.	
	Meat. (3 hrs. after).	Bread.	Vegetables.	Meat. (3 hrs. after).	Vegetables.
CO_2	40·1	38·8	47·2	74·2	65·1
H_2	13·9	6·3	48·7	1·4	2·9
H_2S	—	—	—	0·8	—
O_2	0·5	0·7	—	—	—
N_2	45·5	54·2	4·0	23·6	5·9

Ruge analysed the intestinal gases of man, as given off per anum, with the following results:—

Gas.	Milk Diet.		Flesh Diet.		Vegetable Diet.	
	I.	II.	I.	II.	I.	II.
CO_2	16·8	9·9	13·6	8·4	34·0	21·0
CH_4	0·9	—	37·4	24·4	44·5	55·9
H_2	43·3	54·2	3·0	0·7	2·3	4·0
N_2	38·3	36·7	45·9	64·4	19·1	18·9

C. S. Hofmann never detected methane or marsh gas in his work on the intestinal gases of dogs and rabbits, but hydrogen was constantly present, with traces of oxygen and sulphuric acid.

As shown by the tables, carbonic acid always occurs in large quantities, particularly after a vegetable diet. It may be developed by different processes, by cleavage of the alimentary carbonates, lactates, acetates, and citrates; by alcoholic fermentation of glucose; by putrefaction of carbohydrates (particularly of cellulose) and proteins; by butyric fermentation of lactic acid; lastly by diffusion from the capillaries of the mucous membrane of the intestine.

The hydrogen, which is present in large quantities, especially in a milk diet, is undoubtedly due to the butyric fermentation of lactic acid, during which carbonic acid and hydrogen are developed.

The methane, which is developed in man in large quantities after a diet of meat and vegetables, while it is scanty in a milk diet, originates in the decomposition of acetates and lactates (Hoppe-Seyler) and of cellulose (Hoppe-Seyler, Tappeiner, Henneberg, and Stohmann); also to a small extent from the decomposition of the choline, derived from lecithin. It is difficult to explain the absence of methane in the intestinal gases of the dog and rabbit.

Nitrogen is always present, though it varies much in quantity with different diets. For the most part it comes from the swallowed air, left behind after absorption of the oxygen; it may arise partly, however, from diffusion through the wall of the intestine (Bunge), and also from putrefaction of the proteins, with simultaneous development of ammonia.

The sulphuric acid, of which traces are normally present in the intestinal gases, originates undoubtedly in the putrefaction of proteins, during which ammonia, sulphuric acid, ammonium sulphate, fatty acids, amines and amino-acids (especially leucine and tyrosine), and aromatic ethers (particularly indole, scatole, phenol, and cresol) are developed.

II. The excreta which accumulate in the lower part of the intestine accordingly comprise two kinds of substances:—

(*a*) *Those derived from the food, i.e.* indigestible or undigested alimentary residues of ingesta, or non-absorbed and non-absorbable decomposition products.

(*b*) *Chemical compounds* discharged from the wall of the alimentary canal as secretory products of the adjoining glands, which are not or cannot be reabsorbed by the lymph and blood; and detritus shed off in the epithelial regeneration of the mucous coat.

The exact determination of the first group of substances is of great importance in defining the *digestibility*, or better the more or less perfect *utility-value*, of the individual food-stuffs. It is clear that the less the amount and the simpler the chemical composition of these products the more complete will be the utility of any given diet.

The determination, on the other hand, of the total waste products in the second group, is more valuable in determining the importance of the intestine as an *organ of excretion*; also in deciding whether the intestine expels specific products of metabolism, and to what point it is able to assist or replace the excretory function of the kidneys.

No exact distinction between the two kinds of substances has, however, yet been possible, either because the analytical methods at our disposal are inadequate for the quantitative determination under different circumstances of the individual components of the faeces (which, moreover, vary greatly even within physiological limits), or because a considerable proportion of these can arise both from decomposition of the food, and from katabolic processes in the glands adjoining the intestinal canal, and in other tissues of the body.

A simpler problem, capable of experimental solution, is to decide which of the two groups forms the largest and most important part of these excreta, the alimentary residues, or the residues of the intestinal secretions and epithelial detritus.

From the fact that in ordinary, normal faeces the residues of the digestive secretions, especially bile and the epithelial detritus, are present in small quantities only, it was formerly supposed that the faecal mass consisted mainly of undigested alimentary residues. C. Voit and his school (1860, 1884, 1892) first demonstrated the fallacy of this theory.

Voit investigated the *meconium*, which is formed and collects during intra-uterine life in the intestine. He also found that a blackish, pitchy, faecal mass, similar to meconium, is formed in the dog's intestine during a protracted fast. On a flesh diet, moreover, similar faeces are formed in the dog, with the same characters as in fasting; the amount is scanty, sometimes increasing if more meat be

given, but never in proportion with it. Meconium and the faeces of fasting consist exclusively in the residues of the secretions poured into the intestine, which contain certain metabolites that are excreted neither by the kidneys nor by the skin and lungs. But even on a strict flesh diet the faeces have, as a rule, the same composition, a minimal amount of alimentary residues only being visible under the microscope.

If sugar, starch, and fat be added to the flesh diet, the residues of these substances appear in the faeces only when they are administered in large quantities. So that on this mixed diet also, the faeces consist mainly of the waste products of the digestive secretions. It is only on feeding with certain foods that are very rich in starch, *e.g.* bread and potato, that the faeces are found to contain alimentary residues (for the most part little altered) along with a reduced amount of metabolites.

These results were extensively confirmed in Voit's laboratory by Fr. Müller and Rieder (1882). This last author estimated the amount of nitrogen found daily in the faeces and urine of both dogs and man, on a diet entirely or almost entirely free from nitrogenous substances; and obtained results which induced him to think it probable that not only in the dog but in man also the faeces consist mainly of katabolic products, excreted by the digestive organs. In fact, from three series of experiments on a man fed on this regimen, he obtained the averages shown in the following table:—

Series.	Nitrogen in Urine.		Faeces in Dried State.		Percentage Nitrogen Content of Faeces.		Total Nitrogen Content of Faeces.	
1	9·30 grms.	8·65	13·4 grms.	14·7	4·08 per cent	5·27	0·54 grm.	0·73
2	9·50 ,,		15·4 ,,		5·69 ,,		0·57 ,,	
3	7·16 ,,		13·4 ,,		5·85 ,,		0·78 ,,	

So that on a non-nitrogenous diet a man (weighing about 70 kilos.) excretes a daily average in the faeces of 0·73 grm. nitrogen (an amount not much in excess of that excreted by a dog of 35 kilos., which on an average equals 0·64 grm.). This amount of nitrogen represents about 8 per cent of the total nitrogen eliminated by the body.

During an abundant mixed diet, man excretes on an average 2·53 grms. nitrogen in the faeces (Pettenkofer and Voit). Of this nitrogen it is probable that 1·80 grms., *i.e.* 71 per cent, comes from alimentary residues, and that 0·73 grm., *i.e.* 29 per cent, must be referred to katabolic residues excreted by the intestinal canal. In this case, therefore, the amount of alimentary residues in the faeces

exceeds that of the metabolites from the intestinal canal. But with a diet consisting strictly of meat and eggs (according to Rubner's experiments on man) 13-17 grms. dry faeces are obtained, with only 0·6-1·2 grms. nitrogen. It is therefore highly probable that human faeces, like the dog's, consist mainly of metabolites from the alimentary canal.

A vegetable diet, particularly of vegetables and black bread, increases the amount of faeces, with reduction of the percentage quantity of nitrogen and rise of the absolute quantity. In fact, (according to Rubner) the faeces for one day contain 2·4-4·3 grms. nitrogen.

Even during an absolute fast, a considerable amount of faecal matter is formed in man, as shown by the interesting researches of Fr. Müller on the fasting men Cetti and Breithaupt, as well as by our own observations on Succi during his fasts. The amount of faeces in fasting is, however, considerably less for man than that found by Voit for dogs and cats. Cetti during a fast of 10 days excreted about 38 grms. faeces (when dried), *i.e.* 38 grms. per diem: Breithaupt in 6 days' fast excreted only 12 grms. *i.e.* 2 grms. per diem; Succi in 30 days' fast excreted 150 grms., which corresponds approximately to 5 grms. per diem, a figure somewhat higher than the preceding, because Succi frequently took mineral waters while fasting.

Human faeces in fasting are yellowish-brown balls, of medium consistency, with little odour, and resemble the faeces in a diet consisting mainly of flesh.

The percentage nitrogen content of the faeces in fasting is greater than while taking food. In Cetti it reached 8·28 per cent, in Breithaupt 5·67 per cent: while on an exclusively milk diet it is 3·03-3·3 per cent; with milk and white bread 3·92 per cent (Fr. Müller); with meat and bread 3·1-3·5 per cent (Meyer). It is only on a strict flesh diet that we find 6·5-6·9 per cent nitrogen (Rubner), a figure approximately equal to the nitrogen content of the faeces in fasting. Since the daily excretion of faeces is very small in fasting, it follows that the absolute quantity of nitrogen excreted is less than with the various diets.

As regards the value of these observations it should be noted that (according to Zaitschek, 1903, in Tangi's laboratory) the ordinary method of determining the nitrogen of desiccated faeces is defective, since a by no means indifferent amount of volatile nitrogen is lost in the process of desiccation. The amount of nitrogen which may be lost in this way varies in man from 4-7 per cent, and may amount in the dog to 13 per cent.

These analytical researches ought, therefore, to be repeated with samples of non-desiccated faeces, or at least the figures quoted should be revised, since they were mostly obtained from previously dried faeces.

The faeces of fasting contain a certain amount of fat, which is probably eliminated with the intestinal secretions.

It is interesting in this connection to note that U. Lombroso observed in some cases, after excising the pancreas in dogs, that more fat was given off in the faeces than had been present in the food, and again that fat was eliminated in large quantities with a diet of egg-albumin (which contains only traces of fat). This shows that under certain conditions the elimination of fat by intestinal excretion may far exceed the limits generally acknowledged.

It has further been observed that during a diet rich in fats the faecal fat exhibits a much higher melting-point than the alimentary fat. With a milk diet (milk-fat melts at 42°) a fat is found in the faeces which melts at 51·5° (Müller, Zoja).

This has been explained by a selective capacity of the intestinal epithelium during fat absorption ;—in the sense that the epithelium has the capacity of absorbing specific fats which vary according to the species of animal. This hypothesis, however, does not agree with the fact that on feeding previously emaciated animals on special fats other than that of their bodies (olive oil, mutton suet) these are found unchanged in the adipose tissues. It is therefore not improbable that selective activity is to be referred not so much to absorption as to the elimination of such fatty bodies as are not easily assimilated by the tissues of the animals of the particular species.

The ash of the faeces during a fast does not differ in amount from that with a normal diet. It differs in composition from the ash of the meconium in having less sulphuric acid, chlorine, and alkali, and more phosphoric acid and calcium. In the faeces of a mixed normal diet these last substances are present in a higher quantity than in fasting.

III. Hermann (1890) employed quite a different method to determine the importance of the intestinal mucous membrane in the formation of the faeces. He isolated a loop of intestine in the dog, washed out its contents by a stream of disinfecting fluid, sutured the ends to form a ring within which the substances introduced could circulate, and then replaced it in the abdominal cavity, which was closed up, after renewing the continuity of the rest of the gut by a second suture.

Many animals thus operated on died after a few days from septic peritonitis, owing to the escape of faecal matters through the suture of the circular loop of intestine. Some dogs, however, survived for a long time, and were killed in the 3rd-4th week after the operation in a good state of health. Upon section, the ring was found to be filled with a grey mass of faecal matter, which differed from the normal faeces only in the absence of bile and of alimentary residues. According to Hermann, this more or less

compact mass represented a concentration of the intestinal secretion, which must accordingly play a prominent part in the formation of the faeces.

Hermann's observations were much extended and varied by his pupils Ehrenthal and Blitstein (1891), and by Berenstein (1893). Besides employing the intestinal ring, the two first-named caused dogs with a fistula of the gall-bladder to fast, so as to exclude any bile from the faeces formed in the intestine. They further made observations on the faecal masses produced in the last part of the intestine, after establishing a preternatural anus in the ileum, and occluding the lower end of the bowel as a *cul de sac*. The whole of the digestive juices except the succus entericus are cut off from these faeces.

The results were tolerably concordant. Both within the ring of intestine, and in the faeces of the fasting dog with fistula of the gall-bladder, and also in the last part of the bowel of dogs with a preternatural anus, *i.e.* cut off from the digestive processes, they found on section masses that were partly fluid, partly of a soft consistency, composed principally of epithelial detritus with innumerable hosts of bacteria. According to the above authors these faecal masses must consist principally of the epithelium cells which are continually shed from the mucous membrane, and which mingle with the succus entericus, and are converted by bacterial action into structureless detritus.

It is a remarkable fact that no unmistakably epithelial structures can be recognised in the masses collected within the intestinal ring, or in the blackish faeces formed during fasting by dogs with fistula of the gall-bladder. Ehrenthal ascribes this to the fact that in the first case the bacteria (which increase enormously within the closed ring), and in the second case the pancreatic juice poured out into the intestine, digest the detached epithelial cells, and convert them into formless detritus. In the faecal masses formed in the last part of the bowel in dogs with a preternatural anus, the microscope, on the contrary, shows not a few well-preserved epithelial cells, perhaps because they can be expelled by the natural anus before undergoing complete bacterial disintegration.

Ehrenthal and Blitstein concluded from these researches as a whole (conformably with the opinion already expressed by Heidenhain), that the chief mass of the faeces formed under the above experimental conditions is derived less from concentrated secretions of the intestine than from the detached and disintegrated epithelia of the mucous membrane.

Berenstein's subsequent work tended to correct this opinion. He modified the method of research, experimenting with short isolated segments of intestine, and also with the isolated Thiry-Vella loop, and disinfected the isolated segments of the gut more

carefully, in order to restrict the action of the bacteria and cocci which develop to such an enormous extent with the method of the intestinal ring. Even under these conditions, in which the intestine was not abnormally excited, he found that a slight epithelial regeneration took place, but he concluded that a large proportion of the excrements must under all circumstances be formed, according to Hermann's original opinion, from the excretory products of the intestinal mucosa.

Fritz Voit (1892) supported the same conclusion. He observed that in a short isolated tract of intestine (35 cm. long) it was possible in 3 weeks to obtain 14-20 grms. faeces (about 0·6-1·0 grm. per diem).

We can hardly suppose that the chief part of such a large mass can consist of shed and disintegrated epithelium. It represents, indeed, about $\frac{2}{3}$ the amount of epidermis and hair which the dog (according to C. Voit) loses daily from the entire surface of the cutis. On the other hand, this conspicuous loss of substance from the bowel is readily explained on the assumption that it depends essentially upon secretory processes, and that epithelial desquamation plays a minor part.

In a careful series of new and more minute researches and comparisons Fr. Voit confirms the fundamental facts put forward by C. Voit, Fr. Müller, and Hermann, *i.e.* that in an ordinary diet without excess of nitrogen, a considerable part of the faeces, and on a flesh diet almost the whole mass, consists of the same excretory products as are poured out in fasting, and are to a certain extent increased with alimentation.

The larger digestive glands, *i.e.* the liver and the pancreas, take hardly any part in the formation of the faeces. C. Voit in fact found that in dogs with a fistula of the gall-bladder, the flesh or mixed diet daily results in almost the same amount of faeces as appeared on the same diet before the fistula was established, showing that the bile is almost entirely reabsorbed, and takes only a small share in the formation of the faeces.

Fr. Voit's work shows that the formation of faeces is a physiological function almost exclusively confined to the small intestine. On comparing the faeces formed in a short isolated segment of intestine with those formed in the remainder of the bowel in the same dog, he found that approximately the same amount of faeces was obtained per unit of intestinal surface, which leads one to suppose that not only the bile, but also the pancreatic, gastric, and salivary secretions are for the most part reabsorbed. The intestine, besides its *digestive* and *absorbing* functions, has thus an *excretory* function, *i.e.* it is one of the channels by which the waste products of the body are eliminated. That this last function is of no little importance may be gathered from the fact that a dog of 30 kilos. body-weight is capable, during starvation, of

forming daily 1·4-5 grms. faecal matter, consisting largely of katabolites eliminated by the intestinal crypts.

Fritz Voit's results further show that the nitrogen of the faeces formed during a moderate flesh diet comes, not from the alimentary residues, but almost exclusively from the intestinal secretions. The ash of the ingested flesh, on the contrary, is not completely absorbed, and partially mixes with the faeces. Lastly, he finds that along with the waste nitrogenous products and a moderate quantity of salts, the isolated intestine also excretes a not inconsiderable amount of fatty substances, which constantly appear in the faeces.

Fritz Voit also attempted to solve the problem of the absorption and elimination of *lime* and *iron*. It is known that for adults the quantity of *lime* introduced with the food is usually in excess of what is required to maintain the calcium-balance in the body. The question then arises as to whether the excess of lime is absorbed or not, and if it is eliminated by the kidneys or by the intestine.

The experiments made on dogs show that with a normal mixed diet, particularly when rich in calcium, the greater part of the lime salts present in the faeces come directly from the food. A certain proportion of the calcium salts eliminated from the body are, however, secreted in the intestinal tube, as shown by the calcium content of the faeces in fasting. This secretion of lime in an isolated segment of intestine increases somewhat with feeding; but the increment is very slight, even on a diet rich in calcium. In this case the lime salts excreted with the urine also increase in a moderate degree, which leads us to the conclusion that most of the excess lime introduced is not absorbed, but mixes with, and is eliminated in, the faeces.

As regards the absorption and elimination of *iron*, the results of experiment lead us to conclude that its absorption in the digestive canal is small; that what is absorbed is eliminated to a small extent by the kidneys, more by the intestine, least by the liver; that, lastly, the small amount of iron eliminated with the bile is mainly reabsorbed by the intestine.

Since little of the iron of the food is absorbed, the amount excreted by the intestine and mixed with the faeces is also small (a few milligrammes only). Most of the iron found in the faeces comes directly from the food.

IV. Other interesting contributions to the theory of the excretory function of the intestine were published from the Institute of Hygiene at Prague by Prausnitz, Moeller, and Kermauner (1897).

From a series of careful microscopic investigations of human faeces during an ordinary mixed diet, Moeller concluded that, given a perfectly healthy condition of the digestive apparatus,

the *starch* introduced with the cereals or other important vegetable food is completely digested and absorbed.

Starch is never found in the faeces on feeding with wheat, rye, or wholemeal bread, or with rice, potato, or pulse. It only occurs when fresh vegetables, salad, and leguminous products cooked whole are ingested; or in the faeces of diarrhoea, when the digestive apparatus is not able to perform its normal functions. The cell-membranes, which consist of cellulose, are less digested in proportion as they are thicker and harder: and these protect the starch, protein, and fat from the action of the digestive juices. The thin walls of the cell, on the contrary, can be dissolved by the digestive juices. In any case, the amount of starch, protein, and fat which escape the action of the digestive juices, owing to the enclosing cellulose membrane, and are found undigested in the faeces, is extremely small on an ordinary diet, since salad and fresh vegetables do not usually form the staple food, but only supplement it, cereals being ingested only after they have been ground and converted into bread or farinaceous foods.

Kermauner studied the amount of undigested residues of *meat* found in the faeces with a full flesh diet. Nearly every one agrees that the faeces of normal individuals constantly contain more or less modified muscle fibres, in an amount that varies with the quantity of meat ingested. The residues of meat found in the faeces are thus not confined to indigestible parts, such as elastic fibres, tendon, and cartilage, but also include a certain quantity of undigested muscle. Kermauner shows, however, that the total amount of these substances, under normal conditions of digestion, is always very small, and seldom exceeds 1 per cent of the meat ingested. In an ordinary mixed diet, therefore, the non-digested food residues are a negligible quantity. The same may practically be stated for man, as was determined by Voit for the dog, *i.e.* that in a strict flesh diet no food residues occur in the faeces, the meat being almost entirely digested and assimilated.

From the physiological and hygienic standpoint, the *chemical investigation of human faeces* methodically undertaken by Prausnitz is more important. He attempted to ascertain the variations in percentage composition of the content of nitrogen, ethereal extracts (fats), and ash constituents, on different diets.

In five normal individuals (two doctors, a medical student, and two laboratory servants) he analysed the faeces formed during an exclusively vegetable or mainly animal diet, both represented by foods that can be almost entirely absorbed (meat, rice, fine wheat, bread, butter). The values obtained were then compared with the faecal analysis of a vegetarian.

The following table sums up the results:—

No. of Experiment.	Chief Ingredient of Diet.	Nitrogen.	Ethereal Extract.	Ash.	Subject.
		Per cent.	Per cent.	Per cent.	
1	Rice.	8·83	12·43	15·37	1st Doctor.
2	Meat.	8·75	15·96	14·74	
3	Rice.	8·37	18·23	11·05	Student.
4	Meat.	9·16	16·04	12·22	
5	Rice.	8·59	15·89	12·58	2nd Doctor.
6	Meat.	8·48	17·52	13·13	
7	Rice.	8·25	—	14·47	1st Servant.
8	Meat.	8·16	—	15·20	
9	Rice.	8·70	—	16·09	2nd Servant.
10	Meat.	9·05	—	15·14	
11	Rice.	8·78	18·64	12·01	Vegetarian.

As these figures show, the percentages of nitrogen, of ethereal extract, and of ash constituents vary within narrow limits, independent of the nature of the diet. This appears both from the five individuals accustomed to an ordinary mixed diet, and from the vegetarian who had been nourished for many years on vegetable foods only (*plus* milk, eggs, and butter).

Seeing that in all these individuals the nitrogen content of the faeces oscillates between 8 and 9 per cent, both on an exclusively vegetable diet (rice and fine wheat bread) which only contain about 1·5 per cent nitrogen, and when a comparatively large amount of meat was added in which the percentage of nitrogen is much higher, we have a new argument in support of the theory of Voit and his school, to the effect that *normal faeces consist almost exclusively of katabolic products from the intestine.*

Prausnitz gives the name of *normal* faeces exclusively to those obtained on a diet of substances which can be almost completely digested and assimilated, and in which the percentage of nitrogen fluctuates between 8 and 9 per cent. When less readily absorbable vegetable foods are ingested, the percentage of nitrogen in the faeces falls considerably (to 4·3 per cent), in proportion with the amount of non-digested alimentary residues present. In a few rare cases the percentage of nitrogen may increase, as occurs on feeding substances which are not very absorbable, and which contain a large amount of nitrogen.

Accordingly, the composition of the faeces is never in ratio with that of the diet. Even on a diet which is badly digested and ill absorbed, the faeces formed always (in consequence of the excretion of large amounts of intestinal juice, which mixes with the alimentary residues) contain a relatively large amount of nitrogen in comparison with that of the food ingested. In the apparent exceptions to this rule, the relatively low nitrogen content of the faeces depends on the relatively high content of

ash constituents and other non-nitrogenous substances (ethereal extracts).

The final conclusions arrived at by Prausnitz may be summed up as follows:—

(*a*) There is no fundamental difference between plant and animal foods as regards their utility in the human intestine. Assimilation and absorption depend rather on their preparation (cooking, trituration) than on their animal or vegetable origin.

(*b*) The foods best utilised or absorbed are those of vegetable origin (rice, white bread or other preparations of finely ground flour), only small traces of which are found in the faeces. With the most profitable animal food, on the contrary, *e.g.* meat, undigested residues are always found in the faeces, although in small quantities only. Milk and cheese give more copious faeces, which are relatively poorer in nitrogen as compared with meat, because they yield a larger amount of mineral residues.

(*c*) Human faeces, with few exceptions, consist chiefly not of alimentary residues, but of the excretory products of the intestine.

(*d*) The quantity of faeces depends principally on the nature of the food, some kinds requiring more succus entericus for their digestion than others. It seems, therefore, more accurate to differentiate the foods into those which cause the production of much or little faeces than to speak of foods which can be more or less assimilated.

V. Stich (1853) was the first who directed attention to the fact that faecal matters contain substances which have a toxic action on the living body. He saw that if excreta were introduced per os or per rectum from one animal into another of a different species, more or less serious symptoms of intoxication set in. From the fact that the toxic substances which habitually accumulate in the alimentary canal are normally innocuous to the animals which manufacture them, he was led to think that each kind of animal has the power of destroying the toxins which it produces. He assigned a predominating importance to the protective action of the epithelium in resistance to auto-intoxications of intestinal origin (cf. also Chapter V. § 14). But the other facts we have discussed show that this protective function is at any rate shared by the liver, which arrests or converts not a few of the poisons absorbed by the roots of the portal system.

Without entirely rejecting the *protective function* of the intestinal epithelium in Stich's sense, its *excretory function, i.e.* the fact that by its means many katabolic products are eliminated from the blood and mix with the faeces and gases of the intestine, is certainly admitted by almost every doctor. This theory is based on a number of suggestive observations, both clinical and experimental, some of which attracted the attention of Bouchard. It is a fact

that persons who frequent anatomical theatres or dissecting-rooms emit foetid faeces and effluvia which have the putrid odour of corpses. Many physicians in ancient and modern times have considered the *intestinal catharsis* by which the faeces become diarrhoeic, either from natural causes or from the use of purgatives, as a salutary function, *i.e.* an excretory process which frees the blood from toxic waste products. "Des personnes," says Bouchard, "qui avaient vécu pendant des années avec la diarrhée en conservant les apparences d'une santé parfaite ont vu disparaître en même temps leur diarrhée et leur santé." It is certain that the unquestionable therapeutic value of purgative waters can only be explained on the assumption that they excite the excretory functions of the intestine, on which the katabolic products accumulated in the tissues and blood are rapidly expelled through the mucous membrane of the intestine.

The toxicity of faecal extracts can easily be demonstrated by intravenous injection. An aqueous extract of faeces injected into the veins of a rabbit causes exhaustion, diarrhoea, and other serious symptoms premonitory of death. An alcoholic extract is toxic even in small doses. According to Bouchard, alcoholic extract of 17 grms. faeces causes the death of the rabbit with strong convulsions.

These experiments were repeated and more exactly described by Arloing and Nicolas, with both aqueous and alcoholic faecal extracts injected into the jugular vein of rabbits. The toxicity of these extracts varies; but the alcoholic is always twice as toxic as the watery extract. The principal symptoms of intoxication are convulsions, diarrhoea, hypothermia. Death sometimes occurs rapidly, at other times slowly, sometimes after several days. In the last case the animals become feverish

We do not know to what substances the toxicity of the faeces is due. In 1882 Bouchard extracted from the faeces substances which exhibit characters common to the alkaloids (*Selmi's ptomaines*). Some of these were soluble in ether, others in alcohol. He failed, however, to extract a sufficient quantity to produce intoxication of the animal. In one case he succeeded in extracting 15 grms. per kilo. faecal matter. He regarded the alkaloids of the faeces as the source of all the alkaloids in the body, and assumed a certain parallelism between the alkaloids of the faeces and those of the urine, in which, however, they are always present in a less amount. If these data had been confirmed they would have been of great importance; but later analysis carried out by accurate technical methods gave only negative results. Selmi's ptomaines were absent not only in normal urine and faeces, but also in the excreta of various diseases, excepting typhus, cholera, dysentery—diseases due to specific bacteria, which develop toxic alkaloids as products of their metabolism.

Halliburton noted that *choline*, one of the toxic alkaloids of animal origin, is decomposed by the intestinal bacteria into simpler innocuous products. He therefore thinks it probable that if other alkaloids are normally formed in the intestine by bacterial action they are at once broken up, like choline, by other bacteria, or even by those which produced them.

Bouchard, in explanation of the toxicity of faecal extracts, gives a predominating importance to the salts of ammonia and potash. He found that on eliminating these salts from the alcoholic extracts by means of tartaric acid, the toxicity of the latter disappears to a very marked extent. It is also certain that the stercobilin formed from the bile pigments, which is soluble in alcohol, must contribute to the toxicity of the alcoholic extracts. Probably, however, many other waste products of the body which are soluble in alcohol, and have not yet been chemically differentiated, contribute to the toxicity of the faeces.

In fact this question, which is of great importance from the clinical point of view, has hardly been attacked at present. Future research must be directed towards determining not only the chemical nature of the various substances that co-operate in the toxicity of the faeces, but also their possible origin, *i.e.* whether they are derived partly from alimentary residues, partly from the metabolites of the body, or partly again from the toxins excreted by the intestinal bacteria. We must confine ourselves to indicating this possible threefold origin, without positive data as to which of the three sources supplies most of the normal toxic products of the faeces.

Nor can we decide how far the excretory function of the intestine is able to replace functional insufficiency of the kidneys. Clinically we know that diarrhoea induced by strong purgatives can diminish the toxicity of the urine, which means that part of the toxic waste products normally eliminated by the kidneys may be expelled with the water discharged from the surface of the intestine (Bouchard). The urinary constituents excreted by the intestine do not consist mainly of *urea*—which is the most important component of urine. According to Bouchard the intestinal epithelium exerts no selective action on urea, which is only excreted in the same proportions in which it is present in the blood. Urea, however, is the least toxic substance of the urine, perhaps because it has a pronounced diuretic action. To explain the reduced toxicity of the urine after drastic purgatives, it is therefore necessary to assume that other extractives of the blood, which have a more toxic action than urea, may be excreted by the intestines.

A striking clinical phenomenon in reference to this excretory function of the intestine, as a coadjuvant and vicarious agent for the much more pronounced action of the kidneys, is exhibited in

the prolonged *oliguria* and *anuria* which sometimes accompany the course of those complex and uncertain forms of nerve diseases known under the generic name of *hysterical neuroses.*

After two cases imperfectly described by Laycock (1838), Charcot (1872) gave a good description of a case in which long periods of total or quasi-total suspension of the renal functions were accompanied by sickness, urea and other urinary substances being vomited. Still more classical and important, owing to the accessory phenomena, are two cases of *hysterical anuria* described by Rossoni (1885), which may be briefly summarised.

In a hysterical youth of 21 the periods of anuria occurred irregularly, and differed in duration; there were brief periods perfectly tolerated by the body, and long periods (up to 22 days) with slight disturbances (some headache, malaise, worry, nausea, but complete absence of vomiting). The periods of anuria could always be cut short by pilocarpine, which, besides considerable sweating and flow of saliva containing urea, induced a comparatively abundant secretion of urine. The exhibition for experimental purposes of 12 grms. urea during the anuria produced an uraemic attack, which gave way to the subcutaneous injection of 0·02 grm. pilocarpine hydrochlorate. During the disease the diet was very scanty, with little nitrogenous food (fruit, dressed vegetables, farinaceous preparations). The patient was kept altogether in bed with complete rest. There was constant constipation from intestinal paresis. The faeces were removed every two or three days by enemata, in amounts varying from 150 to 250 grms. (No chemical examination was made of the faeces.) For twelve days there was acute fever (from 38·8° to 40·7° C.), after which it subsided; but the temperature for months was above 38° C.

After about 8 years this patient was suddenly, so to speak "miraculously," cured of all hysterical phenomena, including the periods of anuria or oliguria, in consequence of a strong joyful emotion.

Another youth of 18 became hysterical after a sudden psychical shock. Violent convulsive attacks, with obstinate nasal and gastric haemorrhage, were followed by ischuria, which in turn was succeeded by irregular periods of oliguria and complete anuria, usually accompanied by vomiting of a fluid which had all the physical and chemical properties of normal human urine. At other times, however, the period of anuria ran its course without grave symptoms (headache, peripheral disturbances of circulation, slight tremor of extremities), and without vomiting as a substitute for the suspended functions of the kidneys. During the illness there was an interval of 50-60 days, in which the periods of total anuria were not accompanied by vomiting. In this patient the administration of pilocarpine during anuria produced sweating and

salivation, but never started the urinary secretion as in the first hysteric. Hypodermic injection of 15 grms. urea, during absence of vomiting and persistent anuria, produced a violent attack of convulsions with subsequent tetany and coma, which gradually gave way under a flow of saliva containing urea and sweating promoted by pilocarpine. On the other hand, an injection of 14 grms. urea during a period in which abundant vomiting accompanied the anuria produced no disturbance. The daily diet was restricted, and the patient was kept entirely in bed.

Since the tendency of hysterical patients to simulate extraordinary phenomena is well known, Rossoni (in order to obtain an unexceptionable proof of the long periods of total anuria) requested the surgeon Crespi to perform a perfect ureterorrhaphy during a period of anuria. After seven days there was complete cicatrisation, with perfect occlusion of the urethral meatus. On the 20th day after the operation, since the patient did not complain of any particular trouble, the urethra was reopened in presence of several well-known Roman doctors, and it was shown by means of a catheter that the bladder did not contain a single drop of urine. A large rubber syringe was kept permanently in the bladder for 10 more days, during the whole of which time it was not possible to obtain any urinary secretion.

These two clinical cases have a double interest for physiologists: (*a*) because they afford a new objective proof of the excretory function of the entire gastro-intestinal system with its glands, as a substitute for the normally more important function of the kidneys; (*b*) because they demonstrate the astonishing fact of a total and prolonged suspension of the renal secretion owing to simple nervous causes.

Leaving to Chapter VIII. the critical examination of the second phenomenon (which is certainly the most important) we will here confine ourselves to the first point.

To begin with, we must note with Rossoni that clinical observation does not confirm Charcot's statement that prolonged anuria, as observed at irregular periods in hysterical subjects, must be accompanied by urinous vomiting in order to avert uraemic attacks, and to be compatible with life without grave functional disturbances. In the first case vomiting *never* occurred during the repeated and prolonged attacks of anuria; in the second there were periods of anuria with vomiting and urinous salivation, which were evidently substitutive for the function of the kidneys, but long periods of anuria without vomiting and with mild disturbances were not wanting. When the anuria is accompanied by vomiting, the entire gastro-intestinal canal with its glands (the salivary glands included) takes an active part in the vicarious excretory function; but when vomiting is absent, we must logically conclude that the lapse of acute uraemic

symptoms during the anuria is more particularly due to the vicarious action of the entire intestinal tract. Although direct evidence for this is wanting (since the faeces were not examined chemically for urinous products) it seems from the physiological point of view to be incontestable. Rossoni, to account for the absence of acute uraemic phenomena during the anuria without vomiting, invokes the extreme slowness of metabolism in the two hysterical patients. There is not, however, the slightest proof of this, and even if it were proved, it would at most explain the oliguria and not the prolonged periods of total anuria.

Rossoni's statement, that injections of pilocarpine were always able in the first subject to interrupt the anuria by reactivating the renal function and improving the general state of the patient, while in the second they only promoted the vicarious functions of the skin and salivary glands, is interesting. But according to what we stated in Chapter IV., the pilocarpine, both in the first and the second subject, must have activated the secretion of all the glands connected with the gastro-intestinal canal, particularly the liver and the crypts of Lieberkühn, from which it is probable that the most highly toxic products poured out into the blood from the tissues were eliminated by the intestine, during the total suspension of renal secretion.

Since the innocuous character of injections of urea, when the kidneys are functioning normally, is well known (Chapter VII., pp. 411, 413), the fact which Rossoni observed is very interesting, *i.e.* that the administration of 12 grms. urea during anuria caused a uraemic attack, due no doubt to a sudden rise in the osmotic pressure of the blood. In the second hysterical patient, hypodermic injection of 15 grms. urea during the anuria without vomiting produced the same effect, while a second dose of 14 grms. urea was tolerated without toxic symptoms, because it was given during the anuria accompanied by abundant urinous vomiting, *i.e.* when the patient was urinating not by the kidneys, but by the stomach.

VI. The complex task of the intestinal apparatus, as expressed in the triple function of *digestion*, *absorption*, and *excretion* or *formation of faeces*, ends with the mechanical process of *defaecation*. It is generally assumed for man that the intestinal chyme remains in the majority of cases for about 4 hours in the small intestine, and about 22 hours in the large bowel (Nothnagel). The peristaltic movements which drive it onwards become progressively slower in proportion as it descends into the lower parts of the small intestine. Along with this delay there is a constantly increasing condensation of the intestinal contents, in consequence of the absorption of water, and of the absorbable constituents of the chyme. In proportion as the contents of the intestine assume

a firmer consistency, their colour, odour, and external characters approximate to those of the faeces.

On reaching the lower end of the ileum, the substances which have accumulated and escaped absorption, are forced on by the peristaltic movements through the cleft of the ileocaecal valve, and pass into the large bowel. The lips of this cleft lie transverse to the caecum, and are so arranged that the distension of

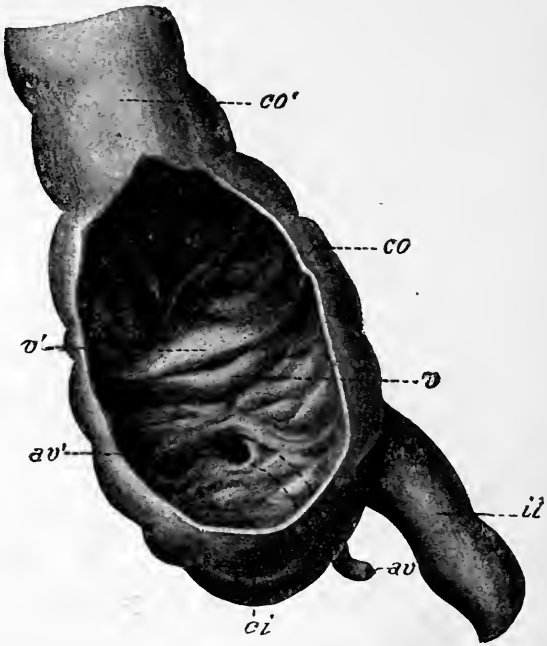


FIG. 102.—The caecum in connection with the ileum and colon. (Luciani.) The anterior external wall of the caecum has been cut away to show the cleft and labra of the ileo-caecal valve, with the orifice of the vermiform appendix. *ci*, fundus of caecum; *av*, vermiform appendix; *av'*, its opening into the cavity of the caecum; *il*, last tract of ileum; *v* and *v'*, lower and upper labra, which circumscribe the cleft of the ileo-caecal valve; *co* and *co'*, first and second segment of ascending colon.

the caecum brings them together in the position of closure (Fig. 102). The watertight closure of the ileocaecal valve becomes still more perfect when the peristaltic movements of the large intestine begin in the fundus of the caecum. The content of the caecum is then voided into the colon without any possibility of reflux of faecal matter into the ileum, because the increase of intracaecal pressure applies the lips of the valve still more firmly together. This passage of the excreta from the small into the large intestine has been regarded by some (Viault and Jolyet) as a first, *internal defaecation*, in which the faeces, freed from all useful constituents (like the exhausted residues on a filter) pass

from the digesting part of the intestine into the large bowel, which acts as a sort of reservoir, while the valves hinder any reflux that might disturb the digestive processes still going on throughout the small intestine. However acceptable this theory may be from the mechanical point of view, it is less valid for the chemist. The digestive processes effected by the juices with which the faeces are saturated can go on in the large intestine also. In fact, the fermentative and putrefactive processes set up by the intestinal bacteria are continued, and even reach their maximal development, in the large bowel. For while the contents of the ileum are slightly alkaline, neutral, or faintly acid, the reaction of the large intestine in carnivora, and in man, is always decidedly acid. This depends not on any acid property of the secretion of the mucous membrane of the large bowel, but upon the acid fermentation developed in its contents, as proved by the development of methane and hydrogen which, as we have seen, is conspicuous in the large intestine. We know, on the other hand, that although the large intestine is provided along its entire length, from the vermiform appendix to the anus, with innumerable crypts (see Fig. 44, p. 125) its secretion is alkaline, and rich in mucin, with no constituent capable of acting chemically upon the three main groups of food-stuffs. All the chemical changes in the large intestine (with the exception of such as may be due to the enzymes from the small intestine, before the acidity of the medium arrests their activity) must therefore be caused by the intestinal bacteria.

In all probability the chemical changes that take place in the large intestine are unimportant in the carnivora and in man, but they have an enormous importance in the herbivorous rodents, and for solipeds, in which the caecum is much larger than the stomach. The contents of the caecum in the horse and in ruminants, unlike those of the carnivora and of man, are always very abundant; not acid, as stated by Tiedemann, Gmelin, and others, but always decidedly alkaline, even (according to numerous observations of Colin) more strongly alkaline than the contents of the different parts of the small intestine and the entire colon, where the reaction becomes gradually acid owing to the fermentation which gives rise to formation of lactic, butyric, and other fatty acids. According to Colin, the alkaline fluid which saturates the contents of the caecum is derived principally from the mixture of digestive secretions poured out into the small intestine, and only to a minimal extent from the mucous secretion of the crypts of the caecum. Since the incompletely digested food-stuffs remain for a long time in the caecum, it is evident that the digestive processes initiated in the small intestine must be continued there.

Colin's logical conclusion was experimentally confirmed by Paladino (1875), who demonstrated in a series of researches into

the caecal digestion of the horse, that the fluid collected from the caecum of this animal exerted a marked digestive action on food-stuffs (starch, proteins, oats, vegetables) either *in vitro*, or when introduced into the cavity of the caecum through an artificial anus (at the point of the caecum) by the help of which the successive changes could be examined.

Ellenberger and Hofmeister (1881) confirmed the alkalinity of the caecal juice and its capacity of digesting both starch and cellulose, with evolution of gas. They also found a small quantity of peptone in the contents of the caecum, while none was present in the colon or rectum. It is probable that part at least of this peptone is formed *in situ*, and that the caecal juice has also the power of digesting protein.

It was, however, shown by Bergman and Hultgren (1903) that the caecum was not a vital organ even in herbivora. After cutting out the whole of the caecal tract from the remainder of the intestine in adult rabbits, they made quantitative investigations of alimentary absorption, as compared with what took place in normal, control animals. Although they came to no definite conclusion as to the importance of the caecum in the digestion and absorption of *cellulose*, their researches indicate that the capacity for assimilating other food-stuffs was unaltered. Nothing abnormal was noted in rabbits deprived of their caecum, except a diminished capacity for ingesting large quantities of food, which did not, however, interfere with their general health.

Apart from the digestive processes carried on in the caecum of herbivora by means almost exclusively of the juices secreted in the small intestine, it is certain that the principal function of the caecum (and, generally speaking, of the whole large intestine) is, not only in these animals but also in carnivora and in man, to act as a reservoir for the faecal masses, so that a large part of the water and nutrient matters which they contain may be absorbed and utilised.

This fact was especially brought out by the work of Marcacci (1888). He tied or excised the caecum in various animals (dogs, rabbits, sheep, fowls), after which he observed disorders of defaecation with emission of liquid faeces, containing dextrose and sometimes a trace of peptones, when the animals were allowed as much water as they pleased with their food.

Berlatzky (1902) established a fistula of the caecum in dogs, separating it from the large intestine and uniting its orifice with the abdominal walls. He saw that a minimal secretion took place during fasting, which increased considerably after ingestion of food. The quality of the food had no influence on the amount of secretion. The caecal juice was strongly alkaline, partly fluid and partly slimy. It was incapable of digesting either fibrin or egg-albumin, and failed to activate other enzymes

(enterokinase). It did, however, contain an amylolytic ferment and Cohnheim's erepsin.

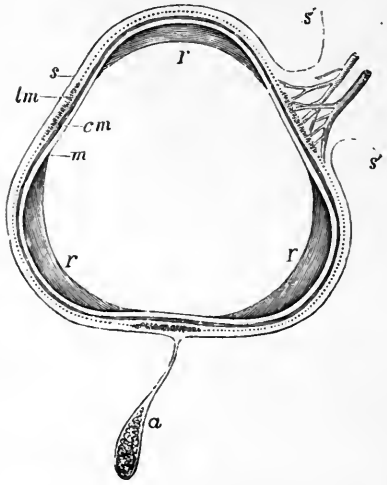
While nothing definite is known, we are justified in assuming that along with digestive functions, the fermentation and putrefaction of substances accumulated in the large intestine, and the absorption of water and of certain soluble products, the large intestine also excretes the waste products of the body, which mingle with its contents, and increase the mass of the faeces. From these products we must distinguish the *mucus*, which is by a long way the chief constituent of the secretion from the epithelial cells of the large intestine, both of the superficial cells and of those which line the numerous crypts. This mucous secretion has, as we showed elsewhere, the specific function of lubricating the external surface of the faecal balls, so as to facilitate their expulsion by the anus.

In proportion as the faecal masses are condensed by the active absorption that takes place in the large bowel, and assume a pasty, or more or less hard, consistency, absorption of the toxic substances contained in the faeces becomes more and more difficult. The phenomena of auto-intoxication are thus avoided, because under normal conditions the toxic constituents of the faeces are so slowly absorbed, that they are eliminated by the urine as fast as absorption takes place. As soon, therefore, as the faeces have attained a proper consistency, absorption ceases entirely, and the toxic matters are expelled with the faeces in defaecation (Bouchard).

VII. In man the Large Intestine with its three parts (*caecum, colon, rectum*) is 1·50-1·80 m. long, *i.e.* about one-fifth of the whole length of the intestinal canal. Its diameter is greater than that of the small intestine, and varies in the different parts from 5 to 12·5 cm. The caecum has the largest diameter, which diminishes gradually in the three segments of the colon (ascending, transverse, sigmoid), and in the rectum, except that near the end of the latter there is a well-marked dilatation (*rectal ampulla*). Like the stomach and small intestine, it has four coats (serous, muscular, submucous, and mucous), but the greater part of the large intestine (caecum, colon) differs very much from the even, cylindrical form of the small intestine, its surface being thrown into numerous sacculi. This comes from the arrangement of the longitudinal muscle fibres, which thicken in the form of three strong bands (sometimes known as the *ligamenta coli*) and are shorter than the part of the tube through which they run, so that it exhibits three series of saccular dilatations, separated by constrictions; these correspond inside the gut with three more or less prominent ridges composed of all the coats, by which the canal is thrown into sacculi (Fig. 103). This arrangement is certainly intended to delay the advance of the faecal mass along the large intestine,

and to favour absorption of the soluble substances and concentration of the faeces. Another peculiar feature of the large intestine is the so-called *appendices epiploicae*, which, however, are of little physiological importance.

In the rectum the longitudinal muscle fibres are reduced to two bundles, one anterior, the other posterior. They do not give rise to any formation of ridges and sacculi. In the rectal ampulla the mucous coat alone exhibits longitudinal folds, which are



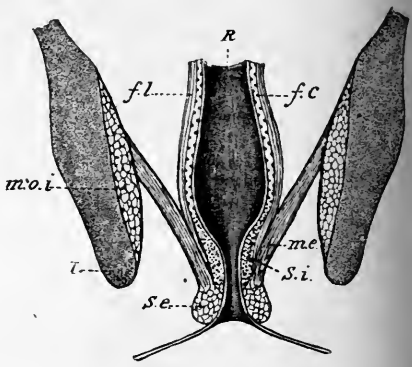


FIG. 103.—(Left.) Outline sketch of a section of the ascending colon. (Allen Thomson.) *s*, serous covering; *s'*, *s'*, reflection of this at attached border forming a short wide mesocolon between the folds of which the blood-vessels are seen passing to the colon; *a*, one of the appendices epiploicae hanging from the inner border; *lm*, indicates at free border one of the three bands formed by the thickening of the longitudinal muscular coat; the dotted line continued from the margins of these bands represents the remainder of the longitudinal muscular coat, and the thick line within it, marked *cm*, represents the circular muscular layer; *m*, the mucous membrane at the flattened part; *r*, the crescentic bands of indentations which divide the sacculi.

FIG. 104.—(Right.) Diagram of last part of rectum, with the sphincters and muscles of the anal region. (Testut.) *R*, rectum; *f.c*, circular coat; *f.l*, longitudinal coat; *Si*, internal sphincter of plain muscle; *S.e*, external sphincter of striated muscle; *m.e*, levator ani; *m.o.i*, obturatorius internus; *I*, os ischiadicum.

obliterated when it is distended by the faecal masses. At the level of the anal canal, the longitudinal fibres completely surround the rectum, and the circular fibres thicken and form the so-called internal sphincter. At the end of this layer of plain muscle a firm ring of striated muscle forms the external sphincter. Beyond this last is another striated muscle, the levator ani, which forms a sort of diaphragm, the concavity being turned upward and forward (Fig. 104).

With these anatomical premises, it is easy to understand the mechanism of defaecation, which, as distinguished from that which takes place through the ileocaecal valve, may be termed

external defaecation. It is preceded by peristaltic movements of the muscles of the large bowel, which differ from those of the small in being slower and less vigorous, the muscles of the large intestine being comparatively scanty in comparison with the diameter of the canal, which far exceeds that of the small intestine. The three longitudinal bands must shorten the canal in contracting, and compress the sacculi, thus facilitating the propulsion of the faecal masses from one saccule to another. While one of these empties itself by the combined contraction of the circular and the longitudinal fibres, the next dilates by the relaxation of its muscles, and fills with the faecal masses expelled from the preceding.

The mechanism of the movements of the large intestine corresponds on the whole with that of the small intestine, as shown by Bayliss and Starling (1900-1), who extended their earlier work (see p. 240 *et seq.*) on the small to the large bowel. But while antiperistaltic movements are, as we have seen, the exception in the small intestine, Cannon's experiments (1901) with the Röntgen rays show that they occur normally in the large bowel.

The peristalsis of the large bowel is not a continuation of that of the small; while the latter ceases at the ileocaecal valve, the former commences at the fundus of the caecum and extends from the caecum to the colon, till it reaches the end of the sigmoid flexure, where the faeces are supported by the bladder and sacrum.

O'Beirne of Dublin (1833) was the first to state on the strength of numerous observations that under normal conditions, *i.e.* when they attain a certain degree of consistency, the faeces remain in the sigmoid colon, and do not descend into the rectum during the interval between one evacuation and the next. It is a fact that on digital exploration of the rectum, even at the moment that precedes evacuation, *i.e.* when the subject feels the need to defaecate, the rectal ampulla is empty, and the exploring finger is seldom smirched. Even after an operation for anal fistula in which the sphincters are divided, the patient can usually retain the faeces during the interval between two evacuations. These observations show that the faeces normally stay in the sigmoid colon, supported by the bladder and sacrum, and only descend into the rectum when the excessive accumulation of the faeces, and the pressure these exert upon the walls of the colon, arouse the need of defaecating, and reflexly exaggerate the peristaltic movements of the large bowel.

After the faecal mass has descended into the rectum, the mechanical excitation of its sensory nerves still further increases the desire to defaecate.

Defaecation can be inhibited for a certain time by voluntary contraction of the external sphincter and the levator ani. By this mechanism it is sometimes possible to postpone the act for

a while, probably because the faeces which have descended into the rectum are partly pushed back into the colon by the action of these muscles. But when the tension of the walls of the colon and rectum exceeds certain limits, this voluntary mechanism not only fails to remove the sensation of desire but even increases it, by reflexly promoting the active movements of the lower part of the rectum, which makes the need to defaecate more urgent, and aids evacuation where it is sluggish.

A spurious desire to defaecate may be aroused by pressure exerted *ab extrinseco* on the walls of the rectum from a large calculus in the bladder, a tumour of the prostate, or the presence of the head of the foetus in the pelvis. The same effect may be produced by internal haemorrhoids, or an inflammation of the rectal mucosa such as is commonly associated with dysentery. The term *tenesmus* is employed in medicine for this spurious desire to evacuate.

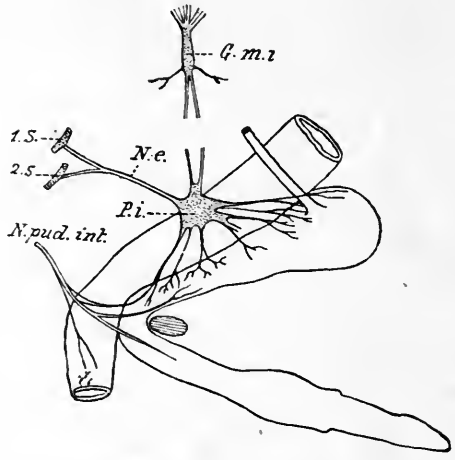


FIG. 105.—Schema of dog's hypogastric plexus, with afferent nerves, and efferent nerves to rectum, anus, and bladder. (François-Franck.) *G.m.i*, inferior mesenteric ganglion; *N.e*, nervous erigens from *1* and *2* sacral nerves (*1S*, *2S*); *N. pud.int*, nervous pudendus internus; *P.i*, hypogastric plexus, which with the nervous pudendus innervates the rectum, anus, and bladder.

Three mechanical factors normally co-operate in the act of defaecation: (*a*) active peristalsis of the muscles of the sigmoid colon and rectum; (*b*) inhibition of the tone of the sphincters, aided by the contraction of the levator ani; (*c*) active intervention of abdominal compression, by contraction of the diaphragm and forcible and prolonged contraction of the abdominal muscles with closure of the glottis. The association, succession, and co-ordination of these factors varies in different cases, according as there is a tendency to diarrhoea or to constipation.

It is certain that of the three mechanical factors which thus take part in the act of defaecation, the first is the most essential. In fact (as we shall see), under certain experimental or pathological conditions the entire process of evacuation may take place as a pure reflex, independent of any active intervention of the voluntary muscles.

VIII. The nerves of the large, like those of the small, intestine come from the cerebrospinal and from the sympathetic

system. The former are branches of the lumbar and sacral nerves, the latter of the inferior mesenteric plexus and the hypogastric plexus (see Fig. 83, p. 247). The sensory fibres from this last plexus cause the excessive sensibility of the mucous membrane of the rectum and anus, and its motor fibres discharge the movements of defaecation. The hypogastric rami from the lumbar cord run in the same plexus after traversing the inferior mesenteric plexus, along with the fibres from the anterior roots of the first and second sacral nerves, which under the name of the nervus erigens (Eckhard) innervate the corpora cavernosa, and give off the nervus pudendus, from which the haemorrhoidal rami run to the sphincters of the anus (Figs. 105 and 106).

The closure of the ileocaecal valve is also effected by nervous action (Katz and Winkler, 1902). Stimulation of the central end of the sciatic relaxes the closed valve, or brings it to, if previously open. Stimulation of the vagus usually produces closure of the splanchnic opening. The nervi erigentes and the hypogastrics are ineffective, so that its innervation again shows the ileocaecal valve to belong to the small intestine.

The question already discussed in Chapter IV. (p. 265 *et seq.*) as to the simultaneous or alternate action of the longitudinal or circular fibres of the small intestine, comes up again in relation to the muscles of the colon and rectum. Certain experimenters (Courtade and Guyon, 1897) stated that electrical stimulation of the *sympathetic rami* in the dog produces contraction of the circular fibres of the colon, rectum, and anus, and inhibits the contraction of the longitudinal fibres; *vice versa*, stimulation of the *sacral nerves* contracts the longitudinal and inhibits the circular fibres, including those of the sphincter. There would thus be a functional antagonism between the two orders of nerves. On the other hand, Langley and Anderson (1895-96), experimenting on the rabbit, state that stimulation of the sacral nerves throws both longitudinal and circular muscles into contraction, while stimula-

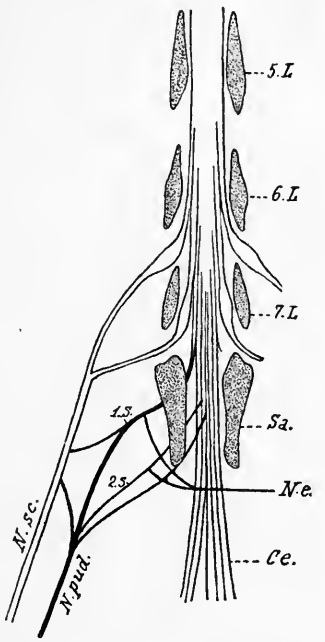


FIG. 106.—Schema of nerves which arise (in dog) from last part of lumbar cord, and in sacral cord. (François-Franck.) *Sa*, os sacrum; *5L*, *6L*, *7L*, lumbar vertebrae; *N.sc*, sciatic nerve; *N. e*, nervous erigens from *1* and *2* sacral nerves (*1S*, *2S*); *N. p*, nervous pudendus; *C. e*, cauda equina.

tion of the sympathetic rami sometimes produces a brief contraction, but as its principal effect causes inhibition of all the movements of the last part of the gut. The action of the sacral and sympathetic fibres on the colon, rectum, and anus would thus be analogous to that exerted by the vagus and splanchnics on the rest of the stomach and intestines. It is an open question, left for further investigation to decide.

The tonic contraction habitual to the sphincters of the anus is due, in part at least, to the action of a nervous centre situated in the lumbar segment of the cord. According to Budge and Masius (1868) this *ano-spinal* centre is localised in dogs in the tract corresponding with the level of the fifth lumbar vertebra, in rabbits, on the other hand, in the tract between the sixth and seventh lumbar vertebrae. If in these animals the cord be divided below the ano-spinal centre, or if in rabbits the abdominal aorta be compressed for a long period (Gaglio), relaxation of the sphincters follows. If, on the contrary, the cord be cut above the level of this centre, the sphincters regain their normal tonicity as soon as the inhibitory effect of the operation has passed off.

More recently, however, Goltz and Ewald (1895) observed in dogs deprived of the whole of the lumbar-sacral cord that the phenomenon of incontinence of faeces disappears after some months, and the anal sphincters regain their normal function. The sympathetic ganglia can thus regulate the tone of the sphincters independently of the ano-spinal centre. In fact, after the destruction of the spinal centre, Courtade and Guyon (1897), and subsequently Frankl-Hochwart (1900), saw that centripetal excitation of the hypogastric rami, which give off sensory fibres to the ano-rectal mucous membrane, can produce reflex contraction of the sphincters. The reflex ceases after destruction of the inferior mesenteric plexus. The central station of the reflex therefore lies in this plexus, since all relation of the latter with the spinal centre has previously been abolished.

The sphincters are also capable, after some months, of regaining their natural tone, when the whole of the nerves that supply the rectum and the anal sphincters have been completely occluded, along with the central action of all the extra-rectal sympathetic ganglia. This was established for dogs by Arloing and Chantre (1897-98) by repeated experiments. This fact can only be explained by admitting that the intra-rectal peripheral ganglia of Auerbach's plexus can exercise a reflex tonic action upon the sphincters, independent of the connections with the extra-intestinal nervous system.

We must therefore conclude that in cases of incontinence of faeces of central origin there is, along with the depression of the tonic action of the ano-spinal centre, also a functional inhibition

of the ganglia of the inferior mesenteric plexus, and the intra-rectal peripheral ganglia.

Another interesting phenomenon first observed by Gluge (1868) on the rabbit, and subsequently noted by Goltz (1874) on the dog, and by Ott (1879) on the cat, appears to show that the tonic action normally exerted on the anal sphincters by the ano-spinal centre depends in its turn upon an influence transmitted to this same centre from the brain. In these animals, after dividing the cord between the last dorsal and the first lumbar vertebrae, it is seen, both with digital exploration of the anus and by the graphic method, that the sphincters have lost their *tonic contraction*, and exhibit *rhythmical contractions* instead. Goltz counted 20-25 per minute in the dog. They may arise spontaneously, or may be provoked by stimulation of the anal muscles, or inhibited by excitation of the sensory nerves of the lower limbs. Ott recorded

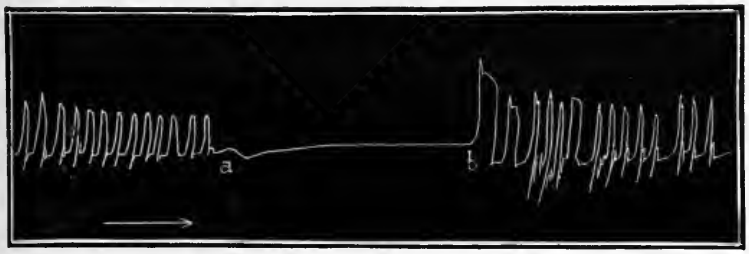


FIG. 107.—Rhythmic contractions of anal sphincter (in cat), after transverse division of lumbar cord, recorded by rectal sound. (Ott.) *a*, stimulation of sciatic: arrest of sphincter-beats; *b*, end of stimulation: return of beats which are more vigorous and irregular.

the same phenomenon on the cat with the graphic method (Fig. 107). After ablation of the lower part of the cord, or division of the anal nerves, these rhythmic movements of the sphincters are abolished (Chauveau, Arloing), but after a few weeks or months they may appear again. Goltz and Ewald in fact observed this phenomenon in a dog that had undergone almost complete ablation of the spinal cord two years previously.

Many observers have shown that the brain exerts an influence upon the ano-spinal centre and the homologous sympathetic centres, by transforming the rhythmic contractions of the sphincters (which they excite) into a tonic contraction. After stimulating the base of the crura cerebri a spastic constriction of the anus is readily seen, along with other diffuse movements. On cutting the optic thalamus of the cat, Ott (1879) saw rhythmic movements of the anus. Sherrington (1902), in a more exact experiment, found that an induced current applied to the posterior portion of the paracentral lobe in the ape produced spasm of the anal sphincters. Mayer (1893) observed similar effects in the dog, on stimulating the posterior part of the sigmoid gyrus near its

outer border. Mann (1895) in the cat and rabbit, on stimulating certain points of the motor cortex, obtained co-ordinated movements of defaecation. Ducceschi (1898), in dogs deprived of the motor cortex, observed rhythmic contractions of the anus entirely comparable to what is seen after section of the lumbar medulla. This is not seen in dogs after removal of the cortex of the frontal or occipital lobes. On stimulating the superior and anterior margin of the precruciate convolution of the sigmoid gyrus with an induced current he obtained contractions of the anus, associated sometimes with movements of the tail.

On the strength of these facts we may conclude that there is an *ano-cortical* motor centre, which controls the function of the *ano-spinal* centre. It is this centre that puts into voluntary motion the external sphincter of the anus and the levator ani, either to retard the act of defaecation, or to promote it, by increasing the intra-rectal tension and reflexly determining a more energetic peristalsis of the sigmoid flexure and rectum. Inhibition or temporary paralysis of this centre (*e.g.* from fright) may produce involuntary evacuation.

The whole act of defaecation may take place periodically, independent of the cortical centres, by a pure reflex act, regulated by the lower spinal or sympathetic centres. This was particularly observed by Goltz, both in dogs with divided cord and in those deprived of the lower part of the cord.

These reflex actions are determined by the distension of the last part of the intestine due to accumulation of faeces, which excites the sensory nerves of the mucosa. Diminished excitability of these sensory nerves or the centres with which they are in relation is probably the cause of habitual costiveness and obstinate constipation.

Deficient oxidation of the blood circulating in the walls of the last part of the intestine, again, or a sudden arrest of the vascular circulation, may reflexly produce powerful peristaltic movements which expel the faeces, independent of voluntary control. This explains the defaecation frequently seen in cases of sudden death from asphyxia or suffocation, as well as the exaggeration of intestinal peristalsis observed on opening the abdomen of animals immediately after death (Foster).

In conclusion there are certain specific functional characteristics by which the external sphincter of the anus is differentiated from all other striated muscles.

We have seen that when completely withdrawn from the influence of the cerebrospinal nerve centres, it regains its normal tonicity after some months, does not atrophy, nor undergo fibrous degeneration, and preserves its normal excitability to electrical stimuli (Goltz). It must further be added that, even under normal conditions, the external sphincter differs from the other

striated muscles in the special form of its contraction curve, which is slower in all its phases, resembling that of plain muscle (Ducceschi). Lastly, the external sphincter, shortly after destruction of the cord, becomes insensitive to the paralysing action of curare (Goltz), or at any rate much larger doses of curare are required to paralyse it than are necessary for other skeletal muscles (Frankl-Hochwart and Fröhlich).

From the later work of these authors (1900) we may also conclude: (*a*) that the internal sphincter alone (excluding the co-operation of the external sphincter) is able to ensure the tonic closure of the anal orifice; (*b*) that curare has no visible effect on the tone of the internal sphincter; (*c*) that the external sphincter is responsible for 30-60 per cent of the total energy with which the tonic closure of the anal orifice is normally maintained; (*d*) that the nervi erigentes (Eckhard) contain fibres which on excitation produce contraction of the external sphincter; (*e*) that excitation of the hypogastric rami with previous division of the nervi erigentes usually (9 out of 12 times) determines the dilatation of the sphincters; (*f*) that stimulation of the sciatic excites reflex contraction of the sphincter, and dilates it reflexly after section of the nervi erigentes.

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CHAPTER VII

ORIGIN OF KATABOLIC CONSTITUENTS OF URINE

CONTENTS.—1. General characteristics and composition of human urine. 2. Formation of urea. 3. Formation of uric acid and the purine bodies. 4. Formation of creatine and creatinine. 5. Formation of hippuric acid and aromatic substances (ethereal sulphates). 6. Formation of pigments and chromogens (urochrome, urobilin, uroerythrin, indican). 7. Formation of non-nitrogenous organic acids (oxalic acids, lactic acids, volatile fatty acids). 8. Carbohydrates of normal and pathological urine (glucose, lactose, animal gum, acetone, glycuronic acid). 9. Proteins of normal and pathological urine (serum-albumin, serum-globulin, fibrinogen, enzymes). 10. Inorganic constituents of urine (chlorides, sulphates, alkaline and earthy phosphates, carbonates, ammonium compounds). 11. Toxicity of urine and uraemia.[1] Bibliography.

WE stated in the introduction to the last chapter that the kidneys represent the principal organ of excretion in the animal body. All the waste products, in fact, which originate in the foods that are introduced into, and absorbed from the digestive canal leave the body sooner or later by the kidneys, with the exception of the few substances permanently retained, of those which are constituents of the body at the moment of death, and of those, lastly, which are eliminated in the form of gas or fluid by the other excretory systems—the lungs, surface of the skin, and internal mucous surfaces, particularly the mucous membrane of the intestines. If we sum up the products not eliminated by the kidneys, they obviously form a very minor quantity in comparison with the sum of the metabolites that are thus excreted. The predominating importance of the renal apparatus is plain, when we consider the chemical nature of the excreta eliminated by the kidneys. The majority of the nitrogenous compounds, *i.e.* the waste products of the proteins, which form the main substrate of living protoplasm, are discharged with the urine.

I. So much can be gathered from the composition and character of the Urine as to the general metabolism of the body and its principal organs and tissues, that it is no wonder this

[1] EDITORIAL NOTE.—Owing to the impossibility of giving adequate directions for laboratory work in connection with this chapter, the technical instructions contained in certain passages of the Italian text have been entirely omitted from the English version.

subject should have been investigated long before chemistry had developed into an exact science. The earliest attempts of Van Helmont to determine the nature and origin of the urinary constituents date from the commencement of the seventeenth century. Towards the middle of the same century, Brand, the alchemist-physician of Hamburg, first obtained phosphorus from the urine, while Kunkel, shortly after, described it more exactly. At the beginning of the eighteenth century the famous Boerhaave made the first analysis of urine, which is now only of historical interest, but was thought marvellous at the time it was drawn up.

The most important nitrogenous constituent of urine, which received the name of *urea*, was first recognised by Hilaire Rouelle (1775), the younger brother of that G. Rouelle who was Lavoisier's teacher. But the actual discovery of urea was due to Cruikshank (1797), who first obtained crystals of urea nitrate. Scheele and Bergmann (1775-88) discovered the compound now termed *uric acid*, in calculi of the bladder. Fourcroy and Vauquelin (1799) made a more profound study of the chemistry of urine, and particularly of the composition of the urinary calculi. The first quantitative analysis of urine, by Berzelius (1809), is quoted in the classical *Text-book* of Johannes Müller. Comparison of this with the analyses of modern times shows the enormous advances made in the chemistry of the urine, owing to the labours of a long succession of workers, between the beginning and the close of the nineteenth century.

We must limit ourselves to a summary of the characters and composition of urine, referring for more minute details to recent text-books of chemical physiology, and the special monographs which deal with this subject from the standpoint of theoretical and practical medicine.

Human urine, when first given off from the bladder, is normally a clear straw-coloured fluid, with a peculiar, somewhat aromatic odour, saltish-bitter taste, acid reaction, and mean specific gravity of 1020.

The amount of urine excreted in the 24 hours varies greatly under different conditions: the age and weight of the individual, the diet, the quantity of fluid imbibed, the season or external temperature, muscular rest or exercise, etc. In a normal, well-nourished adult it may fluctuate, owing to these or other circumstances, from 1300 to 1600 grms. in man, from 900 to 1200 grms. in woman.

The specific gravity of the urine varies with the amount secreted, and the content of solid substances dissolved in it.

Under normal conditions the specific gravity, as measured by the urinometer, varies between 1016 and 1025. To calculate with approximate accuracy from these values the amount of solids dissolved in 1000 c.c. urine, it is only necessary to multiply the two

last figures of the specific gravity by the constant coefficient 2·33 (Haeser). A litre of urine of normal mean specific gravity, *e.g.*, contains solids to an approximate amount of $20 \times 2{\cdot}33 = 46{\cdot}60$ grms.; and $1\frac{1}{2}$ litre of this urine secreted on an average in the 24 hours contains $20 \times 23 \times 31{\cdot}5 = 69{\cdot}90$ grms. solid substances.

The acidity of the total urine in man in the 24 hours is, under normal conditions, about equivalent to that of 2 grms. oxalic acid, with which it is usually compared. It is largely due to the presence of *acid sodium phosphate* (Liebig). But the degree of acidity naturally varies at different times of the day. During gastric secretion, owing to the formation of hydrochloric acid and reabsorption of the liberated sodium in the blood, the alkalinity of the blood increases and the acidity of the urine therefore diminishes (Cl. Bernard, Bence-Jones, Gley), increasing again when gastric digestion is over. The nature of the diet has more influence on the reaction of the urine. With vegetable food, which contains an excess of alkali, the acidity of the urine diminishes, so that it may exhibit a neutral or amphoteric, sometimes even an alkaline reaction, when, *e.g.*, only potatoes, which are very rich in potassium salts, are eaten. On a flesh diet, on the contrary, in which the earthy bases predominate, the urine is always distinctly acid.

For the same reasons the urine of herbivora is normally alkaline and that of carnivora acid. But in fasting, when both carnivora and herbivora consume their own tissues, the urine of the latter also becomes acid (Cl. Bernard).

The acidity of human urine sometimes increases for a certain time after micturition, owing to a fermentation which gives rise to the development of new acid substances (Scherer). This causes a precipitation of acid urates which makes the whole of the urine cloudy, and slowly forms a sediment consisting principally of urates, plus oxalates, mucus and desquamated epithelial cells from the urinary passages. When present in large amount, these urates may be precipitated, as the urine cools, independent of any fermentation. In this case the acidity of the urine is not increased, but is diminished, owing to the precipitation of the acid urates (Voit and Fr. Hofmann).

As was said above in discussing the reaction of the blood (see Vol. I. p. 94), recent work in chemical physiology has greatly modified our notions as to the reaction of urine and of all the tissue fluids in general. Thus, according to the results of Auerbach and Friedenthal (1903) either with physico-chemical methods, or by simply using a suitable indicator (*e.g.* phenolphthalein), human urine always has a neutral or weakly acid reaction, even when an alkaline reaction is indicated by litmus. In fact, neither litmus paper nor methyl orange can be used as indicators in presence of carbonic acid.

According to Höber (1903) the physico-chemical concept must be distinguished from the purely chemical concept of acidity. While physico-chemical methods only measure the concentration of the hydrogen ions actually present, *i.e.* dissociated from the molecules of the acid, the titrimetric (chemical) method measures not only these, but also the hydrogen ions which at the outset of the experiment are still bound up in the acid molecules, and only become dissociated later on; that is, it measures both the actual and the potential hydrogen ions (Ostwald). In the case of urine also we must distinguish between these two acidities, the ion-acidity and the titration-acidity, which are, not only theoretically, but also (as appears from certain experiments of Höber) practically, two distinct magnitudes, varying independently of each other, and each having its special significance, which must not be neglected in judging of the secretory state of the kidneys, or of general metabolism.

After a longer or shorter time (two or three days) the urine undergoes *ammoniacal fermentation*, and the reaction becomes alkaline. This is due to the action of organised ferments (usually *Micrococcus ureae* and *Bacterium ureae*) which are able to convert urea into ammonium carbonate. This fermentation constantly occurs in urine exposed to non-sterilised air, but it may also take place in the urine within the bladder, if non-sterilised surgical instruments are introduced The urine undergoing alkaline ammoniacal fermentation gives off a foetid ammoniacal odour and becomes turbid, owing to the formation of a sediment which consists principally of crystals of ammonium-magnesium phosphate and ammonium urate. According to Musculus the urea micro-organisms secrete a diastatic enzyme which is the direct agent of the cleavage, and which can be isolated by precipitation with alcohol.

The molecular concentration of human urine, as determined by the cryoscopic method, *i.e.* by the lowering of the freezing-point, differs considerably from that of blood serum. While in the latter $\Delta = 0{\cdot}55°$ C., in the urine it may reach the value of $\Delta = 1{\cdot}85°$ C. (Winter), or even of $\Delta = 2{\cdot}3°$ C. (Dreser). This higher molecular concentration of urine as compared with blood plasma is not, however, constant; even in man it occasionally falls below that of the blood, and may reach a minimum of $\Delta = 0{\cdot}4°$ C. (Dreser). We shall discuss the value of these data for the theory of the mechanism of urinary secretion at a later point.

H. Frenkel and J. Cluzet (1901) also drew attention to another physico-chemical property of urine: its *surface tension*. Since the surface tension of a solution depends not only (as in molecular concentration) on the number but also on the chemical nature of the dissolved molecules, it is clear that, under given conditions, the changes in surface tension may afford indications as to the chemical constitution of a solution. The surface tension of urine,

e.g. (which under both normal and pathological conditions is always less than that of distilled water), is increased by mineral salts, and diminished by organic substances, such as bile salts. The addition of bile to urine causes a perceptible alteration in its surface tension, even with a concentration so low that chemical tests are not perceptible (*supra*, p. 145).

The *determination of surface tension* in any given fluid is most simply ascertained by counting the number of drops required for 1 c.c. of the fluid to fall drop by drop from a pipette. The number of drops is inversely proportional to the magnitude of surface tension.

The chemical composition of urine, both in man and animals, is very complete, as shown by the number of individual substances that can be chemically isolated, and recognised in it. The majority of these, however, are present in such minute quantities under normal conditions that a large amount of urine is required before even a trace of them can be detected.

Only a limited number of organic and mineral substances are found dissolved in the urine in any appreciable quantity. Among the former urea enormously predominates; next follow uric acid and creatinine, but in much smaller amount: among the latter, sodium chloride predominates, and the sulphates and the alkaline and earthy phosphates are the other principal constituents.

The following table will assist us in realising the quantitative relations between the principal constituents of the urine, and the maximal extent to which they vary with the diet. It gives the analyses obtained by Bunge (1887) from a healthy youth, whose total urine secreted in the 24 hours was collected, on an exclusively flesh, and on an exclusively vegetable diet; the former consisted of veal seasoned with common salt, the latter of wheat bread with a little butter and salt. To these data are added the averages obtained by Parkes, under normal conditions, with an ordinary mixed diet.

Urinary Constituents.		Meat (Bunge).		Bread (Bunge).		Mixed Diet (Parkes).	
Volume of urine		1672 c.c.		1920 c.c.		1500 c.c.	
Organic Substances	Urea	67,200 grs.	70,761 grs.	20,600 grs.	21,814 grs.	33·18 grs.	34·64 grs.
	Uric Acid	1,398 ,,		0,253 ,,		0·55 ,,	
	Creatinine	2,163 ,,		0,961 ,,		0·91 ,,	
Mineral Substances	Potassium	3·308 ,,	19·849 grs.	1·314 ,,	13·635 grs.	2·50 ,,	26·73 grs.
	Sodium	3·991 ,,		3·923 ,,		11·09 ,,	
	Calcium	0·328 ,,		0·339 ,,		0·26 ,,	
	Magnesium	0·294 ,,		0·139 ,,		0·21 ,,	
	Chlorine	3·817 ,,		4·996 ,,		7·50 ,,	
	Sulphuric acid	4·674 ,,		1·265 ,,		2·01 ,,	
	Phosphoric acid	3·437 ,,		1·659 ,,		3·16 ,,	

The urine gives an acid reaction with the flesh diet and mixed diet, as well as on a diet of bread. It is easily seen from the above data that in all three tables the content of chlorine and sulphuric acid is more than sufficient to combine with the whole of the alkali in the form of chlorides and sulphates.

It is convenient in considering the total organic and inorganic substances found in the urine to classify them into different groups based on the approximate criteria of their characteristic affinities, chemical constitution, and origin. Hoppe-Seyler and Halliburton distinguish the following groups of substances in the urine:—

(*a*) *Nitrogenous Substances of the Fatty Series.*—Among these are urea, uric acid, allantoin, xanthine, guanine, creatine, creatinine, sulphocyanic acid.

(*b*) *Non-nitrogenous Substances of the Fatty Series.*—These include the fatty acids of the series $C_nH_{2n}O_2$, oxalic acid, lactic acid, glycerophosphoric acid, small quantities of carbohydrates.

(*c*) *Compounds of the Aromatic Series.*—These include the ethereal sulphates formed from phenol, cresol, pyrocatechol, indoxyl, hippuric acid, the aromatic oxy-acids.

(*d*) *Organic Substances not exactly determined.*—This group includes the pigments and chromogens of urine, the enzymes (especially pepsin), the mucin and a small amount of proteins.

(*e*) *Inorganic Salts.*—These are sodium and potassium chloride, potassium sulphate, sodium, calcium and magnesium sulphate, silicic acid, ammonium compounds and calcium carbonate.

(*f*) *Gases, i.e.* nitrogen and carbonic acid.

To these substances normally present in human urine, many others are added in abnormal conditions and special diseases, *i.e.* serum-albumin and other proteins, haemoglobin, and methaemoglobin, bile pigments and salts, leucine and tyrosine, glucose and lactose, glycuronic acid, fat, lecithin, cholesterol and cystine. To these we must add a number of other substances derived from special foods and drugs. Lastly, there are organised cells, *e.g.* epithelia of kidneys and bladder, urinary casts, blood corpuscles.

We must briefly run through the characteristics and origin of the principal substances comprised in these groups.

II. Among the nitrogenous urinary constituents of the fatty series, *Urea* is the most important, and is the end-product of protein katabolism. Chemically considered it is a *carbamide, i.e.* carbonic acid, in which the two hydroxyl groups are substituted by two (amino) groups (NH_2), and its formula is $CO(NH_2)_2$. It was first obtained artificially by Wöhler in 1828 by heating ammonium cyanate, which is the isomer of urea $(NH_4)\cdot O\cdot CN$.

By heating with water at 140° C., by boiling with acids or alkalies, or by the action of the enzymes secreted by the bacilli of

ammoniacal fermentation, urea is readily converted into ammonium carbonate :—

$$CO(NH_2)_2 + 2H_2O = (NH_4)_2CO_3.$$

As we see from the preceding table, about 30 grms. urea are eliminated with the urine in the 24 hours, on a normal mixed diet. Yvon and Berlioz (1888) obtained from a large number of comparative researches on the daily output of urea, 26·5 grms. for man and 20·5 grms. for woman. As shown by Bunge's results, the urea increases considerably with an exclusively flesh diet and diminishes in a vegetable diet; this is in evident relation with the amount of nitrogenous substances introduced. It also bears a relation to the body-weight and age of the individual. According to Uhle's analyses, the quantity of urea in the 24 hours varies with the age with each kilogramme of body-weight in the following proportions :—

From 3 to 6 years . . .	1 grm.
„ 8 to 11 „ . . .	0·8 grms.
„ 13 to 16 „ . . .	0·4-0·6 grms.
In Adults	0·37-0·6 grms.

The secretion of urea increases directly after a meal (particularly if rich in protein) and reaches its maximum in 4 hours (Tschlenoff), or in 7-10 hours, when the total quantity of the urine secreted becomes maximal and its concentration minimal (Camerer, 1888).

As we saw in Chapter V. (p. 335 *et seq.*), urea is formed not in the kidneys but in the liver. This fact was first discovered by Meissner, and subsequently confirmed by Brouardel, Roster, v. Schröder, Minkowski, and others. It is, however, probable that other organs (spleen, lymphatic glands, glands in general) take some share in the formation of urea. Although it diminishes greatly it does not entirely cease after removal of the liver or in profound morbid changes of this organ.

The problem of the origin of urea, *i.e.* the process of its formation in the body, is one of the most important, and at the same time one of the most difficult in physiology. It is certain that urea, like all the other nitrogenous constituents of urine, originates in the decomposition of the complex protein molecule; but there is great discussion as to whether, or how far, it is directly derived from the successive oxidation of these molecules, or whether it is formed by synthetic processes indirectly, *i.e.* after the protein molecule has undergone the maximal degree of cleavage.

Urea was formerly supposed to be the end-product in the oxidation of the protein molecule, while uric acid, creatinine, xanthine, and in general the whole group of the nitrogenous substances of the fatty series which are present in urine, repre-

sented different stages in this oxidation, and as such were the precursors of urea. This theory was inspired by the undeniable fact that the oxidising process is the most important in the animal body, as also by the fact that in many reactions uric acid and creatinine give rise to urea by oxidation.

Later work, however, has shown that urea cannot be looked on merely as an oxidation product of protein, although it undoubtedly comes indirectly from the cleavage of the protein molecule.

We saw in Chapter IV. (p. 211) that protein, when acted upon by the tryptic enzyme, gives rise by simple hydrolytic cleavage to large quantities of peptone, leucine, and tyrosine (Kühne). Other researches have shown that the same process gives rise to aspartic acid (Salkowski, Knieriem) as well as to large quantities of glycocoll, on the tryptic digestion of gelatin and collagens in general (Nencki). These same cleavage products (which are known as amino-acids) are obtained from proteins by long boiling with strong acids or alkalies. According to the most recent work, a series of basic compounds is also formed by the same means, *i.e.* lysine, arginine and histidine (Hedin).

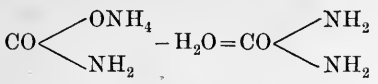
All these nitrogenous compounds into which the complex protein molecule breaks up may perhaps be regarded as precursors of urea, the more so since some of them, particularly leucine and tyrosine, if not normally present in the urine, are found in certain tissues, *e.g.* spleen and pancreas.

Experimental evidence shows that some of these substances are converted into urea in the body. On injecting leucine or glycocoll into dogs, they are not found in the urine, but, on the other hand, the urea increases (Schultzen and Nencki, Salkowski). Aspartic acid, again, if given to the animal, reappears in the urine only in the form of urea (Knieriem).

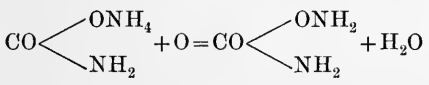
But the transformation of this and other amino-acids into urea can only be chemically explained by synthetic processes. Leucine, glycocoll, and aspartic acid contain only one atom of nitrogen, while urea contains two. It is, therefore, probable that amino-acids previous to their conversion into urea undergo a further decomposition in the body, leading to the formation of *ammonia* (NH_3). The ammonia combines with the carbonic acid, forming *ammonium carbonate*, which is again converted, with the loss of one molecule of water, into *ammonium carbamate*, as shown by the equation :—

$$CO\begin{matrix}\diagup ONH_4 \\ \diagdown ONH_4\end{matrix} - H_2O = CO\begin{matrix}\diagup ONH_4 \\ \diagdown NH_2\end{matrix}$$

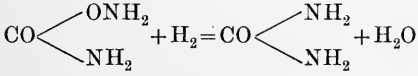
The ammonium carbamate is then converted with loss of a second molecule of water into urea :—



Schmiedeberg is the author of the theory that urea is derived from *ammonium carbonate.* He demonstrated that on treating protein with barium hydrate ammonium carbonate is formed, which when injected into the body is (at least partly) converted into urea with loss of two molecules of water. The theory that urea may be formed from the dehydration of *ammonium carbamate* is due to Drechsel (1875), who showed that ammonium carbamate is formed on oxidising leucine and glycocoll. When an aqueous solution of these substances is exposed to the electrolytic action of 4-6 Grove cells (with an automatic commutator, by which the direction of the current can be rapidly changed, so as to produce at each electrode alternate processes of reduction and oxidation), it is converted through an intermediate product into urea:—



Ammonium carbamate. Intermediate product.



Urea.

This theory of the derivation of urea either from ammonium carbonate or from ammonium carbamate, by successive and alternate oxidations and reductions taking place in the liver, has been substantially confirmed by the experiments of v. Schröder, Salomon and Minkowski, as also by those of Nencki, Hahn, Pawlow and Massen, on dogs with an Eck's fistula, to which we referred in Chapter V. (p. 335). Taken as a whole, the results of these experiments show the hypotheses of Schmiedeberg and Drechsel to be justified, and further make it probable that carbamic acid and ammonium carbonate are katabolic products from the spleen, pancreas, and gland cells of the intestinal tract, which, when absorbed and carried by the portal system to the liver, are converted into urea.

On another theory, maintained by Hoppe-Seyler, urea is derived from *cyanic acid.* This is founded on the fact that part of the amino-acids (leucine, tyrosine, glycocoll) introduced into the body, appear in the urine in combination with the group (CO·NH) or cyanic acid, forming the so-called *uramino-acids* (Salkowski, Hoppe-Seyler, Baumann). This fact leads the above authors to conjecture that cyanic acid can be formed in the body. On this

supposition urea can be derived from cyanic acid as follows (Salkowski) :—

$$2(HOCN) + H_2O = CO\begin{matrix}NH_2\\NH_2\end{matrix} + CO_2$$

Cyanic acid. Urea.

It may also be assumed (Hoppe-Seyler) that the cyanic acid on combining with ammonia forms ammonium cyanate (NH_4OCN), which is isomeric with urea ($CO{\cdot}(N{\cdot}H_2)_2$) and from which, as we saw, Wöhler obtained urea by synthesis.

To this theory Hofmeister objected that cyanic acid had not yet been discovered in the body, and particularly in the liver. It was also noted that if salts of ammonium, or ammonia, were introduced into an organism poisoned with cyanic acid, the syndrome was not altered, showing that the two substances did not combine to form urea, as assumed by Hoppe-Seyler.

Hofmeister experimentally discovered an important fact, viz.: that urea can be obtained from a large series of organic compounds, by oxidation with permanganate of potash, in the presence of ammonia. Among such are ovalbumin, glutin, asparagine, leucine, glycocoll, hydrocyanic acid, and lactic, malic and tartaric acids. This shows the extreme importance of the oxidising processes to the formation of urea outside the body. But it has not at present been decided how far similar processes may occur within the living body.

III. In the urine of birds and reptiles nearly all the nitrogen introduced is eliminated in the form, not of *urea*, but of *uric acid*. Uric acid is often absent from the urine of carnivora, while that of herbivora shows no trace of it. In human urine, however, it is always present in a small quantity which normally fluctuates between 0·25 grm. and 1·40 grm. On an exclusively vegetable diet it rarely exceeds 0·3 grm. in the 24 hours: on an exclusively flesh diet it may reach 2 grms. or more. Its relation with the total nitrogen of the urine is from 1 to 3 per cent; its relation with the urea may vary from 1·15 to 1·82.

Uric acid is not normally present in human blood, but it has been noted in minute quantities in the glandular organs, particularly in the liver, spleen, and lungs (Gorup-Besanez and others). Evidently, therefore, it is not a product of the kidneys, the more so as in pathological conditions (arthritis, leucaemia, pneumonitis, pulmonary tuberculosis) it also occurs in the blood. It is normally present in the blood of birds (Salomon, Meissner), and becomes abundant there after ligation of the ureters (Colasanti).

The empirical formula of uric acid is $C_5H_4N_4O_3$. One atom of hydrogen is easily replaced by bases. On bringing uric acid

into a solution of sodium carbonate, *acid sodium urate* is obtained ($C_5H_2NaN_4O_3$). On dissolving it in caustic alkali, the second atom of hydrogen is replaced, and the *neutral urate* ($C_5H_2Na_2N_4O_3$), which is highly unstable, is formed.

Both uric acid and the acid urates are soluble with difficulty in water: 6-7 litres of water are required to dissolve 1 grm. uric acid at body temperature (Bunge). This would lead us to suppose that the urates are present in urine in the form of neutral salt. But against this conjecture must be set the fact that the urine, which is clear and acid when passed, forms on cooling to the temperature of the air, especially in winter, the *sedimentum lacteritium*, which contains large crystals of uric acid coloured dull yellow by the red pigment of the urine. The crystalline sediment dissolves in heating the urine to body temperature. C. Voit and Hofmann demonstrated that this fact depends on the presence in the urine of acid sodium phosphate, which when the urine cools is converted into neutral phosphate, thus removing the bases from the urates, and causing the precipitation and crystallisation of free uric acid. On the formation of the sediment the acidity of the urine falls and rises again when the sediment re-dissolves, the uric acid being once more converted into acid urate.

As regards the origin of uric acid, it was formerly held that it arose from incomplete oxidation of the cleavage products of the proteins (Liebig). The following facts can be mustered in support of this view: (*a*) by means of oxidising agents uric acid can readily be converted into urea and carbonic acid outside the body; (*b*) when introduced into the body of a dog it almost entirely reappears in the urine in the form of urea (Zabelin, Frerichs, Wöhler); (*c*) when mixed with the blood and circulated in the liver, it is converted into urea (Ascoli).

These facts, however, do not prove that urea is normally formed by direct oxidation of uric acid as shown in the last paragraph. On artificially obstructing respiration in dogs, cats, and rabbits (Senator), or on bleeding these animals (Naunyn, Riess), no perceptible increase of uric acid is obtained.

It is a striking fact that the ingestion of ammonium salts increases the production of uric acid in birds (v. Schröder), and that urea injected into the portal vein is partly converted into uric acid (Meyer and Jaffé). After excising the liver in geese, a diminution of uric acid and corresponding increase of ammonia and lactic acid has been observed in the urine, which seems to show that in birds the liver is able to form uric acid synthetically from ammonia and lactic acid (Minkowski). On the other hand, it has been shown that amino-acids (leucine, glycocoll, aspartic acid), which give rise to a formation of urea in mammals, also give rise to uric acid in birds (Knieriem).

As regards mammals and man, however, no data can be

adduced to show that uric acid is derived from ammonium compounds. On the contrary, an important series of experimental data show that uric acid in mammals and man is derived directly from the group of the *purines* (traces of some of which exist in the urine), which in their turn are formed from the *nucleins*; these nucleins in the cell nucleus of plants and animals correspond with what histologists term *chromatin*.

The work of Kossel and his school (1879-96), to which we owe the greater number of determinations of the *mother-substance of the purines*, has proved the existence in the organs, tissues, and cells of a group of bodies termed *nucleins*, which are present in the free state in the form of *nucleic* acids, or in combination with protein in the form of *nucleo-protein*. Such organs are the thymus, spleen, lymph glands, spermatozoa (particularly of salmon and sturgeon), erythrocytes (of geese), etc. They further demonstrated that the purines, *e.g.* xanthine, hypoxanthine, guanine, adenine, sarkine, etc., can be readily obtained from these tissues or cells. Hence nuclein is probably the source of the xanthine bodies.

On the other hand, Fischer (1884) has clearly demonstrated that there is a close relation in the constitution of purines and of uric acid, that they contain a nucleus which he terms *purine*, and that uric acid, xanthine, and hypoxanthine might be regarded as oxidation products of this nucleus.

The most important experimental data on the physiological side which confirm this theory and tend to clear up the question of the origin of uric acid in the body, are specially due to Horbaczewski (1889-93). Minkowski (1887) had already obtained increase of uric acid in fowls after the injection of xanthine bodies, and Marès (1888) recognised that uric acid is formed by a process distinct from that which gives rise to urea, because the relative quantity of urea changes at different hours during abstinence and after an abundant meal.

Starting from the well-known clinical fact that increase of uric acid is constant in *Leucaemia splenica*, Horbaczewski sought to discover if it were possible to obtain xanthine, hypoxanthine, and uric acid from splenic pulp. The positive results obtained show that the splenic pulp, which contains many leucocytes, also contains the mother substances of the purines and uric acid. On oxidising the splenic pulp with defibrinated blood, hydrogen peroxide, or air, uric acid is obtained: when, on the contrary, it is hydrolysed by boiling, xanthine and hypoxanthine result.

These experiments of Horbaczewski were confirmed in Italy by Giacosa, who obtained uric acid not only from the spleen but also from the liver when left to oxidise with blood; by Zagari and Pace, who obtained it from the thymus by the same method; and by Ludowenj and Formánek in Horbaczewski's laboratory, who

obtained uric acid from a variety of other tissues and organs: brain, kidneys, liver, gastro-intestinal mucous membrane, lungs, thymus, muscles, etc.

That uric acid arises from nuclein, not merely *in vitro* as Fischer showed but also *in vivo*, was demonstrated by Horbaczewski on man by administration of nuclein, which produced an increase of uric acid in the urine. He also showed that the increase of uric acid coincided with an increase of leucocytes in the blood, which suggests that the circulating nuclein caused a hyperformation of leucocytes on the part of the lymph organs. On these facts he based the theory that nuclein is derived from the leucocytes, that uric acid is formed from the nuclein, and that all the means which increase the leucocytes determine a simultaneous increase in the formation and elimination of uric acid.

Clinical and experimental investigation of this theory, however, militate against the supposed parallelism between the increase in the number of leucocytes of the blood and the uric acid content of the urine, although they confirm the fact that there is a relation between the nuclein introduced and the uric acid excreted.

Krüger and Wulff (1894) invented a method for estimating the total nitrogen of the purines, and endeavoured by its means to establish the ratio between the nitrogen of the uric acid and that of the purines. They saw that this ratio varies considerably in normal individuals, but that the nitrogen of the uric acid always exceeds that of the purines, on an average by 4 : 1.

Weintraud (1895) studied the effect of feeding substances rich in nuclein on the elimination of uric acid, by substituting *thymus* —which is an organ very rich in nuclein—for alimentary protein, in an adult man. He found a relative increase in the elimination of uric acid without any constant augmentation in the number of leucocytes in the blood. From this he concluded that the purine bases are formed in the alimentary canal, independent of leucocytosis, and that on absorption they determine an increment of uric acid.

Zagari, in collaboration with Pace (1897), experimented on six normal and two leucaemic subjects and one nephritic, and observed that when thymus and nuclein were added to the usual diet of these individuals, there was no constant hyper-production of leucocytes, but there hardly ever failed to be a considerable increase of uric acid, both in healthy subjects and in invalids: that in leucocytosis of varying degree the value of the uric acid excretion was not parallel with the fluctuations of the leucocytosis; that in the rare cases in which there was no increase of uric acid the total nitrogen of the urea did increase. We are not at present able to account for these differences of result, which are certainly due to special conditions of metabolism in different individuals.

Laquer (1896) studied the influence of water and milk on the

elimination of the purines. On administering water he saw that the nitrogen of the uric acid and that of the purine bases was almost doubled; on administering milk the nitrogen of the purine bases was more than doubled, while the uric acid, on the contrary, diminished—the normal ratio between the two being inverted. These results were confirmed by Zagari and Pace.

These and other experiments, which space compels us to omit, are sufficient to show that the production of uric acid is largely influenced by the nature of the diet; it increases on ingestion of substances rich in nuclein and purines, and diminishes on ingestion of foods in which, as in milk, they are scanty. As urea represents the final result of the conversion of alimentary protein, so uric acid and the purines represent the katabolic products of the alimentary nucleins.

Of the later work on this subject special mention must be made of that of R. Burian and H. Schur (1900-1). They endeavoured, by a number of researches, to ascertain the fate of the purine bodies in human metabolism, and arrived at the following results:—

Every healthy adult eliminates a definite and constant quantity of purine bodies by the urine. These result from metabolic processes, which are to a certain extent independent of the diet. The amount of this *endogenous purine*, which, as we have said, is approximately specific and constant for each individual, can be directly determined on dieting the subject for a sufficiently long period exclusively on foods that contain no nucleo-protein (milk, cheese, eggs, potatoes, rice, salad, white bread, etc.). In ordinary human diet these endogenous purines are reinforced in a variable degree by other purines which are derived from the preformed purines of the food, and must therefore be distinguished by the name of *exogenous* or *alimentary purines*. The usual fluctuations in the elimination of the purines depend mainly upon their varying content in the food. The amount of exogenous purine eliminated with the urine does not, however, correspond exactly with the amount of alimentary purine; a greater or lesser part of the latter is broken up in the body by decomposition of the purine-ring.

The amount of nitrogen eliminated in the form of endogenous purine in the course of the day fluctuates between 0·1 and 0·2 grms. The principal formation of endogenous purine takes place, according to Burian's latest work, in the muscles.

In all mammals, both the exogenous and the endogenous uric acid are an intermediate product of metabolism, *i.e.* one which undergoes or may undergo further cleavage in the body. That this holds also for endogenous uric acid is shown by the fact that in dogs, after removal of the kidneys and the liver, which is the most important organ in the destruction of uric acid, endogenous uric acid is found in the blood, which is not the case after removing the kidneys only. Since, however, the mammalian body

has the power of breaking up both endogenous and exogenous uric acid, and since the faculty of destroying uric acid manifested by different organs is very considerable, a fraction of the uric acid which circulates in the blood is always eliminated as such, *i.e.* that which passes with the blood directly to the kidneys, and thus escapes further decomposition.

The mean value of the fraction of uric acid excreted is approximately constant for each individual; so that in every case there is an integral factor by which the quantity of uric acid eliminated must be multiplied, in order to calculate approximately the total quantity of uric acid that enters the vascular circulation.

This constant integral factor is the same in man even for different individuals, while in carnivora there may be individual differences. It varies, on the contrary, very much in the different species of mammalia; carnivora eliminate only about $\frac{1}{20}$ or $\frac{1}{30}$ of the uric acid which reaches the circulation in an unaltered form; rabbits excrete a larger amount, about $\frac{1}{6}$; man, as a rule, fully $\frac{1}{2}$. These striking differences evidently depend on the varying number and capacity of the organs which destroy uric acid in the different species of animals.

IV. *Creatinine*, as we have seen, is one of the principal nitrogenous constituents of urine. The amount excreted in man in 24 hours varies considerably—according to Neubauer from 0·6 to 1·3 grms.; according to Johnson from 1·7 to 2·1 grms.; according to Hofmann from 0·5 to 0·9 grms. In young and robust individuals Grocco as a rule obtained 0·98 grm. on an average, while in old people of 70 only 0·45 grm. was obtained. But the amount varies greatly with the diet. We saw in fact that in the healthy young man on whom Bunge experimented 2·16 grms. creatinine were obtained with an exclusively flesh diet, and only 0·91 grm. on a regimen consisting entirely of bread.

The *creatinine* of the urine is certainly derived from the *creatine* of the muscles, from which it differs only by the absence of one molecule of water. According to Voit and Meissner, a small quantity of creatine is always present in the urine of mammals along with the creatinine; this increases when the urine secreted has an alkaline reaction. It is further to be noted that the reciprocal transformation of these two substances by hydration or dehydration is very easy. In an acid solution the creatine is dehydratised and converted into creatinine; in an alkaline solution the opposite occurs by hydration.

Creatine is the most abundant nitrogenous katabolic product of the proteins in the body. In the muscles alone creatine is present in a quantity of about 3 per cent, and the muscles of adult man as a whole contain about 90 grms. of this substance. Seeing that urea, of which 30-40 grms. are daily excreted with the urine, is present only in small quantities in the blood, and

has not been detected at all in muscle, it might reasonably be assumed that most of the creatine of the muscles is converted into urea, and given off into the blood in proportion as it is formed, to be eliminated from the blood with the urine by the kidneys. But the fact, as demonstrated by Meissner (1865, 1866, 1868), that the whole of the creatine ingested, or injected into the veins, passes into the urine without conversion into urea, contradicts this opinion, as maintained by some physiologists. Bunge, however, holds that although the creatine introduced into the body is not converted into urea, this does not prove that such a conversion does not occur in the creatine *formed* by muscle, since muscle only picks up the nutrient substances from the blood, and not the katabolites artificially introduced into the circulation, such as it habitually excretes into the blood. He thinks it highly probable that creatine is a mother substance of urea, more particularly as creatine contains three atoms of nitrogen and only four atoms of carbon.

These hypotheses of Bunge do not appear to us to be compatible with Baldi's investigations (1889), carried out in our laboratory upon Succi during his fasts. Baldi found that the creatinine never entirely disappeared from the urine between the 1st and 30th days of fasting, but that it diminished in proportion with the total nitrogen of the urine. If the urea is derived from the creatine, then during inanition, when the organism is living at the expense of its own tissues, the creatine should be entirely converted into urea and disappear from the urine. If it does not disappear even when the nitrogen of the urine is reduced to a minimum of 3 grms. per diem, but keeps in almost constant ratio with the urea, this implies that the latter is formed (at least mainly) by processes which are entirely independent of the conversion of creatine.

Although creatine has been synthetically obtained by Volhard and by Strecker from the combination of *sarcosine* with *cyanamide*, it has not yet been artificially produced by cleavage of the different proteins. By the hydrolytic cleavage, with acids, of caseinogen, conglutin, gelatin, and other proteins the compound *arginine* has been obtained, which is homologous with creatine and creatinine ($C_4H_7N_3O$). Both from creatine and arginine urea is split off on boiling with baryta water. This shows that the whole of the urea may not be formed synthetically after oxidation, but that part of it may be formed by hydrolytic cleavage from either creatine or arginine.

A large part of the creatinine of the urine of man and carnivora comes directly from the creatine of the alimentary flesh. Another part is formed from the katabolic processes in the muscles of the body, which, as stated above, contain a considerable amount of creatine. The urine of herbivora also contains creatinine, like the

urine of fasting, and that of dogs fed on meat that has been exhausted, and entirely or almost entirely deprived of its creatine (Rubner). Another fact which shows that creatinine is specially formed by the muscles, is that muscular work and fatigue increase the quantity of creatinine in the urine (Grocco, Moitessier, Ackermann).

V. The urine of man and other mammals constantly contains a group of *aromatic compounds*, among which *hippuric acid* largely predominates. This results from the combination of *benzoic acid* with *glycocoll* with loss of one molecule of water :—

$$C_6H_5COOH + CH_2(NH_2)\cdot COOH = C_6H_5CO - NH\cdot CH_2\cdot COOH + H_2O$$

Benzoic acid. Glycocoll. Hippuric acid.

Hippuric acid (in combination with alkalies), although it is present only in small quantities in human urine, is never absent even during an exclusively flesh diet and in fasting. It arises from the aromatic substances of the food, which are converted as the result of bacterial fermentation in the intestinal canal into benzoic acid: this, after absorption, combines with the glycocoll, with formation of hippuric acid, by loss of water. These aromatic substances come from hydrolytic cleavage of the proteins, which, as we know, contain an aromatic nucleus. Glycocoll is another cleavage product of the same substances, formed by katabolic processes in the tissues.

With an ordinary mixed diet the hippuric acid content of the urine fluctuates from 0·1 to 1·0 grm. per diem, the usual average being 0·7 grm. per diem. But it is much increased by a vegetable diet, especially after a large consumption of fruit and vegetables. Hippuric acid is plentiful in the urine of herbivora, and to a large extent replaces uric acid, which is present only in a small amount. These facts show clearly that the chief part of the hippuric acid of the urine is of alimentary origin, because the food-stuffs contain either benzoic acid itself or substances which are capable of conversion, in the intestinal tube or within the tissues, into this acid.

In 1824 Wöhler discovered that it is only necessary to mix benzoic acid with the food of any mammal in order to see it reappear in the urine in the form of hippuric acid. This discovery, which was confirmed by subsequent observers, was the first well-established instance of synthesis within the animal body. In 1876 Schmiedeberg and Bunge made an exhaustive study of the question in which organ the synthesis that gave rise to hippuric acid took place. They excluded the possibility of its being the liver, because in dehepatised frogs the subcutaneous injection of benzoic acid, or benzoic acid and glycocoll, gave rise to the formation of hippuric acid. They found that in dogs the organs which

synthetise hippuric acid are exclusively the kidneys, for when these organs are excised, and benzoic acid and glycocoll injected into the blood, the animal then being killed after 3-4 hours, there is no trace of hippuric acid, either in the blood, or in the liver or muscles, but, on the contrary, free benzoic acid is found. To this negative proof that the kidneys formed hippuric acid by synthesis, they added positive proof, by establishing artificial circulation with defibrinated blood, to which they added glycocoll and benzoic acid, in the freshly excised kidneys of a dog. Hippuric acid was found to be present both in the blood that left the kidneys and in the fluid that escaped from the ureters. The phenomenon occurred equally when the blood was warmed to the temperature of the body, and when it was cold. If benzoic acid only was added to the blood, the amount of hippuric acid formed was less.

The synthesis also took place partially when the kidney was broken up into small pieces, steeped in the extracted blood to which benzoic acid and glycocoll had been added, and then agitated (Kochs); but if the kidney is reduced to a homogeneous pulp, so as to exhaust the vitality of all its cells, or if a kidney excised several hours previously is used, there will be no trace of hippuric acid (Schmiedeberg and Bunge). It is clear that this synthesis does not depend on specific chemical compounds in the renal tissue, but on the metabolic activity of the surviving cells of the excised kidney.

No hippuric acid is formed when serum that has been entirely deprived of corpuscles by the centrifuge is employed, instead of circulating defibrinated blood containing benzoic acid and glycocoll in the kidney. The participation of the blood corpuscles is, therefore, indispensable to the synthesis effected by the kidneys, probably because they supply the oxygen. This is proved by the fact that the synthesis also fails when the artificially circulated blood has been previously saturated with carbon monoxide.

If in dogs the kidneys alone have the power of effecting the synthesis of hippuric acid, the same cannot be affirmed of other animals. In fact, Schmiedeberg and Bunge saw a formation of hippuric acid in frogs after the extirpation of the kidneys: Salomon found hippuric acid in the blood, muscles, and liver of the rabbit, after nephrectomy, when benzoic acid was introduced.

We do not know whether the synthesis of hippuric acid takes place in man exclusively by the kidneys, as in dogs, or by means of other tissues also, as in rabbits. We only know that in renal diseases in which there is a conspicuous degeneration of the epithelia, a lesser amount of hippuric acid is formed, and if benzoic acid be administered in these cases some of it reappears as such in the urine (Stokvis, Kronecker).

If benzoic acid is injected into birds, it does not, according to Jaffé (1877), reappear as hippuric acid, but in combination with

another compound, which he terms *ornithine*, and which, with benzoic acid, forms ornithuric acid.

In his *Text-book* Hoppe-Seyler cites a whole series of compounds similar to hippuric acid, in which the benzoic acid is replaced by other aromatic bodies, *e.g.* salicylic, toluic, anisic, cuminic, and other acids, which with glycocoll give rise to salicyluric, toluylisuric, anisuric, cuminuric acid, etc. According to Salkowski, *phenaceturic acid* is found in the urine of the horse, and perhaps in small traces in that of man also. It arises from the combination of *glycocoll* with *phenylacetic acid.*

Among the aromatic substances of normal urine, the *ethereal* or *conjugated sulphates* are more important from the physiological standpoint. Städeler in 1861, while distilling the urine of ox and man, discovered the presence of *phenol* or *carbolic acid.* Buliginski, and at a later date Hoppe-Seyler, found that the phenol of the urine present is not in the free state, but bound up with an acid from which it separates on distillation. Baumann (1876) first discovered that phenol forms an ethereal compound with the radical of sulphuric acid (HSO_3), and that in the urine several potassium salts of ethereal sulphates were present, the principal being those containing phenol, cresol, catechol or pyrocatechin, indoxyl, and scatoxyl. The latter are formed from indole and scatole by oxidation, and they form with sulphuric acid indoxyl- and scatoxyl-sulphuric acid.

In the urine of herbivora the group of ethereal sulphates is more abundant than in that of the carnivora or man, but it is present in small quantities in the urine of all animals.

The ethereal sulphates present in the urine of herbivora are undoubtedly formed from the aromatic substances contained in the vegetable food: they are formed in the intestine from the aromatic compounds by putrefactive processes; after absorption they enter the circulation, combine with the sulphuric acid radicle, and are eliminated (in the form of potassium salts) as conjugated sulphates.

In dogs and man the aromatic substances introduced with the food are small in quantity; they are excreted as ethereal sulphates and give a measure of the putrefactive processes carried on in the intestine. When intestinal putrefaction was arrested in dogs by strong doses of calomel or iodoform, Baumann and Morax observed a total disappearance of ethereal sulphates from the urine. In man it is difficult to obtain this result, since too strong a dose of the disinfectant would be required, but it is possible to reduce the amount of ethereal sulphates considerably by other means.

Rovighi's experiments (1891) are interesting from the clinical point of view. He found the elimination of ethereal sulphates to be relatively higher in the daytime than at night; ingestion of fluids increases excretion of aromatic bodies as compared with

sulphates in the urine; both the total sulphuric acid and the ethereal sulphates are scanty in children, while they are abundant in older people. In other experiments on himself, on his patients, and on dogs, Rovighi tried to determine which substances were most effective in diminishing the putrefactive processes of the intestine, and therewith, the ethereal sulphates of the urine. His conclusions are as follows:—

(*a*) The group of terpenes and camphor, especially oil of turpentine and camphor, administered in large doses to dogs, produced a considerable diminution in the aromatic products of intestinal putrefaction, which lasted for some time.

(*b*) The same substance, introduced by the mouth or per rectum, acted less efficaciously on man.

(*c*) The use of Carlsbad and Marienbad salts increases the elimination of ethereal sulphates during the first few days, but subsequently has the opposite effect, which is more marked in proportion as the previous intestinal disturbances had been conspicuous.

(*d*) Milk fermented with kefir taken in an amount of $1\frac{1}{2}$ litres a day is effective in checking intestinal putrefaction, owing mainly to its lactic acid content.

The fact that saline purgatives and mineral waters (including those in which the main content is sodium chloride) diminish the putrefactive processes of the intestine and reduce the amount of ethereal sulphates in the urine, was afterwards confirmed by Ewald of Berlin, by Fedeli and Casciani, and others.

A relative increase in the ethereal sulphates of the urine has been noted (Coggi), not only in disorders of the intestine, but also in chronic suppurative lung diseases, the putrefactive processes in this case arising from the pulmonary bacteria.

According to Baumann the synthesis of ethereal sulphates probably takes place in the liver. Kochs observed a partial synthesis of phenol and sodium sulphate, on adding them to blood which was left to digest with the liver and kidneys.

Reale further found that if phenol is injected into dogs, after tying all the hepatic vessels (an operation which they only survive for 2 to 4 hours) no phenyl sulphate of potassium is found in the urine or the bladder, which proves that under these conditions no other tissue or organ is able to synthetise the ethereal sulphates. The liver thus seems to be the only organ which performs this synthesis.

The ratio between the ethereal sulphates and the total sulphates of human urine is on an average, according to a number of analyses, 1:10. In the diseases in which the putrefactive processes of the intestine are increased, the value of this quotient also increases in proportion. According to Hoppe-Seyler, this is regularly the case: (*a*) in peritonitis and intestinal tuberculosis,

in which absorption of the products of intestinal digestion is defective; (*b*) in gastric disease, which causes a block of food in the stomach, and thus obstructs the fermentative processes; (*c*) also in diseases localised outside the digestive canal (cystitis, abscesses, suppurative peritonitis), in which putrefactive processes develop.

It is remarkable that in abdominal typhoid and in cases of simple intestinal constriction, the ethereal sulphates of the urine do not increase to any large extent.

VI. The urine collected under normal conditions, and still more in different pathological states, is rich in pigments, and substances readily converted into pigments and therefore known as *chromogens*. When examined in the spectroscope, however, normal urine exhibits no special absorption bands, but only a simple and partially diffused absorption, which varies in intensity in the different regions of the spectrum. It increases in the direction of red to violet, but in a different degree in different urines (Vierordt), showing that the quantity and number of the urinary pigments may vary, even under physiological conditions.

Few of the pigments detected by different workers have been obtained in quantities sufficient for chemical analysis: so that the distinct chemical individuality of many of them may be doubted, the more so as they are highly unstable, and readily undergo decomposition on treatment with strong reagents. The better-known pigments are *urochrome* and *urobilin*, the first being that which gives the urine its normal colour, while the second is usually present only in the form of its chromogen in fresh urine, so that it cannot be held (as many claim) to be a primary urinary pigment.

Urochrome, isolated by Thudichum (1864) in an impure state, mixed with other pigments, was obtained as a distinct chemical substance by Garrod (1894). He showed it to be a nitrogenous but iron-free substance, which gives the xanthoproteic reaction, and must therefore be regarded as an aromatic body. Although in the dry state it is amorphous and brown in colour, its aqueous solutions have, according to their concentration, the normal hue of urine in its various shades of clear yellow to orange and brown. Examined through the spectroscope it shows no special absorption bands, but absorbs the light diffusely, with increasing intensity from red to violet, like normal urine as a whole. It is therefore evident that urochrome is the principal pigment of normal urine.

The relationship between urochrome and urobilin is shown by their reciprocal conversion, on treating the former with a reducing and the latter with an oxidising agent. Garrod (1897) found in fact that the alcoholic solutions of urochrome treated with pure aldehyde give a pigment that shows all the reactions of urobilin. Riva (1896), on treating the latter with permanganate of potash, obtained a pigment which seems identical with urochrome.

Urobilin was separated from the urine of fever-patients by Jaffé (1868), but in normal urine he found a chromogen which is readily converted into urobilin, not only by the action of acids, but also by mere exposure of the urine to air and light. On spectroscopic examination the acid solutions of urobilin show an absorption band which corresponds with the transition from green to blue, more precisely between *b* and F. (See Vol. I. Fig. 35, p. 110.)

Maly's *hydrobilirubin* gives a very similar spectrum, as also the *stercobilin* found by Vanlair and Masius in the faeces. It is therefore not improbable that urobilin is identical with hydrobilirubin and stercobilin. But they differ in other respects, and the question has not yet been decided.

The amount of urobilin in normal urine after the whole of the urobilinogen has been converted into pigment varies, according to Saillet, from 30 to 130 mgrms. per diem. According to Arcangeli and Cavazza, under normal conditions, 65 mgrms. urobilin are obtained on an average from man, and 60 mgrms. from woman. It increases considerably in fevers, in many infectious diseases, in all the anaemias accompanied by exaggerated haemolytic processes, in many hepatic diseases, etc.

Urobilinogen is undoubtedly derived from blood pigment and the bile pigments, particularly from bilirubin. It is certain that the chief part of the urobilin and urobilinogen of the urine originates in the intestine from the bile pigments, in consequence of the fermentative processes due to intestinal microbes. The following facts can be adduced in support of this theory:—

(*a*) Urobilinuria occurs when the putrefactive processes of the intestine are exaggerated (Harley).

(*b*) Urobilin is absent in the urine of the newborn before any bacteria penetrate the intestine (Fr. Müller), while stercobilin is at the same time absent from the faeces (Riva).

(*c*) Urobilin is absent in adults after complete occlusion of the bile passages, and makes its appearance again when the flow of bile to the intestine recommences (Beck, Riva, and Zoja).

(*d*) On estimating the urobilin and urobilinogen of the urine and the faeces, there is in every case a certain proportionality (Riva).

The formation of urobilinogen from bilirubin in the intestine does not take place by simple hydrolysis, as Maly believed from his work on hydrobilirubin, but by a more profound metamorphosis of the bilirubin molecule. This loses half its nitrogen, as shown by Garrod and Hopkins from quantitative elementary analyses of the elements of these substances, as obtained by various means and from various sources.

The most favourable conditions for the formation of urobilinogen from bilirubin occur in the normal course of the functions of the intestine. Nearly the whole of the urobilinogen formed in the

intestine is eliminated with the faeces, the remainder is absorbed and carried by the portal vein to the liver, where it is partially poured out again into the intestine with the bile, partially traverses the hepatic veins and is excreted with the urine (Riva).

It is possible from daily determinations of the quantitative fluctuations of the urobilinogen content of the urine and faeces, together with estimations of the variations in the haemoglobin content and number of erythrocytes in the blood, to calculate the value of the haemoglobin exchange, *i.e.* the extent to which the haemoglobin is destroyed and formed again (Zoja). The bilinogen content of the urine and faeces increases after hard muscular work, in fevers, and, generally speaking, with exaggerated haemolysis, and diminishes during convalescence from febrile maladies and in chlorosis.

According to Riva's interesting studies, the urobilinogenesis is in strict relation with the quantity of bilirubin secreted by the liver-cells. Estimation of the urobilin content of the urine and faeces therefore gives a criterion of the normal or more or less degenerated hepatic cells. The persistence of the urobilin (and still more its increase) must indicate a favourable prognosis, even in serious cases of hepatic disease. This theory of Riva is confirmed by observing the way in which the formation of urobilinogen alters in the course of intoxication by phosphorus and nitric acid.

The possibility is not, however, excluded of a certain amount of urobilin and its chromogen being formed, along with other bile pigments, by the metabolic activity of the hepatic cells (Hayem), and also by the reducing action exerted on the bile pigments by the various tissues, especially the kidneys (Quincke, Kiener, Engel, Mya). This view, which assumes in addition to the *intestinal*, a *hepatic* and *renal origin* for urobilinogen, is supported by the fact that in the descending phase of cholaemia bilirubin alone is found in the blood, urobilin alone in the urine, which can be explained on the assumption that the first is converted by the action of the renal epithelia into the second.

Urobilin must not be confounded with the pigment that produces the dull red colour of the urate sediment. This comes from the *uroerythrin* present in minute quantities in normal urine, to a larger extent in fibrile urine. Uroerythrin has specific chemical and spectroscopic characteristics which differ from those of urobilin. Probably it is contained in the urine as a sodium salt in combination with the urates.

The genesis of uroerythrin and its relations with Garrod's urochrome and urobilin are unknown. According to Riva, Primavera and Reale, uroerythrin is found particularly in diseases of the liver (cirrhosis), and generally in all morbid conditions in which urobilinuria is present. It is probable from clinical observations that the presence of uroerythrin connotes some alteration of

the hepatic cells (even if slight and fugitive), such as usually arises from gastro-enteric disorders.

Of the chromogens contained in the urine, the most important from its physiological significance is undoubtedly *indican*, which is readily oxidised, and gives rise to *indigo-blue* and its isomer *indigo-red*. Jaffé was the first who recognised, by special experiments with diet, that *indole* is the mother-substance of the indican of the urine. Baumann proved that *indoxyl* is formed by oxidation of indole, and that it is, as we have seen, normally present in urine in combination with sulphuric acid and potassium in the form of *potassium indoxyl-sulphate* (indican). From this compound the indoxyl resists oxidation: it is liberated by hydrolysis with acid, and on oxidation to indigo the urine may be stained blue or red.

The practical importance of the indican reaction of the urine rests on the fact that indole, its mother-substance, is the most characteristic product of the protein putrefaction that takes place in the intestine. From the relative indican content of the urine we can therefore make an approximate estimation of the putrefactive processes in the intestine. Quantitative estimation of the whole of the ethereal sulphates, however, gives a more exact criterion of the degree and intensity of intestinal putrefaction, because indole is not the only aromatic body present in the urine.

VII. Small quantities of non-nitrogenous organic acids are very frequently present in normal urine, among which we must confine ourselves to noting oxalic acid, lactic acid, and various fatty acids.

Although not constant (Neubauer), the presence of *oxalic acid* in the form of calcium oxalate in the urine is held to be normal. It crystallises readily a few hours after the urine has been passed, probably in consequence of an acid fermentation. Normally it is held in solution by the acid sodium phosphate.

According to Fürbringer the oxalic acid content of human urine fluctuates from a hardly perceptible trace to 20 mgrms. per diem; according to Schultzen, on the contrary, it may amount to 10 cgrms. per diem. In the urine of certain animals (horses, pigs) it is found in much higher quantities.

Part of the oxalic acid of the urine is undoubtedly alimentary in origin. Many fruits and vegetables, as well as herbage, contain oxalic acid, which resists oxidation in the body, and is largely excreted again in the urine (sorrel, spinach, asparagus, grapes, apples, rhubarb, gentian, etc.). Still it is a well-established fact that oxalic acid can be detected in the dog's urine independent of vegetable food during an exclusive diet of meat and fat (Mills). The katabolic processes of the tissues can thus give rise to a formation of oxalic acid. The specific conditions of this process are not yet known. According to some interesting observations

of Gaglio, delayed circulation is a condition favourable to the formation of oxalic acid. In fact, if a frog is immobilised by curare (Vulpian) or other means (Gaglio), calcium oxalate appears in the urine. Any artificial diminution of the oxidative processes, again, promotes formation of oxalic acid. In dogs Reale and Boeri observed this on obstructing the respiration; Terray on diminishing by half the oxygen of the inspired air. In pathological conditions *oxaluria* has been observed in fevers, in illnesses accompanied with serious respiratory disturbances, or grave depressions of the nervous system, and above all when general metabolism is sluggish.

Increase of oxalic acid is often associated with increase of uric acid. With artificial introduction of uric acid and urates, again, Wöhler and Frerichs succeeded in obtaining an increase of calcium oxalate in the urine. Since uric acid splits under the action of ozone into urea, oxalic acid and allantoin (Gorup-Besanez), it is not improbable that a similar decomposition takes place in the body.

Lactic acid was formerly regarded as one of the normal constituents of urine (Berzelius); later on, this theory was held to be fallacious (Liebig). Recent observations of Hess, however, make it probable that a trace of lactic acid is normally present in the urine. Spiro's researches show that after hard muscular work the amount of lactic acid combined with bases increases conspicuously in the urine. This fact was confirmed by Colasanti and Moscatelli, who found a large amount of *paralactic acid* in the urine of soldiers after a 24 kilometres march. The same phenomenon was subsequently confirmed by Vicarelli in the urine of women in childbirth, after a difficult delivery.

Lactic acid appears as a consequence of various intoxications; in poisoning by phosphorus (Schultzen and Riess), carbonic oxide (Münzer and Palma), curare, morphine, cocaine, amyl nitrite, veratrine (Araki), and, generally speaking, under all conditions which, by obstructing the respiratory gas exchanges, weaken the processes of oxidation. After extirpation of the liver in geese, Minkowski noted lactic acid in the urine. The same was confirmed by Nebelthan for frogs. Zillessen evoked the same phenomenon in dogs, by simple ligation of the hepatic artery,

Taken as a whole, these facts make it probable that the formation of lactic acid is associated with a deficit or check in the oxidative processes in the body.

Normal urine further contains small quantities of *volatile fatty acids*, specially acetic, formic, propionic, and butyric acid (v. Jaksch). According to Jaksch the daily amount of these does not exceed 8-9 mgrms., but it increases to a marked extent on a farinaceous diet, and in pathological conditions, in fevers in general, in certain hepatic diseases, in diabetes. In all probability

these originate in the bacterial processes of fermentation and putrefaction which the proteins and carbohydrates undergo in the intestine. The fatty acids of low molecular weight are probably oxidised after their absorption in the blood, while those of higher molecular weight undergo incomplete oxidation only, and are eliminated partly by the lungs, partly by the kidneys. They are more abundant in the urine of the herbivora than in that of carnivora.

VIII. The question whether normal urine contains *sugar* or not has been much discussed. It is difficult to clear up this point because certain substances in the urine have, in common with sugar, the property of reducing the oxides of copper and mercury in alkaline solution; such are uric acid, hippuric acid, creatinine, pyrocatechin. These substances are not, however, like sugar liable to alcoholic fermentation, which is constantly observed when beer yeast is added to urine (Abeles). Nearly every one now believes in the view originally put forward by Brücke, that urine normally contains traces of *glucose* or *dextrose*.

A considerable amount of *lactose* is present in the urine of women during lactation (Blot, Hofmeister, and others). The physiological and pathological conditions under which the sugar of the urine can be increased temporarily (glycosuria) or permanently (diabetes mellitus), have already been treated at length (Chapter V. p. 314 *et seq.*).

According to Landwehr's researches, a carbohydrate similar to dextrin, and non-fermentable, is always present in normal urine: this he termed *animal gum*. It can be isolated by means of its property of forming an insoluble compound with copper. When boiled with acids, animal gum gives rise to a reducing substance (probably a sugar) which increases the total reducing power of the urine. Wedenski and Baisch confirmed the observations of Landwehr. It is probable that the mother-substance of animal gum is *mucin*, the chief constituent of the mucus secreted by the epithelia that line the urinary passages, which under normal conditions is present in small quantities in the urine.

According to v. Jaksch, normal urine always contains a small quantity of *acetone* or *dimethylketone* (C_3H_6O), a compound closely allied to the alcohols, which was first discovered in large quantities in diabetic urine by Petters (1857) and Kaulisch (1860).

The presence of acetone in normal urine was questioned by Albertoni, le Nobel, and Moscatelli; but it has been confirmed by others—in Italy by Boeri, who regularly found 12-15 mgrms. per diem under physiological conditions. It appears in considerable quantities in diabetics, and under various morbid conditions accompanied by fever; in different gastro-intestinal affections; in many pathological or experimental lesions of the nervous system, in various exogenous or endogenous intoxications, in

carcinoma, in various anaemic and leucaemic conditions. According to Boeri and Reale, *acetonuria* is generally induced by the condition which causes *oxaluria*, and an excessive formation of acids in the body, viz. diminished gas-exchanges, and depression of the oxidising processes in the tissues. In fact, on obstructing pulmonary ventilation in dogs by applying Sayre's jacket to the thorax, they obtained marked modifications in the katabolic tissue-processes, characterised by increased consumption of proteins, excessive formation of acids, oxaluria, and acetonuria, with corresponding increase of ammonia in the urine.

Urine also contains a derivative of glucose, which has the characteristics of the aldehydes and acids, and can be readily interchanged with sugar on account of its marked reducing power. This is *glycuronic acid* ($C_6H_{10}O_4$). In normal urine there is, according to Schmiedeberg, a small quantity of glycuronic acid combined with phenol, indoxyl, and scatoxyl with which it forms glycuronic esters, which readily split up when treated with mineral acids.

On the exhibition of certain poisons or drugs, the quantity of glycuronic acid in the urine increases considerably. This is seen in chloroform narcosis; after the use of chloral, camphor, morphine, curare, etc. The apparent glycosuria induced by these substances is due to the glycuronic esters, and should therefore be termed *glycuronuria*.

Addition of beer yeast to the urine does not cause any marked alcoholic fermentation, such as invariably appears in glycosuria. The glycuronuria due to drugs is transitory and has only a clinical interest. The rare cases of spontaneous glycuronuria, on the contrary, *i.e.* such as are not produced by poisons or drugs, are interesting not because they represent any dangerous alteration in the katabolic tissue processes like diabetes, but because they elucidate the physiological problem of the origin of glycuronic acid. For the present we must confine ourselves to the chemical researches by which glycuronic acid has been obtained from sugar; and from which we learn that this acid is an intermediate product of carbohydrate metabolism. It probably appears in the urine when it escapes complete oxidation, by combining with the aromatic bodies or with other substances foreign to the ordinary diet or the normal katabolism of the tissues. In the same way glycocoll escapes oxidation by combining with the benzoic acid, and appears in the urine in the form of hippuric acid.

Pentoses also can be isolated in the urine, particularly after the ingestion of fruits that contain them (*alimentary pentosuria*). A spontaneous pentosuria has also been noted, without any apparent external cause (Salkowski and Jastrowitz, 1892). Luzzatto, who with Reale has specially occupied himself with pentosuria in Italy, was the first to isolate an active pentose

(*l-arabinose*) from a pentosuric urine. In the very rare cases so far described, there is a benign anomaly of metabolism which may be easily confused with diabetes, if the special methods for detecting pentose are not applied to the analysis of the urine.

IX. The urine of normal individuals yields in the great majority of cases no trace of *protein*. This fact is beyond controversy, as all the most reliable authorities agree on it. There is, however, no ground for assuming that *albuminuria* is in every case a pathological phenomenon. Under special conditions even perfectly healthy individuals exhibit a transitory albuminuria which, even if accidental or abnormal, cannot be regarded as morbid.

We saw in Chapter V. p. 287, that a transitory albuminuria makes its appearance after the consumption of a large amount of egg-albumin. Landois stated that he had seen albuminuria in a man 4-10 hours after the ingestion of the raw, salted whites of 14-20 eggs. The albumin content of the urine increased progressively to the end of the third day, after which it began to decrease, and disappeared altogether by the fifth day. The same phenomenon occurs on the direct injection of ovalbumin into the circulation (Stokes, Lehmann, Verdelli, and Gabbi).

Some admit a slight transitory albuminuria, independent of any renal lesion or excessive consumption of egg-albumin, whenever the amount of protein in the blood plasma is abnormal, either from excessive protein alimentation, or from reabsorption when the lacteal function is suspended (v. Bamberger, Posner, Hawkins). This form of transitory albuminuria is termed *haematogenous*.

After excessive muscular work, again, a slight albuminuria described as *physiological* or *functional*, can be detected (Leube, Dukes, Fürbringer, G. Marcacci).

Leube investigated the urine of 119 soldiers, both in the morning before they were drilled, and in the evening after complicated and fatiguing marches. The morning urine of five individuals yielded albumin, *i.e.* in 4·2 per cent; in the evening it was present in 19 individuals, *i.e.* in 16 per cent. In no instance did the amount of albumin exceed 0·1 per cent.

Capitan's researches on soldiers of 21-25, as well as on children from 1 to 8 years of age, confirmed the fact that physiological albuminuria is a very common phenomenon. Not unlike this is the albuminuria that has been observed after the convulsive spasms excited by strychnine, or in man after epileptic attacks (Huppert).

Transitory albuminuria may occur also in consequence of a rapid rise in blood pressure in the vascular district of the kidneys, *e.g.* after cold baths (Lassar, Johnson, Hawkins). Johnson's cases were young, healthy students, who after 15 minutes to 1 hour's

immersion in cold water, complained of fatigue and headache, followed by slight albuminuria of short duration.

Albuminuria can be experimentally produced in animals by abnormal increase of blood pressure in the vascular parts of the kidneys. We shall speak of this in the next chapter, in discussing the secretion of urine.

In almost all cases of spontaneous or experimental albuminuria, *serum-globulin* is associated with serum-albumin in the urine, in proportions that vary considerably from 8-60 per cent of the total coagulum (Hammarsten, Hoffmann, Patella, Czàtary). Serum-globulin may be present without serum-albumin, or *vice versa*. In true nephritis (*Bright's disease*) the so-called urinary casts are invariably present in urine, showing that the *fibrinogen* of the blood plasma is also thrown out by the kidneys, and suddenly converted into *fibrin*, which takes the cylindrical form of the renal canaliculi. The total amount of protein eliminated by the kidneys rarely exceeds 1 per cent, but may, in certain cases, amount to 4 per cent (Hoppe-Seyler).

The cases of *haematuria*, or admixture of blood *in toto* with urine, or of the blood pigment only (*haemoglobinuria* or *methaemoglobinuria*), belong exclusively to pathology.

Enzymes may also be included among the proteins of the urine, pepsin (Brücke, 1861) and the diastatic ferment (Cohnheim, 1863) being constantly present in normal urine.

Pepsin is abundant in the urine passed in the morning before a meal (Sahli, Mees), scanty in the urine secreted in the first hours after a meal (Sahli, Gehring, Hoffmann). After prolonged fasting there is no trace of it, but after consumption of food it appears again abundantly (Leo, Senator). In disease it seems to diminish, but observations on this point are at variance, so that the fact cannot be used in diagnosis (Leo, Wasilewski, Mya and Bonfanti, Stadelmann).

The presence of *trypsin* in urine is denied by Sahli, regarded by others as inconstant. Bendersky, however, always detected a substance in normal urine which dissolved fibrin in alkaline solution. This fact was confirmed in our laboratory by Tarulli in the urine passed before a meal. The substance disappears during digestion, and subsequently reappears.

The *diastatic enzyme* is constant in the urine of man and rabbits. It increases after a meal, and diminishes in the night-urine, and during abstinence (Gehring, Hoffmann).

Till recently it was assumed that these digestive enzymes were included among the specific products of the gastric, pancreatic, and salivary secretions, which, after fulfilling their digestive functions in the gastro-intestinal canal, are reabsorbed previous to decomposition, brought into the circulation, and eliminated by the kidneys. At present the tendency is rather to

conclude that the ferments of the urine are derived from the intracellular ferments which have been demonstrated within every organ, and which give rise to the so-called *autolytic cleavage products* (Salkowski. See Vol. I. p. 34).

Matthes attempted to solve the question of the origin of the enzymes of the urine by experiment (1903-4). On analysing the urine of dogs from which he had previously removed the whole of the stomach, or pancreas, he saw that in the first case no pepsin could be detected in the urine; while after removal of the pancreas ferments were still present, which were able to split up protein in alkaline solution. This led him to conclude that the proteolytic enzyme of the urine which acts in an acid medium, is reabsorbed pepsin, and not an autolytic ferment. On the other hand, even when the possibility of trypsin reabsorption is excluded, proteolytic cleavage can take place in an alkaline medium; this is evidently due to ferments eliminated with the urine, which must be autochthonous in the different tissues of the body.

X. The *inorganic constituents* of urine are chlorides, carbonates, sulphates, and phosphates, the bases of which are represented by soda, potash, ammonia, lime, and magnesia. Small quantities of fluorine, silicic acid, and iron are also found in urine. The total quantity of salts in the urine fluctuates from 9 to 25 grms. per diem.

The salt most abundantly present in the urine is sodium chloride, with which are associated small amounts of potassium chloride and traces of calcium and magnesium chloride. 6-8 grms. chlorine can be found in the urine in one day, which correspond to 10-13 grms. sodium chloride. The whole of the salt used as a condiment reappears in the urine partly on the same, partly on the next day (Dehn). A small proportion of it is decomposed by the glands of the fundus of the stomach in the formation of hydrochloric acid, and is then regenerated in the intestine by the sodium carbonate of the succus entericus. (See Chapter IV. p. 222.)

The sodium chloride of the urine increases after an abundant meal, and diminishes in the night hours. It increases after copious draughts of water. It diminishes temporarily after an abundant secretion of gastric juice. It increases after inhalation of chloroform, and not after taking chloral (v. Mering), although both these are compounds of chlorine. Injection of potassium salts increases the elimination of sodium chloride (Bunge).

It must not be thought that the whole of the sodium chloride remains in a free state dissolved in the plasma, serving merely as a vehicle for the metabolic exchanges of the tissues. Part of it is chemically combined with the organic molecules of the bioplasm, and enters, as it were, into the chain of its metabolic processes—is, in short, a true mineral aliment. In proof of this it is only necessary to consider how the total chlorine content of the urine varies during and after fasting. We ourselves, in the case of

Succi, as also I. Munk on Cetti, observed a progressive diminution of the chlorine content from the commencement to the end of the fast. During inanition, when the plasma and tissues are very poor in sodium chloride, ingestion of this salt produces no corresponding rise in its excretion. On resuming the normal diet a considerable amount of the salt given with the food is retained for two or three days.

Pathological observations support these facts. In febrile maladies in general, especially in pneumonia, rheumatic arthritis, and typhoid, there is a very marked diminution in the sodium chloride excretion by the urine (*hypochloruria*). According to Salkowski this is not merely the result of the decreased consumption of salted foods, but is a true retention of chlorine in the body. In fact, sodium chloride excretion rises again without ingestion of food, as soon as the crisis of the illness is over. In one case of pneumonia, the sodium chloride excreted fell to 1-1·6 grm. per diem, and rose again after the crisis to 7·87 grms., and on the next day to 16·18 grms. This fact cannot be explained simply by reabsorption of the exudate, the molecular concentration of which is always isotonic with blood plasma (Winter and others)—one of the most important functions of the sodium chloride in the blood being to maintain equilibrium in the osmotic pressure of the tissue fluids.

The *sulphuric acid* excreted in the urine, either in the form of *alkaline sulphates* or combined with the aromatic products in the form of *ethereal sulphates*, amounts as a whole in adults, with a mixed diet, to 1·5-3 grms. per diem calculated as SO_3 (Fürbringer and Neubauer). As a rule, the amount of sulphates introduced with the food is scanty, and even when abundantly supplied in the form of magnesium or sodium sulphate the greater part of these salts are eliminated by the intestine, on which they act as a cathartic. The sulphuric acid of the urine thus originates almost exclusively from the oxidation of the sulphur of the proteins introduced with the food, or from the tissue protein consumed. The variations of the sulphuric acid in the urine are therefore almost parallel with those of the urea, both being decomposition products of protein.

The amount of sulphuric acid combined with the aromatic ethers is on an average $\frac{1}{10}$ the total sulphuric acid, but this ratio is subject to many pronounced oscillations according to the nature of the diet and the varying intensity of the putrefactive processes of the intestine (*supra*, p. 395 *et seq.*).

The whole of the sulphur contained in the urine does not appear as sulphuric acid: part of it is present in the form of organic compounds of which some only are known to us. Salkowski gives the name of *neutral sulphur* to these, to distinguish them from the preceding or *acid sulphur*. Neutral sulphur constitutes

about 20 per cent of the total sulphur. It consists partly of the *sulphocyanide* of the saliva, partly of the *taurine* of the bile, partly of compounds homologous with *cystine*.

Phosphoric acid is present in normal urine, in the form of *alkaline phosphates* (mostly sodium, a little potassium) and of *earthy phosphates* (chiefly calcium, a very little magnesium).

The acidity of the urine, as stated, depends principally on the monobasic phosphates of sodium and calcium, the so-called *acid phosphates*. When the urine is neutral, part of the monobasic are replaced by dibasic phosphates. When, lastly, the urine is alkaline, a more or less considerable part of the phosphates is found in the form of tribasic phosphate, sodium, calcium, magnesium. Lastly, it should be noted that part of the phosphoric acid in the urine is combined with ammonia.

The phosphoric acid of the urine comes partly from the food, partly from the decomposition of the organic phosphorus compounds of the tissues. Meat, milk, cereals, vegetables, which represent the principal food-stuffs, are more or less rich in phosphates. Part, however, of these alimentary phosphates (particularly the phosphates of calcium and magnesium) are not absorbed by the intestine, but pass out unaltered in the faeces.

In fact the urine of herbivora is comparatively poor in phosphates, although earthy phosphates abound in their diet. But the tissues are also more or less rich in phosphates, the bones especially so in the form of calcium and magnesium phosphate. There is, further, a group of *organic phosphorus compounds*, in which are included the nuclein, which forms the chromatin of cell nuclei, lecithin, which is most plentiful in the nervous system, and jecorin, found principally in the liver. All these substances are able by oxidation of the phosphorus to form phosphoric acid which appears in the urine.

The amount of phosphoric acid excreted daily fluctuates between 2·5 and 3·5 grms. The earthy phosphates represent about half the total phosphates. In general it may be stated that the fluctuations of the phosphorus content of the urine correspond with the fluctuations of the nitrogen content. This is especially shown when the subject experimented on is kept on a constant diet, so that the amount of phosphates and inorganic phosphorus compounds introduced does not vary perceptibly. On a normal mixed diet, the average ratio between the phosphorus and nitrogen content of the urine is as 1 : 17·45, *i.e.* for one gramme of phosphorus there are 17·45 grammes nitrogen in the urine. During Succi's 30 days' fast at Florence, we found that the quotient $\frac{N}{P}$ was always lower than 17·45, which means that during inanition the excretion of phosphorus increases considerably in comparison with the excretion of nitrogen. I. Munk made the same observation

in Cetti's 10 days' fast, and explained it logically on the assumption that during inanition the bone tissues, which are rich in phosphates and poor in nitrogenous substances, are used up. Evidence in favour of this assumption is afforded by the fact that in fasting the amount of calcium and magnesium, which are the bases of the bone phosphates, also increase in the urine. The excretion of phosphates in fever, which is almost always accompanied by more or less accentuated phenomena of inanition, should be further investigated, in view of this important fact observed during complete abstinence.

According to Ott's researches the influence of diet appears plainly in the daily curve of the total elimination of phosphates, which rises and reaches its maximum in the hours that succeed the principal meal, and falls again in the night hours, reaching its minimum in the hours that precede a meal.

The *carbonic acid* of the urine occurs partly in a *free* state, partly combined as *carbonates*, and *bicarbonates* with soda, lime, magnesia, and ammonia, which are specially abundant in the fresh, alkaline urine of herbivora.

Free carbonic acid, according to Planer, is present in human urine to an amount of 4-9 vols. per cent—according to Pflüger of 13-14 vols. per cent. The partial pressure of the CO_2 in the urine is somewhat higher than in the blood (according to Strassburger it is equal to $\frac{n}{13}$ of an atmosphere), and rises somewhat in fever (Ewald).

The amount of combined carbonic acid in human urine is usually less than that present in the free state (2·5 vols. per cent according to Planer, 0·1-0·7 vols. per cent, according to Pflüger), and does not increase in fever (Ewald). The carbonates and bicarbonates are alimentary, or come from the lactic, malic, tartaric, succinic, and other vegetable acids introduced with the foods, which are readily oxidised by conversion into carbonates. This is the reason why the urine of herbivora and vegetarians is so rich in carbonates, which give it an alkaline reaction, and cause it to become turbid shortly after emission. On filtering off the deposit, it is found to consist of calcium carbonate and phosphates.

Among the inorganic bases contained in urine, special mention must be made of *ammonia*. Only a trace can be detected in the free state previous to the commencement of alkaline fermentation, in which the urea is converted into ammonium carbonate. The chief part of the ammonia is found in the form of *ammonium salts* (phosphates, carbonates, etc.) to an average daily amount of 0·7 grm. (Neubauer). For the same person, Coranda found 0·64 grm. after an ordinary mixed diet, 0·87 grm. after a flesh diet, 0·64 grm. with a vegetable diet. The influence of alimentation on the ammonia content of the urine is therefore striking.

Injection of ammonium salts increases the amount present in

the urine, with the exception of ammonium carbonate, which is converted into urea by the liver (*supra*). Schmiedeberg's theory of the origin of the ammonia of the urine seems to us the most acceptable. He holds that the small amount of ammonium salts in the urine represent the residue of the large quantity of *ammonium carbonate* (and, as we should add, of *ammonium carbamate* also) which are formed along the course of the alimentary canal, and which have escaped conversion into urea by the liver.

The content of ammonium salts in the urine increases under all conditions which produce increase of the acids absorbed from without, or formed within the body (*acid intoxication*). The same factors which tend to form oxalic acid and lactic acid in the dog simultaneously increase the ammonia of the urine (Reale and Boeri). The same occurs in acute poisoning by phosphorus (Münzer). The ammonia content rises in the urine in high and persistent fevers, as almost invariably in diabetes (Hallervorden, Coranda, Schmiedeberg), probably because in these cases there is increased development of acids in the body.

XI. It is evident from this review of the most important constituents of normal urine, that the physiological office of the kidneys is to eliminate from the body the chief part of the waste products developed by the katabolic processes of the tissues, whether these metabolites are derived from the substances introduced in the food, or from those which constitute the materials proper of the bioplasm. This elimination is a real purging of the organism, indispensable to the normal exercise of its functions. Should the greater part of the urinary katabolites, either from abnormal conditions, or from profound degeneration of the kidneys, be retained in the blood and accumulate in the tissues, grave phenomena of auto-intoxication arise which shortly cause the death of the animal.

According to Prévost and Dumas (1822), animals do not survive the loss of the kidneys for more than 42 hours; according to Cl. Bernard (1847-59), dogs can survive 50-75 hours. After 10-12 hours they vomit the food previously ingested, and subsequently become depressed, weak, and refuse food, their respiratory movements become dyspnoeic, and they utter cries. These phenomena grow more pronounced, with a tendency to coma, and at a given moment, without any perceptible external cause, the animal is seized with epileptic convulsions, which get worse and worse, till it dies. On experimenting with a dog that had previously been operated on by gastric fistula, Bernard observed that the secretion of gastric juice, a few hours after nephrectomy, increased considerably in quantity and became continuous even during abstinence; that it contained ammonium salts, and preserved its acidity and digestive powers; lastly, that this

flow of gastric (and intestinal) secretion containing ammonium salts persisted so long as the animal retained its normal vivacity, and diminished progressively during the aggravation of the phenomena of auto-intoxication, during which only was there increase of urea in the blood. In short, toxic phenomena were not developed so long as the gastro-intestinal surface functioned as the vicarious excretory system in place of the kidneys, and when this vicarious function ceased, auto-intoxication set in, and soon led to the death of the animal.

In the advanced stages of *Bright's disease* also, when the impermeability of the urinary passages has become marked, a very complex syndrome of auto-intoxication phenomena makes its appearance, which is known to pathologists as *uraemia*—a most inappropriate term, since this state depends less on the retention of urea than on the sum of the other mineral and organic substances normally present in the urine, which exert a far greater toxic action on the tissues. This was first demonstrated by Gallois in Bernard's laboratory (1859), who found that the injection of strong doses of urea into the blood did not produce permanent disorders, such as are observed in the diseases caused by the so-called "uraemia."

That urea *in* and *per se* is not toxic to vertebrates can also be deduced from the striking fact, first pointed out by von Schröder (1890), that the blood of certain fishes (*Selachia*) normally contains urea in a concentration of 2·6 per cent, which approximately corresponds with that at which it is normally present in human urine. According to Baglioni (1905, see Vol. I. p. 297), the high content of urea in the blood of these fishes is not only innocuous, but even essential, in order that the myocardium shall function properly.

Another method of demonstrating that the urine, as a whole, normally contains toxic substances, consists in its intravenous injection into animals, on which (when the quantity injected reaches a certain maximum that increases with the body-weight) toxic phenomena set in that are rapidly fatal. Feltz and Ritter (1881) first performed this experiment successfully on rabbits, and Bocci, at Moleschott's suggestion, shortly afterwards on frogs. But the credit of establishing the importance of this method of determining the toxicity of natural urine and its principal components, is undoubtedly due to Bouchard (1887). He always employed rabbits, by injecting the fresh urine either of a healthy or of a sick man into the auricular vein, and then observed the toxic phenomena, which varied with the varying dose of urine injected. He gave the name *urotoxia* to the amount of toxic constituents necessary for the lethal dose per kilo. of the animals experimented on, and *urotoxic coefficient* to the amount of urotoxias eliminated with the urine in 24 hours per kilo. body-weight.

According to the average of Bouchard's results, the urotoxic coefficient of man under normal conditions is equal to 0·464, and varies within narrow limits. In pathological conditions it rarely exceeds 2, and rarely falls below 0·10.

The following was Bouchard's method of determining the urotoxic coefficient of the urine: say that in a healthy man of 60 kilos. body-weight 1200 c.c. urine are excreted in the 24 hours. If 50 c.c. of this urine per kilo. of the animal (rabbit) kill it, *i.e.* contain 1 urotoxia, then the 1200 c.c. urine must contain 24 urotoxias. In effect, 50 : 1 :: 1200 : x, therefore

$$x = \frac{1200}{50} = 24.$$

If 60 kilos. of man produce 24 urotoxias per diem, 1 kilo. must produce $\frac{24}{60} = 0{\cdot}4$ urotoxias;

0·4 is therefore the normal urotoxic coefficient.

On the hypothesis that susceptibility to urinary poisons is the same for man as for rabbit, the amount of urine necessary to kill the man by whom it has been excreted can be calculated. We have therefore the following proportion: 24 : 1200 :: 60 : x, whence it results that

$$x = \frac{1200 \times 60}{24} = 3000$$

i.e. 3 litres of urine will kill a man of 60 kilos. body-weight who daily excretes 24 urotoxias, viz. the urine passed in two days and eight hours.

The *toxicity of normal urine* is affected by cerebral activity, muscular activity, sleep, nutrition, etc. The variations involve not only the amount but also the nature of the urinary toxins. The urine of sleep, although denser and richer in solid matters, is nearly always, given the same volume and time of secretion, less toxic than the urine of waking. During sleep, according to Bouchard, man elaborates 2-4 times less poison than during the corresponding period of cerebral activity. Further, the urine of sleep produces convulsions, while that of waking is narcotic. The body must, therefore, when awake manufacture substances which, on their accumulation, induce sleep; during sleep, on the contrary, it accumulates such as discharge muscular twitches and provoke awakening. On mixing the urine of sleep with that of waking, the result is not average toxicity, but a toxicity lower than that of the less toxic urine.

Muscular work, far from augmenting the toxicity of urine, diminishes it by one-third, and this diminution persists for several hours after the muscular activity ceases. According to Bouchard these facts support the conjecture that the toxicity of the urine depends not on its mineral constituents, which certainly do not diminish with movement, but rather on the incompletely oxidised organic substances, the toxicity of which diminishes in proportion as they become oxidised.

Bouchard's results are important to the exact determination of the urinary constituents on which the various toxic phenomena depend, and may be shortly summed up:—

Urea, although present in large quantities in the urine, is certainly not the chief poison. Injection of urea into the veins produces toxic effects only when it is present in such an amount and concentration that the osmotic pressure of the blood is seriously altered (6·31 grms. urea per kilo. of the animal). In moderate doses urea has a diuretic action, so that, far from acting as a poison, it protects the body from auto-intoxication by accelerating the expulsion of endogenous poisons.

Nor can uric acid be regarded as a poison, since as much as 30 cgrms. per kilo. body weight can be injected without effect. Moreover, we know that man only forms 8 mgrms. uric acid per kilo. in the 24 hours.

Although elaborated by the muscles in large quantities, the innocuous character of creatine and creatinine has frequently been demonstrated (Ranke, Schiffer).

An alcoholic extract of the dry residue of urine certainly contains toxic substances, seeing that intravenous injection of an alcoholic solution induces drowsiness, coma, diuresis, salivation. At present we are quite ignorant as to what constituent or compounds the narcotic and scialagogic action depends on: all we can say is that the diuretic action is due to urea.

The urinary constituents which are insoluble in alcohol, on the contrary, produce the opposite effects of convulsion, hypothermia, myosis, without any symptoms of coma, salivation, or diuresis. It is possible that these effects are due to the mineral substances. Potassium salts, in fact, cause death with convulsive phenomena, when injected to an amount of 0·5 grms. per kilo. Ammonium salts also produce the same effect, but they are only present in small quantities in the urine. It seems, however, as if we must assume that there is in addition to these mineral poisons a substance producing convulsions, which is represented by an organic constituent insoluble in alcohol, seeing that night-urine produces convulsive effects, which is not the case with the urine of waking, —even after muscular fatigue, when more mineral salts are present.

All the toxic effects obtained by intravenous injection of urine into rabbits—coma, convulsions, myosis, salivation, hypothermia —are also exhibited in the last stage of *Bright's disease*, and in the *anuria* of *Asiatic cholera*. The sole difference observed in these spontaneous diseases as compared with the effect of experimental injection of urine into the blood consists in the fact that in the latter there is an abundant flow of urine promoted by the urea, which, as we have seen, has a diuretic action that proportionately alleviates the effects of the intoxication.

Our knowledge of the toxicity of urine has been considerably advanced by the work of Colasanti and his pupils (1895-96, 1899). He experimented on dogs instead of rabbits, finding them more resistant to the urinary poisons. Indeed, the mean urotoxic coefficient for normal dogs is, according to Colasanti, 0·182, a much lower figure than that determined by Bouchard for rabbits (= 0·465), showing that in dogs the resistance to these poisons is $2\frac{1}{2}$ times as great as that of rabbits.

On comparing the protective function of the kidneys with that of the liver, Colasanti saw that when the toxicity of the bile is maximal, that of the urine is minimal, and *vice versa*. The kidneys and liver can, therefore, act vicariously as purgative organs, when elimination of the endogenous poisons is inadequately performed by the one or the other system.

While studying the toxicity of the urine in diseases of the liver in which the functions of this viscus are more or less altered, Colasanti constantly observed *urinary hypertoxicity*, in ratio with the degree of hepatic insufficiency. This increase of toxicity in the urine is not in ratio with the amount of nitrogenous products contained in it, which may increase or diminish according to the different lesions of the hepatic parenchyma. It is therefore possible from the increased toxicity of the urine to judge of the gravity of the hepatic lesion, while its diminution may be a sign of recovery of the hepatic functions.

The experimental proof of the relations between the hepatic and renal functions is seen in the fact that after gradual occlusion of the portal vein the urine of the animals operated on becomes hypertoxic like that of liver-patients, since in this case the whole of the toxic substances otherwise eliminated by the bile find no outlet other than the kidneys. The same fact also shows that part of the biliary or urinary poisons are formed in the intestine, whence they are absorbed and carried to the circulation by the portal roots, and on reaching the liver are once more turned out into the intestine with the bile. Colasanti, in fact, showed that the bile secreted after occlusion of the portal system is so much less toxic in proportion as the toxicity of the urine becomes greater, although the chemical composition of the secretion may differ little from the normal.

The increase in the molecular composition of the blood observed in uraemia, depends not so much on the mineral constituents (bases, acids, salts) as on the organic compounds, which result from tissue metabolism. As demonstrated by Viola and by Bickel, the blood of nephrectomised or of uraemic patients does not show any change in electrical conductivity. That the cause of the uraemic phenomena lies in a specific toxic action of these organic metabolites when retained in the body, and not, as Lindemann (1899) concluded, in the increased osmotic pressure of the

blood, was demonstrated by Bickel (1901-3). By injecting indifferent substances into the blood, he succeeded in raising its molecular concentration to a much higher degree than is the case in uraemia, without producing any of the symptoms exhibited by uraemics.

F. Marino-Zuco and R. Onorato (1904-5) have recently found a characteristic poison in urine to which they have given the name of *biotoxin*, because it is found not only in urine, but in all the tissues and fluids of the human and animal body. They extracted it from urine by concentrating 50 litres in a special apparatus, at a temperature of 38° C., under aseptic conditions, till a fluid of syrupy consistency was obtained. From this, after repeated precipitation with alcohol and washing of the precipitate, they obtained the pure toxin in the form of a light, white, amorphous powder, devoid of odour, insoluble in alcohol, and giving no protein reaction.

This biotoxin is constantly present in the urine of man and the higher vertebrates, both herbivora and carnivora, to an amount of 0·3-0·5 per litre. It can, moreover, constantly be detected in the kidneys and the blood; and must therefore be a product of metabolism, removed from the blood by the kidneys, and then excreted. It has not yet been determined whether this elimination takes place solely in the kidneys, or whether other organs share in it. In whatever way biotoxin is isolated it invariably exhibits the same properties. Since on injection into the blood of animals it induces morbid phenomena similar to those of uraemia, while, on the other hand, there is less of it in nephritic than in normal urine, Marino-Zuco and Onorato conjecture that the accumulation of this poison in the blood, owing to functional insufficiency of the kidneys, plays a considerable part in the genesis of uraemia.

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CHAPTER VIII

THE EXCRETION OF URINE

CONTENTS.—1. Structure of the kidneys. 2. Mechanism of urinary secretion. Vitalist theory of Bowman; mechanical theory of Ludwig. 3. Modification of urinary secretion with variations of normal conditions of circulation in kidneys; conclusions as to functions of glomeruli. 4. Effect on renal secretion of alterations caused in the blood by diuretics; criticisms of mechanical theory. 5. Experimental data in favour of vitalist theory; criticisms. 6. Innervation of kidneys. 7. Modifications of epithelial cells of renal tubules during secretory activity and functional rest. 8. Function of ureters. 9. Mechanism of retention of urine. 10. Mechanism of micturition. 11. Innervation of bladder. Bibliography.

THE Kidneys are the organs that secrete urine; the Ureters are the canals that conduct the urine to the bladder, from which it is periodically expelled through the urethra. These organs as a whole form the Uropoietic System, the functions of which will be considered in the present chapter.

I. In order to form any idea of the mechanism by which the chemical constituents of the urine are separated from the blood, it is necessary to start with the *structure of the kidney*. In no other glandular organ do the structural peculiarities, the relations between circulatory system and excretory ducts, correspond as strictly as in the kidneys with the specific character of the functions. For this reason physiological theories as to the mechanism of urinary secretion first assumed a scientific character after the discovery of the highly characteristic structure of the kidneys, by which they are differentiated from all other glands.

The following were the most fundamental discoveries in regard to the morphology of the kidneys: Bellini (1661) first described the uriniferous tubules to which the kidney owes its character of a tubular gland. Malpighi (1669) first described the corpuscles that bear his name, and succeeded in injecting them through the arteries; he regarded them as small glands, for which Bellini's ducts form the excretory system. Huschke (1828) first pointed out that in birds and batrachia the uriniferous tubules end in the form of spherical dilatations. Johannes Müller (1830) shortly after discovered these dilatations in the uriniferous tubules of all vertebrates; but he did not detect their connection with the blood-

vessels, and relation to the Malpighian corpuscles, which he took to be simple vascular tufts, distinct from the dilatations of the ducts. Bowman (1842) first recognised the fundamental fact that the vascular glomeruli are enclosed in the spherical dilatations which he designated capsules—in other words, that the Malpighian corpuscles are terminal expansions of the uriniferous tubules, embracing a vascular glomerulus (Fig. 108).

The Malpighian corpuscles and their relation to the afferent and efferent blood-vessels are plainly seen on injecting the vessels,

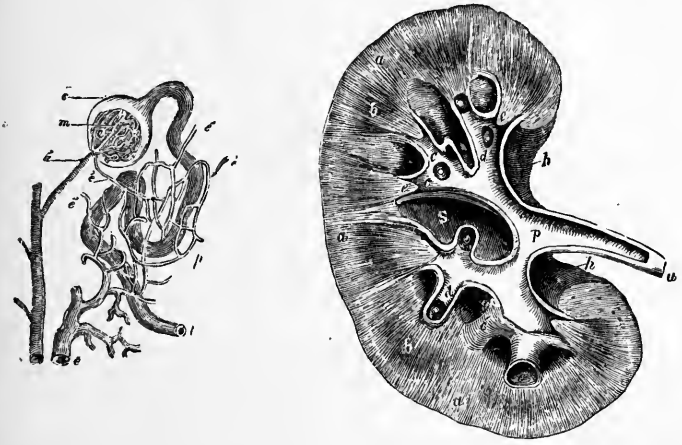


FIG. 108.—(Left.) Diagram showing relation of uriniferous tubules to blood-vessels. (After Bowman.) *a*, one of the interlobular arteries; *a'*, afferent artery passing into glomerulus; *c*, capsule of glomerulus; *t*, convoluted tube; *e' e'*, efferent vessels which subdivide in plexus *p*, surrounding the tube, and finally terminate in interlobular vein, *c*.

FIG. 109.—(Right.) Plan of longitudinal section through pelvis and substance of right kidney. One-half the natural size. *a*, cortical substance; *b*, *b*, broad part of two pyramids of Malpighi; *c*, *c*, the divisions of the pelvis named calices of infundibula, laid open; *c'*, one of these unopened; *d*, *d*, summit of pyramids or papillae projecting into calices; *e*, *e*, section of narrow part of two pyramids near the calices; *p*, pelvis or enlarged portion of ureter within the kidney; *u*, ureter; *s*, sinus; *h*, hilum.

while non-injected preparations show the connection of the capsules with the ducts. All subsequent work has merely extended and completed the discovery of Bowman, who confirmed the physiological concept formed by Malpighi from the corpuscles, and so long contested by Ruysch and his adherents. Bowman, however, made one fundamental modification in Malpighi's theory, inasmuch as he held that the renal corpuscles excreted water, and the uriniferous tubules the characteristic constituents of urine. Malpighi and Johannes Müller were the precursors, Bowman was the creator, of the *physiological theory of renal secretion.*

We must briefly consider the structure of the kidney. It is surrounded by a fibrous coat known as the *capsule,* which can

easily be detached, since it is only connected with the substance of the gland by minute processes of connective tissue and small vessels. If split up longitudinally, it presents the anatomical features shown by Fig. 109. The cortical substance is reddish-brown, the medullary pale and fibrous. In man the latter consists of about ten Malpighian pyramids, the points of which converge towards the pelvis which receives the secretion. An intermediate layer can be distinguished from the cortical and medullary substance, exhibiting characteristics common to both (Henle).

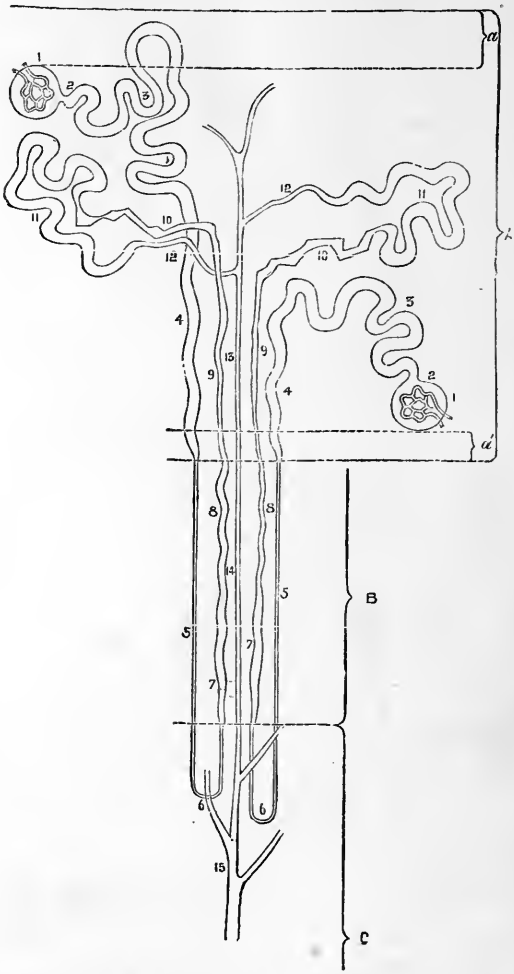


Fig. 110.—Diagram of course of two uriniferous tubules. (Klein.) *A*, cortex; *B*, boundary zone; *C*, papillary zone of medulla; *a*, *a'*, superficial and deep layers of cortex, free from glomeruli.

Each Malpighian pyramid consists of a large bundle of uriniferous tubules, which are straight in the medullary part (*tubuli recti* of Bellini), and convoluted in the cortical part (*tubuli contorti* of Ferrein). The straight tubules of the pyramids are prolonged into the cortical substance almost to the surface of the kidney, where they form the medullary rays, visible to the unaided eye, from which the convoluted tubules deflect to form the labyrinth of the cortex.

Fig. 110 gives a diagram of the course of the uriniferous tubules from their origin in the Malpighian corpuscles (Bowman's capsules enclosing the vascular glomerulus) to their opening upon

the papillae into the calices of the renal sinus. Each tubular orifice with its multiple ramifications represents a pyramid of Ferrein—the morphological unit from which the pyramids of Malpighi arise.

For physiologists the chief interest attaches to the structure of the different parts of the uriniferous tubules, and the epithelial cells with which these are lined, in the hope of distinguishing the *secretory portion* of the tubules from such parts as simply *conduct* the urine.

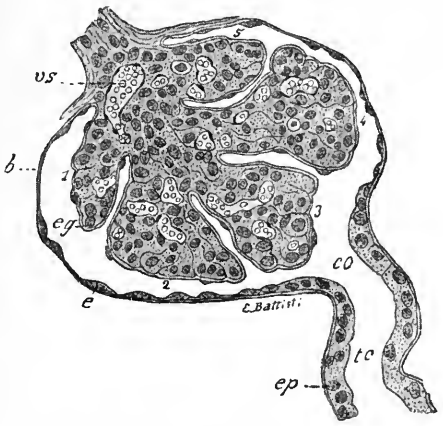


FIG. 111.—Structure of a Bowman's capsule from cortical substance of human kidney. (Böhm and v. Davidoff.) *a*, basement membrane of outer layer of capsule; *e*, epithelium of capsule; *eg*, glomerular epithelium; *vs*, section of blood-vessel; *1*, *2*, *3*, *4*, *5*, lobules of glomerulus; *co*, neck at commencement of uriniferous tubule, lined transitional epithelium; *ep*, epithelium of convoluted tubule.

Bowman's capsule, which surrounds the glomerulus as the serous coat surrounds the viscera, consists of an external layer, formed of a structureless basement membrane, lined with flattened epithelium, and an internal or visceral layer which lines the glomeruli, and dips down between the loops and lobules. In the adult its cells do not form a definite and continuous layer (Fig. 111). In the foetus, on the contrary (when the vascular loops of the glomerulus are still undeveloped), the stratum of cells that completely surrounds the glomerulus is much more distinct (Fig. 112). There is an intracapsular space between the two layers, which almost disappears when the vessels of the glomerulus are injected; and which communicates freely with the neck of a convoluted tubule, where transitional forms between the flattened epithelium of the outer layer of the capsule and the cubical cells that line the tubules, may be detected.

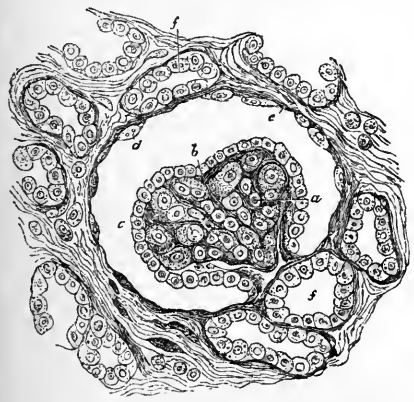


FIG. 112.—Section of cortical substance of kidney; human foetus. Highly magnified. (Klein.) *a*, glomerulus with blood-vessels not fully developed; *b*, connective tissue between the blood-vessels; *c*, epithelium covering it continuous with *d'*, flattened epithelium lining Bowman's capsule; *f*, *f*, convoluted tubes.

The convoluted tubules, too, consist of a structureless basement membrane covered with cubical epithelium, the turbid protoplasm of which is thickly set with granules in such regular lines that (more particularly in the outer basal half) they present an effect of striation. At the inner edge facing the lumen, there is, according to the observations of Fornier (confirmed by many workers, particularly by Sauer, 1895, in Germany, and by R. and A. Monti, 1900, in Italy), a sort of finely striated border, which looks like the bristles of a brush, and is therefore known as the *orlo a spazzola* ("brush border," Fig. 113). Later on we shall see what changes this characteristic epithelium undergoes, according to the functional state of the kidney.

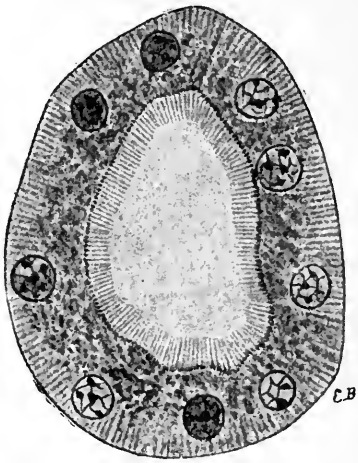


FIG. 113. — Section of convoluted tubule of waking marmot, during functional activity of renal epithelia. (R. and A. Monti.)

The epithelium of Henle's loops differs in the narrow descending and the wider ascending limb. In the former the basement membrane is covered by a flattened epithelium, the nuclei being prominent towards the lumen. As shown in Fig. 114, three cells, more often two, still more often one flattened cell, are enough to line the entire lumen of the canal. The alternating position of these cells gives a spiral character to the tubule. The lumen does not exceed 9-15 μ, *i.e.* it is approximately equal to that of the blood capillaries.

In the ascending limb of Henle's loops the epithelium is cubical, and the cells project so as to restrict the lumen, and make it narrower than in the descending limb, although as a whole the diameter of the tubules exceeds 25 μ.

In the second convoluted tubules, which unite Henle's loops with the ducts of Bellini, the same characteristic cells recur as in the first convoluted tubules. The cells, however, are smaller, while the diameter of the tubule is about the same (36-46 μ).

The epithelium of the straight collecting tubes has clear cells with no appearance of striation. They are cubical at first, and gradually become columnar as the size of the lumen increases. The nucleus is always round and sharply defined.

In the large collecting tubes or papillary ducts the basement membrane is strengthened by connective tissue. The diameter at the orifices upon the papillae may be 1 mm.

The arrangement of *blood-vessels* in the kidneys is no less

characteristic than that of the uriniferous tubules. The renal artery given off from the aorta enters the kidney at the hilum. It is exceptionally large in proportion to the size of the organ. The renal vein, which leaves by the hilum, and opens directly into the inferior vena cava, is still larger. Both artery and vein give off a number of branches which penetrate into the substance of the organ between the papillae (arteriae and venae interlobulares), and form arches at the junction of the medullary and cortical substance (arterial and venous arches, the latter anastomosing

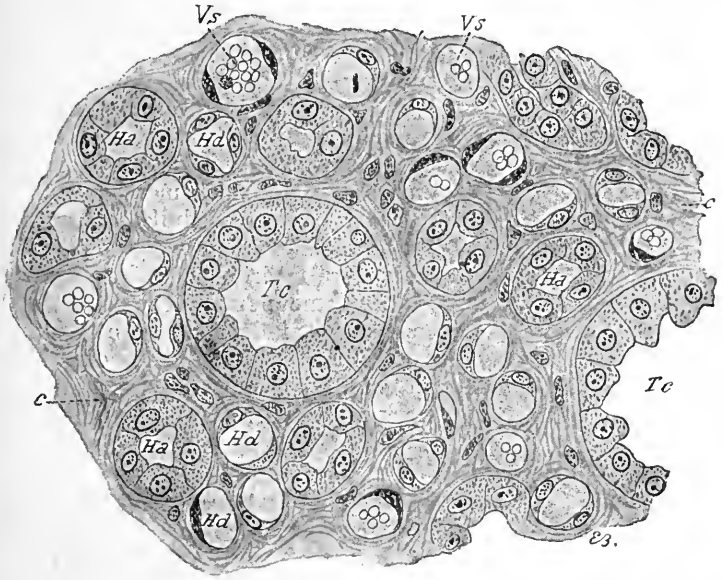
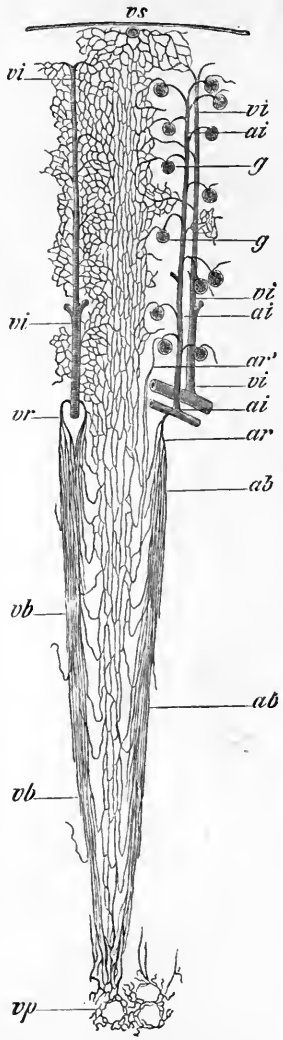


FIG. 114.—Section through fragment of human kidney at the level of Henle's intermediate zone between the cortex and medulla. (Szymonowicz.) *Tc*, collecting tubules of Bellini; *Hd*, descending limb of Henle's loops; *Ha*, ascending limb of Henle's loops; *Vs*, blood-vessels; *c*, intertubular connective tissue.

freely among themselves). The arches give off peripheral branches (arteriae and venae interlobulares) which pursue a nearly straight course towards the surface of the organ, and give off short and usually curved branches at intervals (Fig. 115). The venous branches form a capillary network, and the arterial form the vasa afferentia, which penetrate into the capsule or dilated extremity of the uriniferous tubules. Within the capsule the afferent vessel breaks up into a much convoluted capillary mass, the vascular tuft or *glomerulus*, which is usually divided into lobules anastomosing among themselves. The glomerular capillaries unite into a single efferent vessel which is always smaller than the afferent, and which leaves the glomerulus close to the point at which the artery enters (Fig. 116). This efferent vessel breaks up after the manner

of an artery into smaller branches, which end in a dense capillary network, and ramify over the walls of the uriniferous tubules,—their meshes being polygonal in the cortex, and elongated in the medulla.

While the blood which supplies the cortex of the kidney traverses the interlobular arteries to the glomeruli, and is thence conveyed by the capillary network of the interlobular veins (as well as the venae stellatae), the blood supply for the medulla passes through the arteriae rectae, which are given off from the arterial arches close to the interlobular arteries, and then descend towards the hilum, divide into minute branches which form brushes or bundles, and end in the long-meshed capillary network of the medulla, after which they are collected into the venae rectae which are intermixed with the arteries of the same name. There is thus a comparative independence between the cortical and the medullary circulation, although they unite in a common network of capillaries.



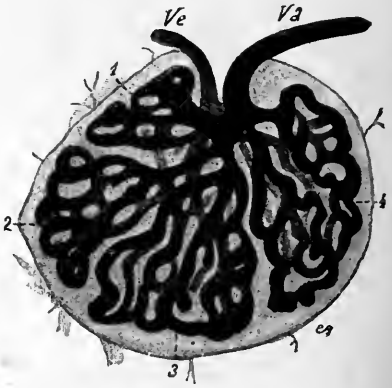


FIG. 115.—(Left.) Diagram of distribution of blood-vessels in human kidney. (Ludwig.) *ai, ai*, interlobular arteries; *vi, vi*, interlobular veins; *g*, glomerulus; *vs*, stellate vein; *ar, vr*, arteriae et venae rectae forming pencil-like bundles, *ab, vb*; *vp*, venous plexus in the papillae.

FIG. 116.—(Right.) Malpighian glomerulus of injected human kidney. (Szymonowicz.) *Va*, afferent vessel enormously enlarged by passive dilatation owing to pressure of injected fluid; *Ve*, efferent vessel, which is always much smaller than the afferent, but the difference in this case is much exaggerated; *1, 2, 3, 4*, vascular lobules of glomerulus.

The uriniferous tubules and blood-vessels of the kidney are united by interstitial connective tissue, which is more abundant in

the neighbourhood of the papillae than in other parts of the kidney substance. The spaces not filled by connective tissue are lined in some places by epithelioid platelets, and form the lymph channels which bring to the epithelial cells of the uriniferous tubules both nutrient materials and the urinary constituents, which, as we shall see, it is their office to expel.

The renal artery, at the point at which it enters the hilum of the kidney, is surrounded by a plexus of nerve filaments (plexus renalis), which consists partly of medullated fibres, varying considerably in size, but principally of non-medullated fibres. The nerves of the renal plexus come chiefly from the great solar plexus, which contains fibres of the vagus, as well as of the greater and lesser splanchnic nerves. Numerous small ganglia are also present in the renal plexus.

The peripheral relations of the nerve fibres of the kidneys with the branches of the small arteries, and with Bowman's capsule and the convoluted tubules, were worked out in 1893 by Berkley. We shall discuss the importance of this discovery later.

Besides the vasomotor and the secretory fibres, there are undoubtedly sensory fibres to the kidney, seeing that in certain morbid conditions the kidneys can be the seat of acute pain.

II. The Secretion of Urine is constant, but it fluctuates considerably with different circumstances, even under normal conditions. On introducing cannulae into both ureters of an animal (or of man by means of the urethral catheter, as clinically employed) it can be seen that, independent of irregularity and asymmetry of *excretion*, due to the peristalsis of the ureters, *secretion* is never parallel in both kidneys, but is greater now in the right, now in the left. Apparently there is a kind of alternation of secretory activity and of blood supply in the two kidneys (Ludwig). This shows that the secretion depends not only upon general central conditions, but also upon local peripheral conditions which vary in each kidney at different times.

Although bilateral nephrectomy is fatal in a short time by causing uraemic intoxication (*supra*), the excision of one kidney alone is compatible with life under normal conditions, not merely in animals but also in man, on whom it has repeatedly been carried out as a surgical operation. This fact shows that removal of one kidney does not diminish the total secretion, and that the kidney which is left may supplement and compensate the lost function of the other, by increased secretory activity.

So long as the urinary secretion is going on, *i.e.* as long as urine continues to trickle from the cannula fixed to the ureter, the blood that leaves the kidney by the efferent vein is not dark like the venous blood returned from the muscles, but bright red, like arterial blood (Cl. Bernard). This shows that the velocity of circulation in the kidney is much greater than in the other organs,

so that the arterial blood from the renal artery, although it meets with an enormous resistance in the glomeruli and still more in the capillary network, does not remain long enough in the kidneys to acquire the characteristics of venous blood.

This peculiar rapidity of circulation in the renal vessels evidently depends on the great difference in pressure between the blood of the artery and that of the efferent vein; the former comes from the aorta, where pressure is maximal, the latter opens direct into the vena cava, where pressure is almost *nil*, owing to the proximity of the thorax. But for a complete explanation of the phenomenon, it must also be remembered that the renal artery is exceptionally large in comparison with the size of the kidney, so that the arterial blood circulates in the kidneys not only with greater velocity, but also in a larger amount than in other organs. Even, therefore, on the assumption that the renal tissue consumes no less oxygen during its secretory activity than the other secretory organs (as proved by the fact that there is a marked development of heat in the kidneys, since the temperature of the urine, according to Grijns, is 0·4° C. higher than that of the blood which flows into it) we can see why the blood that has passed through it retains all the characters of arterial blood.

In regard to the process of Urinary Secretion there are two rival theories, the *physiological* or *vitalist theory* of Bowman (1842), and the *mechanical theory* of Ludwig (1844). Since all the existing data derived from innumerable experiments in this much-contested field relate either to the one or to the other of these, it will be well to summarise them briefly.

Bowman's theory was founded upon considerations derived from the morphological structure of the kidney. As we have seen, he discovered in the Malpighian corpuscles the intimate relation between the blood circulating in the kidneys and the commencement of the uriniferous tubules, and therefore held them to be the apparatus by which the salts and water of the urine are excreted. On the other hand, the secretion of the specific constituents of urine (urea, uric acid, etc.) must be effected by the physiological activity of the epithelial cells that line the uriniferous tubules. As it passes through these tubes, the water which is expelled by the glomeruli must dissolve and carry off the urinary constituents actively withdrawn from the lymph by the epithelial cells, and secreted at their free surface.

To Bowman, therefore, the uriniferous tubules were the true secretory apparatus, similar to that of any other gland, while the glomeruli were a contrivance peculiar to the kidney, which principally served to regulate the water content of the blood and to facilitate the expulsion of the secretion from the tubules.

Ludwig, on the other hand, considered the glomeruli to be an apparatus for filtration, through which not merely water, but also

the whole of the crystalloid constituents of urine contained in the blood plasma, were given off from the blood circulating through them. Filtration is passively determined by the great difference of pressure between the interior of the glomerular capillaries and the cavity of Bowman's capsule. The filtrate from the glomeruli differs from that of the ordinary blood capillaries merely in containing no protein, or traces only, because the walls of the glomerular vessels are more resistant than those of the ordinary capillaries, so long as they are under normal conditions. This filtrate, then, has every characteristic of a very dilute urine. During its passage through the uriniferous tubules it gradually becomes concentrated by reabsorption of water into the lymph that surrounds the tubules, which, having become poor in water and rich in protein owing to the absorption of water in the glomeruli, now takes up water by endosmosis. Thus, on Ludwig's theory, the whole process of urinary secretion can be mechanically explained as an effect of filtration and osmosis, without the intervention of any specific secretory activity of the cells which surround the glomeruli and line the tubules.

We must now review the experimental data of the subject, using them as tests of the value of either theory, by which the ground will be cleared for the construction of another intermediate explanation, which may harmonise better with the physiological facts as a whole.

III. The *mechanism of urinary secretion* can be experimentally modified in two different ways:—

(*a*) Disturbance of the normal conditions of vascular circulation in the kidneys, with various methods.

(*b*) Alteration of the normal constitution of the blood, by various means.

The fact that the secretion of urine is intimately bound up with the circulatory conditions in the kidneys has been established by a series of convincing experiments. It is, however, necessary to define exactly on what circulatory conditions *increase of secretion* depends, and on what its *decrease or total suspension.*

Various experiments on animals show that the amount of urine flowing from the ureters increases or decreases with rise or fall of arterial pressure. Thus on bleeding an animal copiously the flow of urine into the ureters diminishes in proportion with the fall of aortic pressure; on re-injecting the blood that has been lost, the flow of urine is accelerated, as the aortic pressure regains its initial value.

Goll (1854), in Ludwig's laboratory, obtained 8·9 grms. urine from the ureters of a large dog in 30 min. before bleeding, 4·92 grms. after a loss of 530 grms. of blood, 7·66 grms. immediately after transfusion of the blood that had been lost.

Stimulation of the cervical vagus, by which the beats of the

heart are retarded or suspended, causes a fall of aortic pressure accompanied by a diminished flow of urine, which becomes normal again when the ordinary cardiac rhythm is re-established. From the two ureters of a dog, Goll collected 9·15 grms. urine every 30 minutes under normal conditions; 10 grms. after division of the vagi; 2·36 grms. during the stimulation of one vagus; 7·22 grms. immediately after cessation of the stimulus.

When aortic pressure is raised by tying the large arteries, the amount of urine eliminated increases proportionally. Thus in an experiment in which Goll tied both carotids, both femorals, and both cervical arteries, the aortic pressure rose from 127 to 142 mm. Hg, and the amount of urine secreted increased from 8·7 grms. to 21 grms. every 30 minutes.

Transverse section of the cervical cord suspends the flow of urine, by lowering aortic pressure. This fact was first determined by Cl. Bernard (1859), and was more closely studied by Ustimowitsch with Ludwig (1870), and by Grützner with Heidenhain (1875). According to the former the secretion is arrested when the aortic pressure sinks to 40-50 mm., according to Grützner when it falls to a value of 30 mm.

When aortic pressure is constant, the urinary secretion can be modified by increasing or diminishing the resistance which the blood encounters in passing through the Malpighian glomeruli. Thus Max Herrmann (1859), in Ludwig's laboratory, showed that it was possible by moderate compression of the renal artery to retard the secretion of urine, while by occluding the vessels it can be entirely suppressed. In exceptional cases, however, in certain animals, the secretion of urine continues, though much reduced, even after ligation of the renal arteries. This is explained by the fact that in these animals capsular arteries exist which are capable of supplementing the large artery that enters by the hilum.

Division of the nerve filaments which accompany the renal artery to the point at which it enters by the hilum produces vasomotor paralysis of the kidney, so that it increases in volume and secretes a larger amount of urine (Bernard, 1859; Eckhard, 1869). The polyuria commences after a brief secretory pause, augments progressively, and reaches its maximum after 30-60 minutes. The urine secreted after section of the nerves of the renal plexus not infrequently contains albumin, and also haemoglobin (Krimer and others); but this fact is not constant and depends on the gross alterations in the circulatory conditions of the kidney due to the effects of operation. In fact, when the principal nerve filaments are divided with great care, polyuria is produced without albuminuria or haemoglobinuria (Herrmann).

If, instead of section, the renal nerves are electrically stimulated, a vaso-constriction results which diminishes or arrests the secretion.

The same effect is obtained by stimulation of the splanchnic, and of the medulla oblongata or spinal cord (Eckhard), also by arrest of the respiratory movements which produces asphyxia (Grützner). This operation, as we know, causes a conspicuous rise of aortic pressure owing to diffused vaso-constrictor action; but since the branches of the renal artery also contract, the renal circulation is diminished, not increased, consequently instead of a rise there is a fall in urinary secretion. When, on the contrary, the splanchnic and spinal cord are excited after division of the nerves of the renal plexus on one side, there is marked acceleration of urinary secretion on the side operated on, while in the other kidney it is entirely arrested (Grützner).

These experimental facts as a whole seem at first sight to lend substantial support to Ludwig's theory, by which the renal glomeruli are regarded as a mere filtering apparatus. In fact, when blood pressure rises or falls in the renal artery (and therefore in the glomeruli) the secretion of urine also must increase or decrease, because the difference between the glomerular and the capsular pressure, which mechanically causes the phenomenon of filtration, becomes greater in the first case and less in the second. To this it may be objected that under all the experimental conditions above described in which pressure was altered in the renal artery, the velocity of the renal circulation was altered in the same direction. Other experimental data tend to show that the renal secretion depends not so much upon the *pressure* as upon the *rate* at which the blood circulates in the kidneys. In fact, if a rise of blood pressure be artificially produced in the kidneys together with a delay or block in the current, there is no increase in the flow of urine, but the exact opposite occurs, *i.e.* diminution or arrest of the secretion.

It has long been known that compression or ligation of the efferent veins will *ipso facto* produce a decrease or arrest of the urinary secretion (B. H. Meyer, 1844; Frerichs, 1851; Ludwig, 1856).

According to Ludwig this fact does not contradict his filtration theory, because the occlusion of the vas efferens produces such a swelling of the interlobar and interlobular renal veins, that the tubules which conduct the urine are compressed, and the flow of urine from the papillae is impeded. This fact, however, might be due to the arrest of the vascular circulation, which produces asphyxia and alters the nutrition of the glomerular epithelium—as thought by Heidenhain (1883). In fact, when the vein is freed and the circulation re-established, albuminuria sets in for a certain time. In any case Ludwig's interpretation is not applicable to the fact that simple constriction of the renal veins without interruption of the circulation suffices to reduce the flow of urine to a minimum (Senator, Paneth). The same result can also be

obtained on making an artificial circulation through the vessels of a kidney recently excised from the animal (I. Munk).

It is accordingly *rate* of circulation rather than *pressure* which governs the phenomenon of renal secretion. On the velocity of the blood-flow depends not only the amount of excretory material, but also the provision of oxygen required by the secretory cells for their task. In proof of this we have the fact that when the integrity of the living cells of the capsular epithelium of the glomerulus is damaged, their function ceases at once, either for a time or permanently.

If, after a brief occlusion of the renal arteries, the renal circulation is reinstated by opening the vessels, secretion is not resumed at once, but after a certain lapse of time, which may vary from a few minutes to three quarters of an hour. This phenomenon, first observed by Max Herrmann in Ludwig's laboratory in 1859, is not adequately explained by the theory which regards the glomerulus as a passive filter, but is readily explained on the assumption that the secreting epithelia of the glomerulus are highly sensitive even to a temporary deprivation of oxygen, and require a certain time to recover from the effects of asphyxia.

Overbeck's experiments (1863) confirm this hypothesis. He observed that after occlusion of the renal artery, lasting only for one and a half minutes, the secretion came back slowly after forty-five minutes; that the first urine collected was scanty in amount, and contained much protein; that the quantity of urine subsequently increased, while the protein content diminished; that, lastly, the urine gradually regained its normal constitution. Herrmann endeavoured to explain the arrest of the urinary secretion on the hypothesis that the suspension of circulation produces such an accumulation of blood corpuscles in the capillary network of the kidney as to block the renal circulation; but this hypothesis was contradicted by Litten, who proved that even after prolonged occlusion of the artery the renal circulation remained normally pervious.

We hold the only acceptable interpretation to be that the asphyxia of the living cells of the glomerulus alters them so as to render them at first impermeable, and then at a second period, after the circulation has been restored, abnormally permeable (even to colloid substances). The fact that temporary albuminuria can also be produced by suffocation, by strychnine poisoning, and lastly by temporary obturation of the right heart (Overbeck), agrees with this interpretation.

That *velocity* of the blood-flow rather than *pressure* is the determining factor in the formation of urine is a fact of the utmost importance to the theory of urinary secretion. Murri was the first to put forward this idea in Italy, in his clinical lectures on *Haemoglobinuria a frigore*, published 1879, as a rejoinder to

Runeberg. Some months later Heidenhain attacked the same problem in Germany, and criticised the mechanical theory in a communication to the medical section of the Breslau Gesellschaft für vaterländische Kultur (December 1879).

But it must not be concluded on the strength of this fact that Ludwig's theory, by which the Malpighian tufts are regarded as a minute apparatus intended to permit the filtering through of a highly aqueous urine, is to be entirely rejected. If the walls of the glomerular vessels are really permeable, and if the intra-glomerular pressure P is much higher than the pressure in the capsule, or commencement of the uriniferous tubules p, there must be filtration, and the quantity of urine filtered must vary as P-p. If this be allowed, it follows that if the value p is altered by inserting a cannula connected with a manometer into the central canal of the ureter, the flow of urine must cease after a certain time, because the ratio P-$p = 0$. In fact, when this operation is performed on the dog, the mercury column rises slowly till it reaches 50-60 mm., and then remains stationary. At the same time the renal pelvis dilates, the kidney becomes oedematous, and after some hours the capsule of the kidney is seen to be ecchymotic (Ludwig). This result is not, however, decisive in favour of the theory of glomerular filtration, because it lends itself to a twofold interpretation. It can be held with Ludwig, that when the column of mercury comes to rest all formation of urine ceases, and it may also be maintained with Heidenhain that when the rise of the manometer is arrested the secretion of urine continues, but that reabsorption from the tubules into the lymph channels commences.

Another much simpler point, on which Ludwig laid great stress, is that the *efferent vessel* of the glomerulus is always much smaller than the *afferent vessel*. This constant fact must be taken as the natural consequence of the heavy loss of water from the blood during its passage through the glomerular vessels, owing to the resistance there encountered, so that the quantity of water that enters by the afferent vessels is larger than that which leaves by the efferent. In any case, however, even on the assumption that the glomerulus is a filter, it remains true that it is a filter composed of highly sensitive living cells, and that its permeability varies greatly with the alterations in the vital conditions of these cells, as shown by the striking effects of the temporary occlusion of the renal artery. It is this physiological sensibility of the glomerular walls that makes the rate of blood-flow more important than the lateral pressure in the formation of urine.

In other words, the same theory applies to the function of the vessels of the Malpighian glomerulus as was formulated above for the formation of lymph from the common blood capillaries. (See Vol. I. p. 519 *et seq.*) The only difference is that while in that

case the whole of the chemical components of the blood plasma filter through, in the capillary glomeruli (which are more resistant, and are strengthened by the internal layer of the flattened cells of Bowman's capsule) only the crystalloid substances, which contain all the essential constituents of urine, normally filter through with the water. If the concept of a *specific secretory activity* of the glomerular walls be excluded, we must logically exclude the idea that anything more than water and the salts of the blood can be excreted from the glomerulus, and must assume with Ludwig that the normal glomerular filtrate is only a very dilute urine, containing all the crystalloid components of the lymph, less its colloidal constituents.

IV. When we reflect that the main function of the kidney is to purge the blood from the products of the katabolic processes, it is natural to conclude that this excretory activity is in intimate relation with the composition of the blood, and that it undergoes important modifications with the variations of the latter. Many experimental data show this logical deduction to be correct.

Each time the water content of the blood increases or diminishes there is an increase or diminution of the amount of water eliminated in the urine. After copious draughts of water, the volume of excreted urine reaches its maximum after 2-3 hours, and then diminishes and becomes normal again after 5-6 hours (Falck). The excess of water ingested is mainly eliminated by the kidneys, a little being lost by cutaneous secretion (Ferber). After heavy loss of water by profuse sweating, or severe diarrhoea, there is a marked fall or temporary suspension in the excretion of urine, as shown by a number of clinical observations.

These effects, which show the kidneys to be the chief regulators of the water content of the blood, do not depend on changes in the volume of the blood nor on the altered pressure at which it circulates in the kidneys, for it has been shown, on the one hand, that intravenous injection into a dog of the blood serum of the same animal (Ponfick), and also of large quantities of defibrinated blood (Albertoni), produces no marked increase in the excretion of urine, as is the case with injection of water. On the other hand, it is known that after free absorption of water by the alimentary canal there is no rise, but rather a fall of arterial pressure (J. Pawlow). It therefore seems legitimate to conclude that these effects depend upon the altered concentration of the blood, since we know that filtration through permeable membranes (and therefore through the glomeruli) varies inversely with the degree of concentration of the filtering fluid.

The urinary constituents normally contained in blood are even more effective in promoting a secretion of urine. The injection of urea, uric acid, and the inorganic salts of urine in sufficient amount to increase the concentration of the blood, excite urinary

secretion, *i.e.* act as *diuretics* (Ségalas, 1823). Urea, which is abundantly present in the blood, is one of the most potent diuretics, just as we saw that bile is one of the best cholagogues. In experiments with artificial circulation through the excised kidney, it is necessary to add urea to the defibrinated blood in order to obtain secretion of urine (I. Munk and Senator).

According to Ustimowitsch (1870), Heidenhain (1874), and Grützner (1875), the injection of a few grammes of urea into a rabbit increases the formation of urine under normal conditions, and reinstates it when arrested by section of the cervical cord.

The diuretic action of glucose when injected into the vein is similar to that of urea. We have seen in Chapter V. that whenever the normal quantity of sugar in the blood exceeds certain limits it escapes by the urine, carrying with it a large amount of water, so that there is glycosuria associated with polyuria. In *diabetes mellitus* this phenomenon may become very pronounced. From this we may conclude that the kidney regulates not merely the water content of the blood but also the amount of circulating sugar, which (in excess of the normal) has a diuretic action like urea, and probably acts by the same mechanism.

The diuretic action of the different sugars varies; while glucose, maltose, and lactose increase diuresis, laevulose, on the contrary, has little effect, as shown by the experiments of Albertoni (1881-1891). The increase of diuresis with glucose, maltose, and lactose is due in his opinion to increased velocity of circulation and dilatation of the renal vessels, perhaps also to a specific exciting action which these sugars exercise upon the secretory renal epithelium.

The diuretic action of caffeine is similar to that of urea. After a brief delay or block of the urinary secretion, during which the kidney shrinks, secretion begins again, and increases so as considerably to exceed the normal value while the kidney expands. Blood-pressure diminishes in the first stage; in the second it rises, and reaches or slightly exceeds the original level.

The action of digitalis is more complex, because it reinforces and retards the beats of the heart, with simultaneous increase of the tone of the vessel, so that arterial pressure rises. Under normal conditions, therefore, its diuretic action is unimportant; with impaired cardiac activity, on the other hand, it does act as a diuretic by the improvement in the conditions of the renal circulation, due to increase of arterial pressure.

None of these facts militate seriously against the mechanical theory, as regards the function of the glomerulus, in the above sense.

Since the diuretic action coincides with increase of arterial pressure, and ceases on its return to the normal, Limbeck's theory, according to which diuresis depends upon the power of diuretics

to draw water from the tissues, and thus produce a hydraemic plethora which raises arterial pressure and favours glomerular filtration, is legitimate.

But this interpretation of the action of diuretics does not correspond with the facts, because they are able to produce diuresis without causing any rise of pressure. Thus Heidenhain noted diuretic effects with intravenous injection of sodium nitrate mixed with chloral hydrate, although no rise of arterial pressure was visible on the manometer. Paneth afterwards saw that on reducing urinary secretion by compression of the vas efferens, transfusion of sodium nitrate solution or any other diuretic caused a *free flow of urine* from the ureter, even if arterial pressure was lowered.

According to Albertoni a marked secretion of urine also occurs after the spinal cord has been divided on injection of sugar into the blood. In the rabbit intravenous injection of sugar increases the secretion from the kidneys without increasing arterial pressure.

Stefani and Cavazzani demonstrated that urea, when injected into the blood, has a dilatator action on the vessels in general, but acts more particularly upon those of the kidney. By artificial circulation of isotonic salt solution to which 2 per cent urea had been added, at constant pressure, the flow from the renal vessels was increased by 78 per cent, from the vessels of the head by 37 per cent, of the liver by 32 per cent, of the limbs by 20 per cent.

These facts contradict the *mechanical*, and favour the *secretory theory*, indicating that diuretics are specific stimuli of the activity of the kidney cells. This view is strengthened by the fact which Thompson ascertained in 1894, viz. that atropine (which suspends or checks the activity of all glandular tissues) acts upon the kidneys by diminishing urinary secretion and the amount of urine excreted, *i.e.* it acts in the opposite sense to diuretics, although it produces no fall in arterial pressure. Morphine acts in the same way, but by lowering arterial pressure. On administering atropine and morphine simultaneously, urinary secretion is arrested for a certain time (15 to 45 minutes), although the renal circulation continues, for when the flow of urine recommences it is absolutely devoid of protein.

Many other serious objections might be raised to the *second* part of Ludwig's theory, which assumes that the glomerular filtrate, in passing through the uriniferous tubules, condenses gradually by reabsorption of water, which is effected by an endosmotic process in the walls of the tubules, until the filtrate assumes all the chemical characters of urine.

If the whole of the urea, and, generally speaking, all the constituents of urine, were really eliminated from the blood by filtration through the glomeruli, as assumed by this theory, two impossible consequences would ensue, as Heidenhain pointed out:—

(*a*) To obtain the 35 grms. urea excreted daily in the urine, no less than 70,000 c.c. of fluid must filter through the glomeruli of the two kidneys, under the most favourable computation, according to which urea would be present in a maximal amount of 0·05 per cent.

(*b*) Of this enormous quantity of filtrate, the no less enormous amount of 68,000 c.c. must be reabsorbed by the uriniferous tubules on the supposition that the day's urine is represented by 2000 c.c.

The absurdity of these conclusions is obvious when we consider that a man weighing 75 kilos. has about 6 kgrms. blood, which performs some three circulations per minute. On Heidenhain's computation not more than 130 kgrms. can pass through the kidneys in 24 hours, more than half of which (70 kgrms.) has to filter through the glomeruli!

Another still more serious objection to the mechanical theory is presented by the concentration or osmotic pressure of the urine, which is almost always *higher* than that of the blood and lymph circulating in the kidneys. Admitting the second part of Ludwig's theory, *i.e.* that the glomerular filtrate gradually concentrates along the course of the tubules, because the lymph in which these are bathed is more concentrated than the urine, so that reabsorption of water takes place by endosmosis, it is obvious that this reabsorption must cease so soon as the urine becomes isotonic with the lymph; in other words, the urine might reach the concentration and osmotic pressure of the lymph and blood, but could never exceed it. The formation of urine with a higher concentration than the blood cannot be explained as a simple physical phenomenon, but necessitates the intervention of an *active participation* of the secreting cells.

Dreser (1892) calculated the sum of this work for two special cases. One urine secreted in a night to the amount of 200 c.c. had $\Delta = 2{\cdot}3°$ C., while the blood of the same person gave $\Delta = 0{\cdot}56°$ C. According to Dreser's calculation, the work performed by the kidneys in the secretion of this urine must amount to 37·037 kilos. In a cat prevented from drinking for three days, Dreser obtained a urine in which $\Delta = 4{\cdot}72°$ C., while the blood of the same animal showed $\Delta = 0{\cdot}66°$ C. This difference in the freezing-point corresponds with a difference of osmotic pressure = 498 mm. water, or a pressure of 49,800 grms. per square cm. But it should be noted that, according to the observations of v. Rhorer (1905). and Galeotti (1907), this hypothetical value of the total osmotic work of the kidney is in all probability much less than that which is actually performed, assuming that the kidney functions by a mechanism such as is assumed by chemists and physicists, *i.e.* as a semi-permeable membrane. Supposing this concentration to be performed osmotically by the walls of the renal tubules, we should

(on Dreser's calculation) have to admit the absurd conclusion that they are capable of developing an energy six times greater than that exerted by the human muscles, *i.e.* 8000 grms. per sq. cm. So that if we hold with Ludwig that the glomerular filtrate is concentrated and converted into urine along the renal tubules, we are still bound to admit that this concentration is the effect not of simple osmosis, but of a *specific physiological activity* of the epithelial cells that line the tubes.

Another obvious objection to the mechanical theory is the fact that while in all animals the blood serum is alkaline, the urine on the contrary (except that of herbivora) is acid. Is it possible to explain this difference of reaction by a simple process of filtration and osmosis? Some authors maintain that it is, since it has been proved that when an alkaline fluid which (like urine) contains mono- and dibasic phosphates filters through an inert animal membrane, the filtrate is acid because the monobasic phosphates filter through it by preference. Thus the filtrate collected from Bowman's capsules may be acid although it comes from alkaline blood. This explanation, however, does not hold in face of Dreser's experiments (1885).

In order to decide the question he examined the microchemical reaction of the various parts of the kidney in the frog, using fuchsin (*rubin*-S) as an indicator, which loses its bright red colour in alkaline solution. One to two hours after injection of a concentrated solution of fuchsin into the lymph-sac of the frog the acid urine secreted by the animal became red; the kidneys were colourless in the cortical region which contains the glomeruli, while the tubules of the central part were stained red. From this Dreser concluded that the filtrate of the glomeruli is alkaline, and that the acidity of the urine depends on the secretory activity of the epithelium of the convoluted tubules.

This result is confirmed by the use of diuretics. If the filtrate of the glomeruli is alkaline, and becomes acid along the tubules, then the faster the urine passes through the tubules the more rapidly will the reaction of the urine approximate to that of the glomerular filtrate. This can be seen after the injection of a diuretic, *e.g.* caffeine; the urine first becomes neutral, and eventually is little less alkaline than the blood. We shall presently see whether the urine becomes acid in the tubules owing to the secretion in them of acid salts, or the reabsorption of alkaline salts.

Albertoni and Pisenti, after administering a few c.c. of acetone in aqueous solution (1 : 3) to rabbits, for several days in succession, found serious alterations in the epithelium of the convoluted tubules only, while that of Bowman's capsule and of the straight tubules was uninjured. If the acetone had been secreted along with the water by the Malpighian glomerulus, it would, in their

opinion, have been too dilute to produce such lesions in any part of the urinary tubules; while if it had given rise to them, not only the cells of the convoluted tubules, but also Bowman's capsules, the straight tubules, etc., would have been implicated. According to these authors the fact that the epithelium of the convoluted tubules alone is attacked, indicates some special attraction of these cells to the above substance, which contradicts the mechanical theory.

A last fact which shows the inadequacy of the mechanical theory and the necessity for active intervention of the secretory epithelial cells of the kidney, is the formation of hippuric acid, which does not pre-exist in the blood, and which (in dogs at any rate) is exclusively formed by a synthetic process in the kidneys, initiated by the vitality of the epithelium of the urinary tubules. (See Chapter VII. p. 393.)

V. These objections to the mechanical theory led to a revival of Bowman's physiological theory, according to which the elimination of the specific constituents of urine (urea, uric acid, etc.) is the effect of a *specific vital activity* of the epithelium of the convoluted tubules. But before this theory could be unconditionally accepted it was necessary to obtain direct experimental evidence that the vital activity of the epithelial cells of the convoluted tubules and the ascending limb of Henle's loop (which, as we have seen, possess all the morphological characters of specific secretory cells) is expressed in an *external secretion, i.e.* by picking out the urea, uric acid, etc., from the lymph, and excreting them into the lumen of the tubules, and not in an *internal secretion, i.e.* reabsorption of the water and part of the salts of the glomerular filtrate, and return of them to the lymph, so as to condense the filtrate, and bring about the concentration and osmotic pressure proper to urine.

Unfortunately it is not possible, owing to the great diffusibility and solubility of urea (the chief constituent of urine), to follow its course through the kidney by micro-chemical reactions. As regards uric acid, first Bowman and then v. Wittich described the presence of crystals of this acid in the epithelia of the convoluted tubules. If these observations had been confirmed, they would certainly have afforded a strong presumption in favour of Bowman's theory; but the later researches of Adolf Schmidt (1890) showed that uric acid in a crystalline form is never seen in the epithelial cells, even when, owing to ligation of the ureters, the uriniferous tubules are charged with urates. On the other hand, he saw that the urates in this case were never present in the cavity of Bowman's capsule, but always along the tubule. This fact is not, however, sufficient to demonstrate that the uric acid is secreted by the cells of the tubules, because it is also legitimate to assume that it is excreted by the glomeruli, and is

immediately driven out of the intracapsular space towards the tubules by the stream of water, and then deposited in the lumen of the canals in a semi-crystalline form after reabsorption of water.

To clear up this difficult question Heidenhain had recourse to the method of Chrzonszczewsky (1866). This consists in the injection of sodium sulphindigotate (indigo-carmine) into the blood, and subsequent detection of the colouring substance in the kidney, after fixing it, immediately after the animal's death, by injection of absolute alcohol through the renal artery.

Indigo-carmine, when injected into the circulation of a rabbit, is only eliminated by the liver and kidneys. A few minutes after injection of 5 c.c. saturated aqueous solution the urine becomes blue. On killing the animal and making sections of the kidneys, they are seen to be the same colour, particularly towards the points of the pyramids. In order to determine which cells of the kidney expelled the pigment, Heidenhain arrested renal secretion by a transverse section of the cervical cord, and then injected indigo-carmine, killing the animal in 10 minutes, and fixing the stain by injection of alcohol. On slicing up the kidney, he found that the cortical part only was stained, while the medulla was quite colourless. On examining the cortex under the microscope, he saw that the blue colour was due to granules of the pigment deposited in the lumen of the tubules, and also in the striated cells which line them, while the intracapsular spaces, the narrow descending parts of the loops, and the collecting tubules are entirely free of pigment.

If before injecting indigo-carmine (without inhibiting the secretion by division of the cord) a circumscribed zone of the kidney was treated with silver nitrate, only the outer layer of the cortical part stained blue, while the rest of the kidney was diffusely stained.

From these experiments Heidenhain concluded that the secretion of indigo-carmine is due to the secretory activity of the striated cells of the convoluted tubules and ascending limbs of Henle's loops, and assumed further that these cells, which have the power of secreting an *abnormal* constituent from the blood, must also be conceded the property of eliminating urea and the other *normal* constituents of urine.

Serious objections to this conclusion were, however, raised by Pautynski, Henschen, and Sobieranski (1879, 1895, 1903). They noted that if the amount of indigo-carmine injected into the blood is in excess of that employed by Heidenhain, Bowman's capsules and the glomerular epithelium also show a blue tinge. Heidenhain's data can therefore be reconciled with Ludwig's theory by admitting that the blue pigment is excreted by the glomeruli in very dilute solution, which is then concentrated in the tubules

by reabsorption of water, so that the pigment is precipitated and penetrates the striated cells of the convoluted tubules. In fact, Sobieranski observed that in these cells the stain is most conspicuous near the inner surface, as though the pigment had entered by the lumen of the tubules and not by the lymph channels.

This view is confirmed, according to Sobieranski, by the effects of injection with carmine, which, as it is less diffusible than the sulphindigotate of soda, can more easily be followed in its passage through the kidney. If the rabbit be killed 30–40 minutes after intravenous injection of carmine, and the pigment fixed by injection of absolute alcohol through the renal vessels, the glomeruli stain red, and the epithelia of the convoluted tubules are found to contain pigment granules in the part facing the lumen, never in the basement membrane facing the lymph spaces. According to Sobieranski, this shows that the carmine is taken up by the striated cells on the side of the lumen, with the water they absorb. But even if these facts minimise the value of Heidenhain's argument, they do not, in our opinion, prove as much as Sobieranski claims, when he attempts to reinstate Ludwig's theory by saying that the tubular epithelium is an apparatus for concentrating the glomerular filtrate—since this concentration is due not to *osmotic* processes, but to a *special physiological activity* of the cells, analogous to that of the intestinal epithelium as expressed in an *internal secretion.*

In fact, we may suppose that the pigments injected into the blood (both sodium sulphindigotate and carmine) are specially eliminated by the epithelial cells of the uriniferous tubules, and, when present in excess, by the glomeruli also; and that the internal part of these cells stains more than the basal part may depend on the fact that the cells habitually expel the whole of the substances which they take up from the lymph into the duct as fast as they absorb them. Immediately after the death of the animal, therefore, the whole of the substances already absorbed, or able to be absorbed before the extinction of vital activity, are collected in the inner portion of the cell, and are partly excreted into the lumen.

In order to decide which of the two theories holds good, that of Bowman and Heidenhain, who allow a *physiological function of external secretion* to the epithelial cells of the tubules, or that of Ludwig as modified by Sobieranski, who attributes to these cells a *physiological function of internal secretion,* it was necessary to discover some method for studying the function of the uriniferous tubules apart from that of the glomeruli. Nussbaum (1878) endeavoured to solve this problem by certain experiments on the frog which may be summarised as follows:—

The amphibian kidney possesses a double series of vessels—that

of the renal artery from which the afferent vessels to the glomerular tufts are given off, and that of the so-called renal portal vein, which gives rise to the capillaries that ramify between the tubules.

Experimenting with large frogs, Nussbaum found that the secretion of urine is suspended by ligation of the renal arteries; but if urea be injected into the blood, secretion is resumed, showing (according to this author) that urea is a diuretic, *i.e.* a secretory stimulus which excites the activity of the epithelial cells of the tubules, on which it is expelled from the blood along with a certain quantity of water, independent of the function of the glomeruli.

If a solution of peptone, egg-albumin, or sugar be injected into the blood of a normal frog, the whole of these substances reappear in the urine, where they can easily be demonstrated; if the injections are repeated after tying the renal artery, and urea be added to activate the secretion, none of these substances reappear in the urine. From these results Nussbaum concluded that the function of the glomeruli is to eliminate water, salts, egg-albumin, sugar, and peptone, while the renal tubules have the task of eliminating urea, uric acid, and the other specific constituents of urine.

These results of Nussbaum, which seemed to have finally decided the controversy in favour of Bowman and Heidenhain, lost much of their value by the control experiments carried out by Adami in Heidenhain's own laboratory in 1885. He showed that it was impossible in the frog to exclude the vascular circulation of the glomeruli by simply tying the renal artery, because certain branches of the ovarian artery anastomose with those of the renal, so that even after tying the latter it is possible to fill about half the glomeruli with red pigment on injecting carmine into the aorta.

Adami further saw that if the kidneys are removed after injection of defibrinated blood through the abdominal vein of these frogs, and plunged into boiling water, the presence of a clot of haemoglobin can be demonstrated inside Bowman's capsule. This clot consists of haemoglobin and protein, showing that the injected blood must have poured through the glomeruli in considerable quantities. Nussbaum's method is not, therefore, adequate to determine the paths by which substances are excreted from the kidneys.

In dogs, too, according to Adami, after tying the renal artery and injecting defibrinated blood, escape of haemoglobin from the glomerulus into Bowman's capsule can be detected.

Ribbert (1883) made another attempt to distinguish the functions of the various parts of the kidneys. Starting from the view put forward by Fick in his *Text-book of Physiology*, *i.e.* that the urine formed by the glomeruli and convoluted tubules must become condensed by reabsorption of water along the narrow

limbs of Henle's loops, and Bellini's straight tubules, he attempted in the rabbit's kidney (which is the most suitable because the renal medulla is not divided into pyramids) to cut out the medullary substance as far as possible, in order to obtain secretion from the cortical part alone, in the glomeruli and convoluted tubules.

After longitudinally dividing one of the kidneys, scooping out its medulla, and then suturing and replacing the kidney, he excised the kidney of the opposite side. Rabbits thus operated on survived only 3-4 days. On the second day the urine no longer contained blood, and was less highly coloured and *much more dilute* than normal urine. He held that this confirmed Fick's hypothesis; but in reality the greater dilution of the urine (the only result arrived at) was obtained under conditions so far removed from the physiological, that we fail to see how any definite conclusion can be deduced from it, the more so as the urine must necessarily be mixed with lymph.

Bradford's results on dogs (1892) have more weight. He observed that after the extirpation of one whole and the half of another kidney (so that not more than a quarter of the weight of the total kidney substance was left *in situ*) the animal may live a long time, but suffers from *hydruria, i.e.* it eliminates a much larger volume of a urine far more dilute than normal urine, but having almost the same total content of urea.

This result resembles that of Ribbert. The hydruria may be interpreted as the effect of the larger quantity of blood circulated through the remaining bit of the kidney, by which compensation is effected, and exaggerated filtration through the glomeruli takes place. But the function of the lost tubules could only be inadequately compensated or replaced by the few tubules left, whether their function be one of *external*, or of *internal secretion*. In the first case the percentage of urea in the urine would be diminished by the insufficient excretion of urea by the tubules, in the second by the insufficient absorption of water.

The same ambiguous interpretation attaches to the more recent experiments of T. Schilling (1904), under Gerhardt's direction, in rabbits that had undergone unilateral nephrectomy. He found that these animals, when not hindered in drinking freely, are capable of eliminating sodium chloride solutions administered by the mouth as rapidly as normal animals. If, on the other hand, the water supply is limited, the salt is excreted at a lower concentration and more slowly than in the control animal under the same conditions. But when compensatory hypertrophy is complete, the one kidney is capable of eliminating salt under these circumstances as if the conditions were normal. On the ground of these experiments Schilling holds it probable that the single kidney, previous to compensatory hypertrophy, is only partially capable of reabsorbing

the water that filters through the glomeruli. Obviously, however, the opposite interpretation may also be sustained, *i.e.* that the one kidney can only eliminate the salt to a less extent than the normal, so that it is more slowly excreted and in a more dilute concentration.

Bradford also found that on performing a still more radical renal operation in which only one-sixth of the total bulk of the two kidneys was left in a dog, *polyuria* properly so called set in, *i.e.* the excretion both of water and of urea was increased. This more active excretion of urea must be referred to the general conditions which lead to an increased production of urea. The animal, in fact, becomes rapidly emaciated, and soon perishes from marasmus. This result indicates that normal general metabolism depends on the normal functioning of the kidneys. But we are still ignorant of the nature of the process by which renal insufficiency affects metabolism so as to accelerate the katabolic processes. We can only say that, according to some authorities, the kidneys, like many other glands, are the seat of a specific *internal secretion* which regulates metabolism, and which is quite distinct from the supposed internal secretion (absorption) of water ascribed by some to the convoluted tubules, in explanation of the phenomenon of the formation of urine.

Many other workers have sought to distinguish the function of the glomeruli from that of the uriniferous tubules. Lindemann (1901) tried to eliminate the glomeruli by means of the vascular circulation. He took advantage of the fact (see p. 424) that the tubules are supplied not only by the blood from the capillaries of the efferent glomerular arteries, but also directly by the blood from the arteriae rectae, so that the whole of the blood circulating in the kidney does not pass through the glomerular vessels. Blood, therefore, still circulates through the kidney, though three times as slowly as under normal conditions, after eliminating the glomeruli, which makes it possible for the tubules to function independently of the latter. In order to exclude the glomeruli, he injected oil directly into the renal artery, on which (as can be seen under the microscope) the glomeruli, exclusively, are cut off from the circulation, because the oily globules penetrate into the rete mirabile. He found that a kidney thus partially embolised is capable of functioning. It is able to pick up and excrete indigo-carmine from the blood as well as a normal kidney, and also secretes an urine, which, owing to the increase in its organic and inorganic products, is more concentrated than the normal. Hence the kidney thus altered is also capable of excreting the normal constituents of urine. On the strength of these experiments Lindemann came to the conclusion that the uriniferous tubules are able to a certain extent to function independent of the glomeruli, so that the excretion of water is not exclusively the

function of the glomeruli, as claimed by the Bowman-Heidenhain theory.

Some experimenters have made use of *poisons*, which attack the separate parts of the kidneys electively, *e.g.* arsenic, aloin, chromic acid (Hellin and Spiro, 1897), or of *circumscribed pathological lesions*, with the object of establishing a functional distinction between the elements of the kidneys. The able work of Galeotti (1902) deserves special mention. He injected solutions of 10 per cent sodium chloride or 30 per cent glucose solution into the crural vein of dogs; and then at different intervals took small samples of blood from the carotid, and of urine from a catheter fixed in the bladder. He determined the freezing-point and electrical conductivity of both fluids, also for the urine the content of organic and inorganic constituents, so as to obtain an approximate notion of the work of the kidney. This work was carried out partly on normal animals, partly on animals that had been poisoned with corrosive sublimate (which particularly attacks the uriniferous tubules), or cantharidine (which specially affects the glomeruli). His fundamental results are, briefly, as follows:—

(*a*) The increase of osmotic pressure in the blood produced by injection of hypertonic salt or sugar solutions excites the kidneys, by a mechanism of which little is known, to increased activity, in order to bring the osmotic pressure of the blood back to its normal value. This tendency can be detected even in kidneys which are so profoundly altered that they fail to attain their object. The elimination of salt or sugar is begun, according to the principle of least labour, by a marked excretion of water, which makes it possible to secrete many molecules of salt or sugar without raising the osmotic pressure of the urine much above that of the blood. If the dog is prevented from drinking, the excessive output of urine ceases, because the need of the animal to retain water is opposed to the tendency of the kidney to eliminate it. Under these circumstances a concentrated urine must be passed, in order to eliminate the abnormal constituents of the blood. The secretion of this urine occurs, however, with a much higher expenditure of work on the part of the renal epithelial cells, and may involve their exhaustion and degeneration.

(*b*) In the case in which, with unaltered function of the glomeruli, the function of the epithelial cells is almost entirely lost (corrosive sublimate poisoning), a copious urine of low concentration is secreted; *vice versa*, when the glomeruli are damaged and the epithelia intact (cantharidine poisoning), a scanty urine of higher concentration than the blood is formed. Hence there is a certain independence in the function of the glomeruli and the tubules, seeing that injury to either induces different functional alterations.

(*c*) During filtration through the glomeruli the fluids on both

sides of the membrane are isotonic. This membrane is accordingly permeable to water and to electrolytes (at least to sodium chloride); it behaves passively, and does not perform any osmotic work.

(*d*) In its passage through the tubules the solution which was at first isotonic with the blood becomes concentrated. The osmotic equilibrium which prevailed at first between the two solutions (blood and urine), separated by a semi-permeable membrane (walls of the tubules), therefore alters, inasmuch as the osmotic pressure of one of the solutions (urine) increases. The work involved is performed by the tubules, which must therefore possess the property of developing energy; for no analogous phenomenon takes place with a passive, semi-permeable membrane. This is the reason why on the death of the protoplasm of the epithelial cells the higher concentration of the urine ceases also.

(*e*) The fundamental question as to the mechanism by which this increase in concentration is effected by the epithelial cells of the uriniferous tubules, *i.e.* the controversy between the two theories of Bowman-Heidenhain and Ludwig-Sobieranski, is not solved by Galeotti, although many physiological and physical data seem to him arguments in favour of the former.

Another method of cutting out the uriniferous tubules was attempted by Bottazzi and Onorato (1904-5). By injecting a solution of sodium fluoride into dogs' kidneys through the ureters they proved microscopically that only the epithelia of the tubules suffered, and not the glomeruli, since the poisonous solution did not reach them. The following are the principal results of their experiments:—

While in dogs operated on by unilateral nephrectomy the urine secreted by the remaining kidney has a very high osmotic pressure, sometimes twice as great as the normal, the urine secreted after poisoning with sodium fluoride has a much lower osmotic pressure than the normal. The fall in concentration seems to be approximately proportional to the intensity of the alteration of the tubules; it is certainly progressive; the concentration is minimal shortly before the death of the animal.

The amount of urine eliminated from the poisoned kidney depends on the degree of intoxication. If the epithelium of the tubules is so much damaged that it becomes detached from the walls, and blocks the lumen, the amount of urine secreted is diminished: if, on the contrary, the epithelium is only functionally injured and not detached, the amount of urine secreted is in excess of the normal. This last fact can be interpreted in favour of Bowman's theory. Bottazzi and Onorato assume that the abnormal dilatation of the blood capillaries and excessive congestion of the kidney poisoned with sodium fluoride cause a rise in

the blood pressure and rate of circulation, which produces increased filtration through the walls of the uriniferous tubules. According to these authors the water of the urine is eliminated not exclusively from the glomeruli, but from the tubules also (at least in some part of the latter, *e.g.* in Henle's loops), an analogy with what occurs in the sweat glands, where (as we shall see in the next chapter) there is an abundant secretion of water without any vascular apparatus similar to that of the renal glomeruli.

De Bonis (1906), a pupil of Galeotti, who partially repeated the experiments of his master, and made use of Bottazzi's method for eliminating the activity of the tubular apparatus, arrived at the following results:—

The diuresis observed in dogs immediately after intravenous injection of hypertonic solutions depends on the glomeruli, since it takes place in kidneys in which the tubules had been injured. On the other hand, this diuresis is probably in close relation with the rate of circulation and pressure of the blood within the glomerulus.

In the normal kidney the first period of diuresis, with low concentration of urine, is followed by intense osmotic activity on the part of the tubular epithelium, during which numerous saline molecules are admitted into the glomerular filtrate. A rapid increase in the molecular concentration of the urine then appears, while the amount of urine simultaneously diminishes. In the injured kidney, on the contrary, where the damaged epithelium is no longer capable of performing so much osmotic work, the molecular concentration of the urine is always low, and differs little from that of the blood.

Hence we may conclude that the glomerulus also represents an organ which regulates the osmotic pressure of the blood, since while it normally passes a fluid which is hypotonic in comparison with the blood, a fluid almost isotonic with the latter filters through whenever the blood contains an excessive quantity of osmotically active substances, *i.e.* each time the body feels the need of clearing out these substances so as to bring the osmotic pressure of the blood back to its normal value.

Accordingly we must regard the membrane which lines the glomerulus not as a filtering membrane, the permeability of which is invariable, but as a membrane that is variously permeable, according to the needs of the body—as indeed must be admitted for all living membranes.

Lastly it has been attempted to solve the fundamental problem of the function of the two renal systems by artificial circulation through the excised kidney, but without success, since it has so far proved impossible to keep the isolated kidney sufficiently alive for it to yield a secreted fluid similar to that which it excretes normally. Pfaff and Vejnx Tyrode (1903) showed that *defibrinated*

blood is not adequate for the nutrition of the excised kidney. It would be better, in experimenting on artificial circulation, to employ perfectly normal blood prevented by appropriate treatment from coagulating.

VI. The Renal Circulation is certainly under nervous control, so far as regards regulation of pressure and rate of blood-flow in the vessels of the kidney by active constriction or dilatation of the renal artery and its branches. The vasomotor system of the kidneys is no less developed than that of any other vascular region,

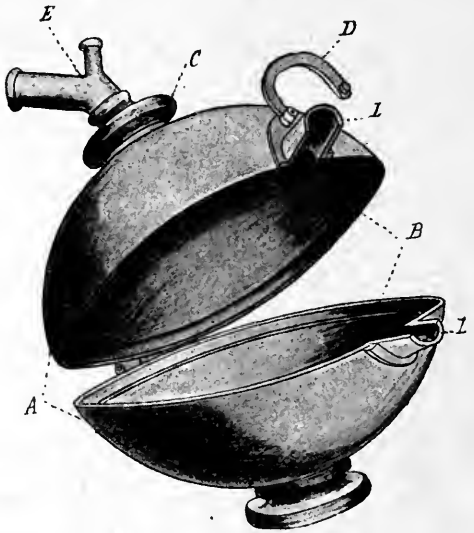


FIG. 117.—Roy's oncometer (open and empty), for study of variations in volume of the kidneys. Metal box, of approximately the same shape as the kidney, which opens by a hinge. Each half of the box contains two chambers, an outer *A*, and an inner *B*. The two upper chambers, from the top of which the two-way tube *E* passes out, are clamped together by screw *C*. The lower chambers are clamped by a similar screw. The box closes by the hook *D*, which surrounds the hollow tube *L*, through which the renal vessels and the ureter pass out from the enclosed kidney.

hence it is not difficult to recognise its effects by the eye. After cutting the branches of the renal plexus that accompany the artery as it penetrates by the hilum, paralytic dilatation of the vessels of the external capsule can be seen. After excitation of the renal plexus or spinal cord, the amount of blood flowing back from the gland by the vein is diminished, and becomes blackish with the character of venous blood, the secretion of urine being arrested, while under normal conditions, when the kidney is functioning, the blood remains, as we have seen, bright red like arterial blood. Stimulation therefore produces constriction of the renal vessels.

The most elegant method of demonstrating vasomotor action on the renal circulation is undoubtedly that of the *plethysmograph*,

which records the variations of volume that take place in the kidney. By the application of this method Roy (1881) devised an ingenious apparatus which he called the *oncograph*, as shown in Figs. 117, 118, 119.

It is plain that the rapid variations of volume in the kidney

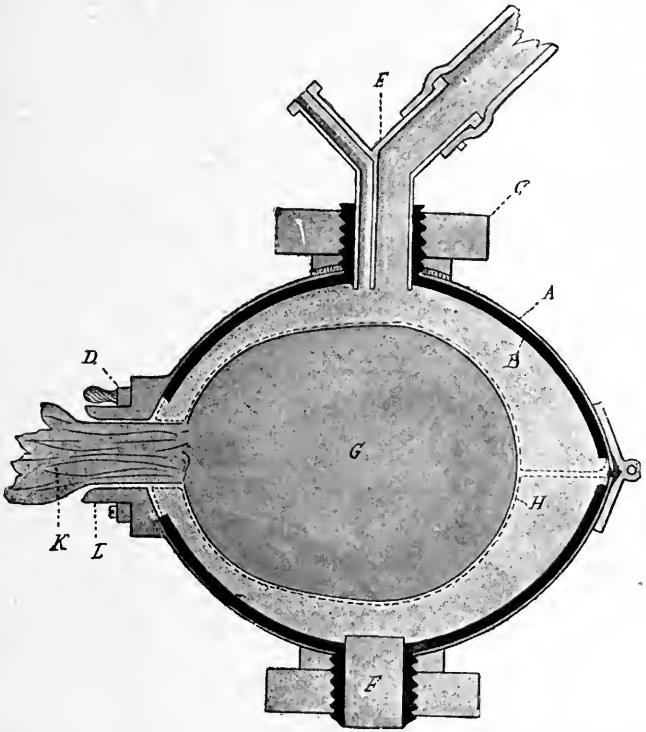


FIG. 118.—Oncometer as in Fig. 117 fitted up for experiment (cross section: proper size). Lettering as in last figure. The dotted line *H* is a thin non-elastic membrane (calf's peritoneum), the edges of which are clamped in each half of the box between the two chambers. *A* and *B*, the space between the membrane and the inner, lower chamber, is filled with oil through the opening, which is then closed by a tap *F*. The kidney *G* is then placed on the membrane raised by the oil, so that the whole of the nerves and vessels with the ureter (which enter the hilum enclosed in a fatty sheath) pass out at the aperture *K* without being compressed. The box is then closed, and the space between the two membranes and the inner chamber of the upper half is also filled with oil, through the tube *e*, which is closed by a tap. Every change of volume in the kidney must now displace the oil, and is transmitted through the tube *E* to the recording apparatus.

can only depend on variations in its vascular circulation; dilatation of the renal vessels produces increase, constriction of the vessels decrease, in the kidney volume. In oncographic curves, as in kymographic tracings from an artery, we can distinguish the oscillations of the sphygmic wave due to the cardiac rhythm, the undulations of the second order due to the respiratory rhythm, and occasionally the slower undulations of the third order

which depend on variations of vascular tonicity (Traube-Hering waves of blood-pressure curves), but run in the opposite direction. This signifies that the volume of the kidney diminishes when the general arterial pressure rises, and increases when that falls, because the rise of pressure is due to constriction of the peripheral arteries, in which the renal arteries also take an active part.

This phenomenon can easily be produced artificially by arresting artificial circulation in a curarised animal during the experiment. The progressive asphyxia, which produces a diffuse constriction of the small arteries and rise of general arterial

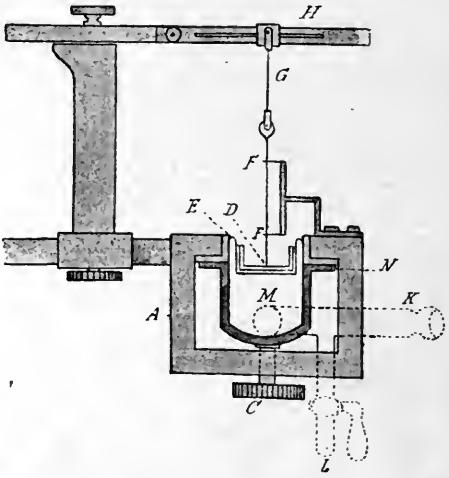


FIG. 119.—Roy's oncograph for recording alterations in the volume of an organ. Half the proper size. The faintly traced tube *K* is connected with the oncometer by a rubber tube. *D* is a piston resting on the oil contained in the cavity *M*. The oil cannot escape at the sides since it is confined by a thin, flexible membrane *E*, which does not interfere with the up-and-down movement of the piston. The recording line *H* is connected with the piston by the needle *G*, which works through *F*, *F*. The screw *C* clamps the membrane near the piston between the two ring-shaped surfaces *N*. The side-tube *L* which carries a tap is used for filling the apparatus with oil.

pressure, causes a diminution in the volume of the kidney, because the renal vessels which participate in this constriction confine the range of the renal circulation (Fig. 120). The same fact is observed on stimulating the vasomotor centre in the bulb of curarised animals, as well as on stimulating the splanchnics which contain constrictor fibres for the renal arteries (Fig. 121).

On repeating these experiments after section of the branches of the renal plexus by which the vaso-constrictors penetrate, the opposite result is obtained, *i.e.* increase of kidney volume from the passive dilatation of the renal arteries, due to the rise of arterial pressure.

The vaso-constrictors of the kidney arise mainly in the dorsal tract of the cord. In the dog the anterior spinal roots from

the 4th dorsal pair to the 4th lumbar (which correspond with the second lumbar pair in man), contain vaso-constrictor fibres for the kidney; but most of them run in the anterior roots of the 11th, 12th, or 13th thoracic pairs. These vascular fibres, after passing through the ganglia of the sympathetic chain, run to the solar plexus, and thence to the renal plexus by the splanchnics, or other paths.

When the anterior roots of these spinal nerves are excited by rhythmic excitation of low frequency, the result is not constriction but *active dilatation* of the renal arteries, expressed in a swelling of the kidney. This fact, discovered by Bradford, shows that these roots contain vaso-dilator fibres to the renal arteries, besides

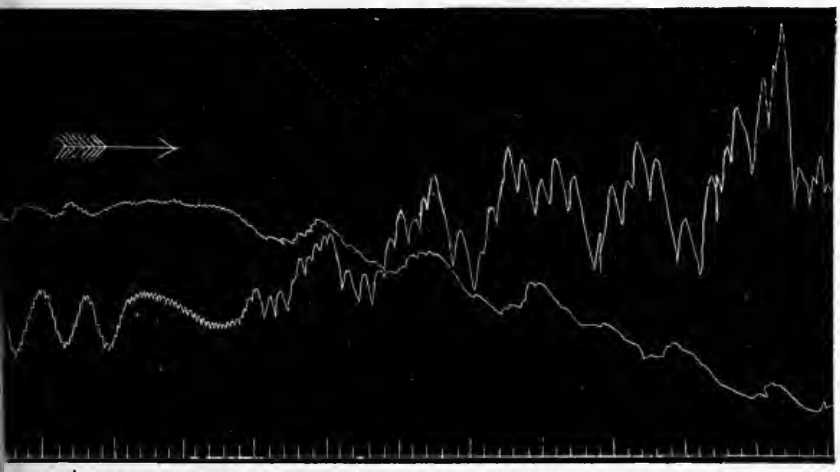


FIG. 120.—Increase of arterial pressure (P), and decrease in kidney volume (V), due to asphyxia commencing at A. (J. Cohnheim and C. Roy.)

the vaso-constrictors. The former are excited by rapid rhythmical stimulation, the latter by a slow rhythm. Both kinds of vascular fibres seem to follow the same path till they penetrate into the kidney.

It is still doubtful whether the spinal fibres from one side innervate only the vessels of the kidney on the same side, or partly those on the opposite side as well. It is also doubtful whether the vagus contains fibres to the kidney. Certain experiments carried out in Belgium by Masius (1888), in France by Arthaud and Butte (1890), and repeated in Italy by Vanni (1893), seemed to show that the vagi may exert a direct vasomotor action on the kidneys, *i.e.* independent of the action of these nerves on the heart and on arterial pressure. But this interpretation is excluded by the subsequent work of Walrawens (1896) in Albertoni's laboratory. He shows:—

(*a*) That stimulation of the vagus in the neck arrests renal secretion by the inhibitory effect on the heart and consequent fall of arterial pressure.

(*b*) That after atropinisation, excitation of the vagus has no effect on renal secretion, which shows that it contains no vasomotor or secretory fibres to the kidney.

Little is definitely known in regard to reflex vaso-constrictor and dilator action in the kidneys, and nothing as to whether its centres are localised in the cerebrospinal system, or situated among the vasomotor centres of the other vascular regions.

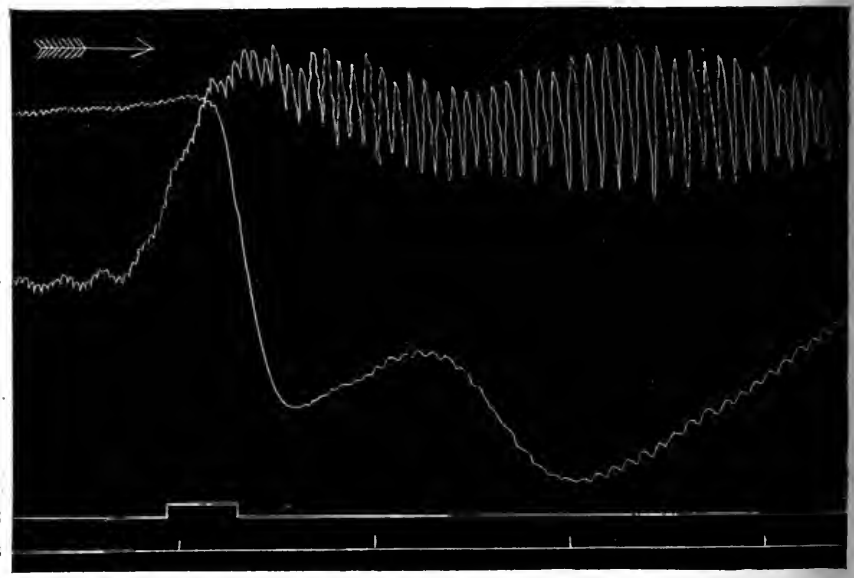


FIG. 121.—Increase of arterial pressure (P) and decrease of kidney volume (V) from stimulation of splanchnic at point marked on line E. (J. Cohnheim and C. Roy.)

While the foregoing and well-established evidence shows that the renal circulation is regulated by a special system of vasomotor nerves, there are so far no definite data to prove that the secretory function of the kidneys is controlled by special *trophic* or *secretory* nerves. Yet, on analogy with what we have seen in the study of the other secretions, it must be taken as probable that the secretion of urine is also under the direct control of the nervous system, though we have at present no definite proof of this, just as a few years ago (*i.e.* previous to Pawlow's work) we had no proof of the existence of secretory nerves for the gastric secretion.

This argument by analogy has gained in value since Berkley (1893) made the discovery that the nerve-endings of the renal

plexus can be seen not only along the arterial vessels, but also along the uriniferous tubules, and in Bowman's capsules. By using Golgi's method for staining black with chromate of silver he was able to follow the nerves of the renal plexus from their entry into the hilum with the arteries to their peripheral destination. He saw that the nerves which accompany the vessels form

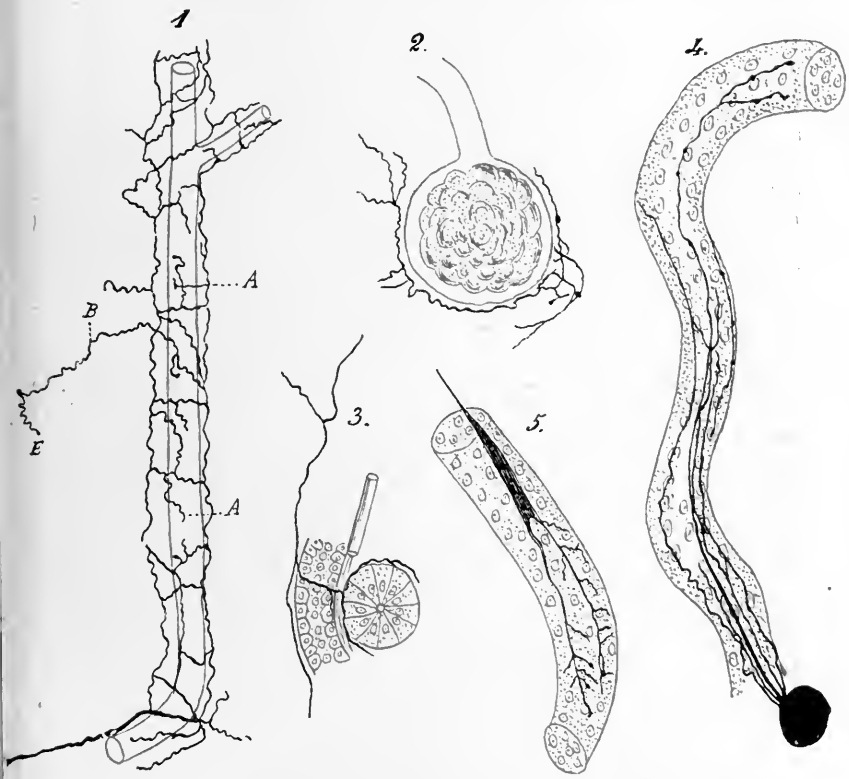


FIG. 122.—Nerves, ganglion-cells, and nerve-endings in kidney of mouse. (After Berkley.) 1. Artery of medium size near hilum of kidney, with its nerve plexus; *A A*, terminal fibres; *B*, diverging fibres; *E*, nerve-ending. 2. Nerve fibres with nerve endings, surrounding a Bowman's capsule. Glomerulus visible inside capsule. 3. Cross-section of collecting tube and longitudinal section of convoluted tubule, showing relation of nerve fibres and membrana propria. Small blood-vessel lying near the collecting tubule. 4. Portion of convoluted tubule in which the distribution of medium-sized nerve fibres arising from a ganglion can be followed. 5. Elongated ganglion cells on convoluted tubule, which appear to penetrate the membrana propria.

rich gangliated plexuses along their course, which are distributed both in the medullary and in the cortical layer as a very diffuse network of nerve fibrils. The primary plexuses that accompany the vessels (Fig. 122, *1*) give off secondary branches and arborisations which surround the capsule of Bowman (Fig. 122, *2*) without, however, penetrating into it, while other ramifications are

distributed to the convoluted tubules, where they terminate in the form of spherical dilatations or delicate fibrils, which penetrate the basement membrane, and are presumably in connection with the cement substance of the epithelial cells (Fig. 122, *3*, *4*, *5*).

These anatomical observations of Berkley were confirmed and amplified later on by Azoulay (1894) and Pensa (1896), and more particularly by the painstaking researches of T. D'Evant (1899), who described four different kinds of nerve-endings in the kidney: —(*a*) the terminations in the walls of the vessels; (*b*) those of the Malpighian glomeruli; (*c*) those of the convoluted tubules; (*d*) the free nerve-endings in the glandular parenchyma, which, according to this author, have a centripetal function.

Evidently the function of these nerve fibrils can only be *trophic* or *secretory*, and, is quite distinct from that of the vascular branches.

As we have stated, however, no physiological experiment has yet given indisputable evidence of the existence of secretory nerves to the kidney. In 1835 Cl. Bernard affirmed that puncture of the floor of the 4th ventricle produced *polyuria*, which is frequently, but not invariably, accompanied by *glycosuria*. He explained the different effects of puncture by the varying position of the lesions. The point at which hepatic secretion of sugar is excited lies rather deeper than that by which renal secretion of urine is excited, but they are so close together that both are frequently involved by the puncture, so that polyuria and glycosuria result.

Eckhard on repeating the experiments was unable to accept this interpretation. In rabbits he found that simple hydruria occurred very seldom. In these animals, on the other hand, hydruria and glycosuria can be produced by mechanical, electrical, and chemical stimulation of that part of the vermis of the cerebellum which covers the rhomboidal sinus; if the nerves to the liver had been divided previous to excitation simple hydruria resulted.

The clinical phenomenon of polyuria or hydruria (also known as *diabetes insipidus*) shows the possibility of increased urinary secretion independent of the internal secretion of the liver. Diabetes insipidus has been observed in cases of inflammation and tumours of the medulla oblongata, and in cerebral disturbance, also as an after-effect in attacks of epilepsy and hysteria (Ebstein).

The polyuria due to puncture is not caused by rise of arterial pressure, since this does not vary, or falls slightly; it might therefore arise from excitation of *renal secretory fibres*, as conjectured by Eckhard. But it is more probable, as Starling holds, that it depends on the excitation of *renal vaso-dilator fibres*.

After division of the splanchnic nerve, the flow of urine at once increases in the kidney of the side operated on, but this increased secretion lasts a long time (3-4 hours), so that it cannot

be interpreted by a stimulation of secretory fibres due to section, but must depend on a paralytic dilatation of the renal arteries, similar to that produced after dividing the nerves that enter at the hilum.

Lastly, if we admit the existence of secretory renal fibres (for which there is some evidence in the histological facts discovered by Berkley), it must be allowed that the system of secretory fibres is able to function independently of the central nervous system. In fact, it results from a series of experiments performed on frogs by Bidder (1844), that in these animals the secretion of urine is not arrested even when the spinal cord had been excised. The same fact was also observed by Goltz and Ewald on a dog from which they had removed nearly the whole of the cord in a number of operations. We may therefore conclude that the secretory nerves to the kidney belong to the sympathetic system,—which entirely agrees with the histological work of Berkley.

As regards the *reflexes* transmitted to the kidneys, Spallitta's results (1891) may be cited. He proved that ligation of one ureter in dogs at a short distance from the renal pelvis often (in 3 out of 7 animals operated on) produced arrest of urinary secretion in the kidney of the opposite side as well. In some experiments this arrest lasted 40-48 hours, an abundant diuresis followed, and sugar was found in the first urine excreted. These results agree perfectly with clinical cases of reflex anuria due to renal calculi with occlusion of one ureter (Tenneson, Carrière). Reflex anuria or oliguria has also been observed in certain diseases of the testicles (Nepveu), and in consequence of the surgical operations of vesico-vaginal fistula (Jobert), and lithotomy (Aricò).

Vinci (1900-2) found in the dog that division of the spinal cord between the third and fourth cervical vertebrae produced total anuria, even if abundant diuresis had previously been aroused by injection of glucose and lactose. Since he could not detect any variation in blood pressure and circulation to account for the anuria, he concluded that a renal centre must exist in this part of the cord.

The clinical phenomenon of *hysterical anuria* (cf. the two classical cases described by Rossoni; Chap. VI. p. 361) is highly important in relation to the hypothetical existence of *renal secretory nerves.*

The well-authenticated fact of *total suspension* of the renal secretion for long periods of time, which are unequal and occur irregularly, lasting in the first case for a maximum period of 22 days, in the second for more than 30, seems to us incontrovertible evidence for the existence of direct secretory nerves to the renal gland. Having already described and estimated the effects of *hysterical anuria* in regard to the vicarious excretory functions of the gastro-intestinal system, we must now investigate its internal

cause or conditions, and endeavour to reconstruct the process by which this absolute suspension of the renal secretion takes place.

Vulpian held that *hysterical oliguria* was *reflex* in origin, and caused by excitation of the renal vaso-constrictor fibres of the splanchnics, which produces spasm of the renal arteries. But he believed this explanation to be insufficient for *hysterical anuria* (which may last for a very long time), and invoked the subsidiary hypothesis of a *reflex inhibition of secretion*, capable of producing arrest of functional work in the epithelia of the renal tubules. Spallitta gave the same explanation of hysterical anuria.

To us this theory seems inadequate and improbable. It is inadequate because in anuria the secretory function is suspended not only in the renal tubules, but in the glomeruli as well; improbable when we consider that the hypothesis of *specific nerves which directly inhibit renal secretion* is contrary to all analogy. We have no data showing the existence of trophic nerves to *inhibit* secretion, while the existence of *trophic secretory nerves, i.e.* nerves which on excitation provoke a copious secretory activity of the epithelia, while their paralysis suspends it absolutely, is a matter of classical demonstration, particularly for the salivary and gastric secretions.

Long-continued anuria is one of the phenomena that make up the syndrome of hysterical neurosis: there can be no doubt as to its nervous origin. But while it is impossible to explain it as an effect of *activity of specific inhibitory nerves* (which is always of very brief duration), it is on the contrary easily interpreted as the consequence of a *paralysis of specific secretory nerves*, hysterical paralysis having been known to last for months and even years, and to cease suddenly for some slight or unknown reason. Admitting this as the only possible theory of hysterical anuria, it is remarkable that such a paralysis of the peripheral sympathetic centres and secretory nerve fibres of the complex renal organ should be capable of suspending not only the specific function of the tubular epithelia, but also that of the glomeruli, which is in no way specific. This is a new and weighty argument to add to those of Galeotti and De Bonis, against that theory by which the glomerular function is conceived as a merely physical process of filtration.

The mechanical conditions of circulation in the glomeruli, which evidently continue even after the supposed paralysis of the secretory nerves, are inadequate to produce any excretion of secretory fluid through their walls. This fact should be remembered in endeavouring to explain why artificial circulation through an excised kidney is not sufficient to produce a formation of normal urine, even when urea is added to the blood circulated (see p. 445).

VII. To complete the physiological study of the kidney as an

organ of secretion, we need only examine whether the epithelial cells of the convoluted tubules, which undoubtedly represent the secretory part of the uriniferous tubules, undergo changes which can be detected in the microscope in consequence of functional activity, as compared with their cytological structure in the state of functional rest. Owing to the continuous flow of urinary secretion, the kidneys and their constituent cells can never, normally, be in a state of *absolute rest.* Yet they are capable of being, and often are, in a state of *relative rest,* under all physiological conditions in which secretion is more or less reduced, *e.g.* in a protracted absolute fast, and especially during hibernation, which for winter-sleeping animals undoubtedly represents a periodically recurrent physiological state.

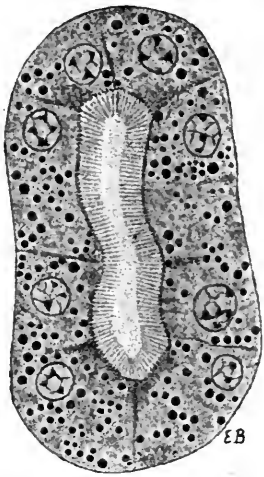
Many physiologists and histologists have taken up this subject (Nussbaum, Gibbes, Kruse, Lorenz, Tornier, and others); here we can only refer to the more recent work of Sauer (1895), Trambusti (1898), and R. and A. Monti (1900).

Sauer, in Heidenhain's laboratory, minutely described the histological structure of the epithelium in the post-glomerular, convoluted tubules of many mammals under various conditions, and decided that the cells of these tubules are constantly provided with the "brush-border" (*orlo a spazzola*), so that those authors are right who regard this structure as a constant morphological character, and those others wrong who regard it as an expression of functional activity in the cells which exhibit it. According to Sauer the resting tubules only differ from those which are in secretory activity in having a narrower lumen.

According to Trambusti, on the contrary, this brush-border of the cells of the post-glomerular tubules is not an integral part of those cells. It is absent in rest, and is a temporary expression of the function of the secreting cells.' Below the "brush-border" there is, according to Trambusti, another small striated border, which he considers a constant character of the cell, and to which he ascribes the greatest importance in the elimination of the secretory products.

As between these two opposite conclusions, the results of R. and A. Monti seem to us decisive, owing to their lucidity and the strictly comparable physiological conditions under which the experiments were carried out. They compared the renal tubules of the marmot after prolonged hibernation (October to the end of February), when the secreting function of the kidney must be reduced to a minimum, with those of marmots that are awake and fully nourished with milk. The difference in appearance of the lumen and epithelial cells of these tubules is shown in Figs. 123 and 124. The uriniferous tubules of the waking marmot are always more dilated than those of the hibernating animal, in which the walls almost touch each other, and the lumen is nearly

obliterated. The "brush-border," however, is plainly visible, and does not differ perceptibly in the two animals. The same may be said of the nuclei which are found in the resting state in both animals; they are situated in the basal third of the cell; and are spherical, with an indistinct reticulum, and large nucleoli which vary in number. On the other hand the cell-protoplasm shows marked differences. In the waking marmot it consists of a series of nodulated threads which radiate from the axis of the lumen (and cause the striated appearance); they are more distinct and regular in the basal half, more fused, nodulated and interwoven in the inner half which faces the lumen. In hibernating marmots



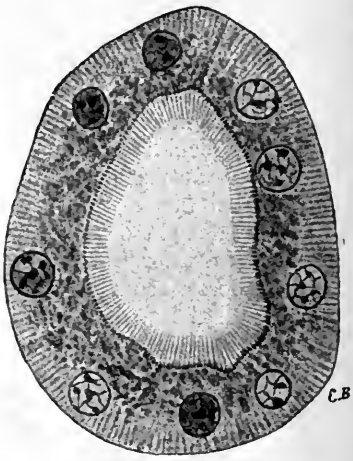


FIG. 123.—(Left.) Section through convoluted tubule of marmot during advanced torpor. (R. and A. Monti.)

FIG. 124.—(Right.) Section of convoluted tubule of waking marmot, during functional activity of renal epithelia. (R. and A. Monti.)

the protoplasm exhibits the same thready and striated composition, but it is much less apparent, because it is masked by a large number of irregularly distributed granules, which differ in size and in their affinity for stains. They are not fat droplets, because they do not disappear on prolonged immersion of the sections in xylol or oil of bergamot. It is therefore probable that they consist of protein, destined to maintain the secretory work of the cell, and that they accumulate when the function of the kidneys is reduced to the lowest terms, as must be the case after prolonged hibernation.

These results of the brothers Monti are still more important from the physiological point of view. To us they appear to give histological evidence of the *active intervention* of the cells of the convoluted tubules in the functions of the kidneys, and therefore prove the inadequacy of the purely mechanical theory to explain

the formation of urine. Of course this would not suffice to decide between the theory of Bowman and Heidenhain and that maintained by Sobieranski. Against this last theory, however, we may adduce almost if not quite all the objections made by Heidenhain to Ludwig's contention. It further seems to us improbable on the argument by analogy, in view of the fact that the epithelial cells in all other tubular glands function as organs of *external secretion*, although this does not preclude the possibility of their simultaneously affecting the constitution of the blood, by an outpour into the lymph of other special products of an *internal secretion*. But this view, which was held by Brown-Séquard, Fränkel, Meyer and others is far from proved, since both the experimental facts and the clinical data on which it is founded lend themselves to quite another interpretation.

Among the later histological researches into the activity of

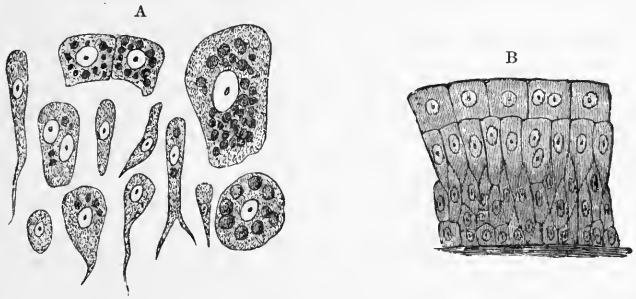


FIG. 125.—Epithelium from pelvis of human kidney. (Kölliker.) 350 diameters. A, different kinds of epithelial cells; B, the same, *in situ*.

the kidney, we must cite the work of Gurwitsch (1902), who investigated the elimination of indifferent aniline pigments on frogs. He saw that they were excreted by means of vacuoles, similar to those observed in Protozoa. The vacuoles, loaded with pigment, gradually advance to the surface of the epithelial cells, where they discharge their content into the lumen of the duct. The latest experiments of Höber and Königsberg (1905) on pigment excretion by the kidneys has completely confirmed and extended the results of Gurwitsch, so that histology also pronounces decidedly in favour of the Bowman-Heidenhain theory.

VIII. The urine flowing from the collecting tubules of Bellini is conducted from the renal pelvis by the Ureters, which are ducts about the width of a goose-quill, 30-40 cm. long, with strong walls consisting of an external fibrous coat, a middle coat of plain muscular tissue (with two layers of longitudinal fibres, and one thicker intermediate circular layer); and an internal mucous coat with an epithelium composed of four layers in which the cells differ in size and shape (Fig. 125).

Small branches of the renal artery pass from the pelvis to the ureter, but other arterioles which come from the spermatic, internal iliac, and inferior vesical arteries have an opposite course, and run from ureter to pelvis. It is these branches that dilate and develop after ligation of the renal artery, in order to re-establish the renal circulation.

Nerve fibres pass in the ureter from above downwards from the renal plexus, and from below upwards from the hypogastric and spermatic plexuses. Ganglion cells are scattered at irregular intervals between these nerve fibres.

The urine passes through the ureters less on account of gravity than from the active peristaltic movements of their walls. On exposing the ureter of an animal, or examining it in man, in cases in which it has become accessible through laparotomy, it can be seen that its contractions invariably begin at the extreme end of the pelvis, and are peristaltically propagated towards the end near the bladder. Antiperistaltic movements are normally never seen in the ureters any more than in the intestine. It is natural to suppose that the peristalsis of the ureters is excited by the urine which trickles into them from the pelvis. In fact, after copious draughts peristalsis is accelerated with the amount of urine secreted. Urine, however, is certainly not a direct chemical and mechanical stimulus, indispensable to the rhythmic movements of the ureters, since the movements persist regularly even in ureters cut out of the living animal with the kidneys, and sometimes even in bits of isolated ureter.

If the ureter be stimulated mechanically or electrically, at any point, the same phenomenon appears that we noticed in the heart, *i.e.* waves of contraction are produced in both directions, one peristaltic, descending towards the bladder, the other antiperistaltic, ascending towards the pelvis (Engelmann, 1869). These are *automatic rhythmical movements*, similar to those of the heart, propagated solely by muscular paths, independent of ganglion cells and nerve fibres. They have been observed by Engelmann even in isolated pieces of ureter taken from the middle of the duct, where no ganglion cells can be detected under the microscope.

The automatic rhythm of the ureters is sometimes regular (in the rabbit three beats per minute can be counted), at other times the movements occur irregularly, at others again they take the form of groups separated by long pauses, which suggest the periodic rhythm discovered by ourselves in the heart.

In cases of atrophy of the human bladder, it is usually found that the vesicular orifices of the two ureters do not open simultaneously, that their peristaltic movements do not follow at regular intervals, that the amount of urine that flows from them in the time unit varies considerably. It has also been stated that the

maximum quantity of urine flowing into the bladder at a single peristaltic contraction does not exceed 4 c.c. (Zamshin, 1887).

It may be assumed by analogy with what takes place in the heart and blood-vessels that the automatic, fundamentally muscular rhythm of the ureters is regulated by the activity of the intrinsic ganglia and the extrinsic ganglia, both in the sympathetic system and in the cerebrospinal system. The experiments of Protopopow (1897) in fact show that section of the great splanchnic produces a delay in the peristaltic rhythm of the ureter of the same side, while excitation of its peripheral end always produces acceleration.

According to Protopopow's numerous experiments, the effect of the various operations by which the circulation in the kidneys and ureters is modified are variously expressed in the movements of the ureters. To cite his principal results:—

(*a*) In acute asphyxia the contractions of the ureters become more marked and frequent, as in all other plain muscular organs. (*b*) When the secretion of urine ceases owing to ligation of the renal artery, the contraction of the ureters becomes slower at first, but subsequently returns to the same frequency as before. (*c*) After occlusion of the aorta above the point at which the renal artery is given off, there is in consequence of the anaemia a marked slowing of the contractions of the ureters, which return to the normal rhythm as soon as the aorta is reopened. (*d*) After occlusion of the inferior vena cava above the mouth of the vas efferens there is a marked and persistent acceleration in the rhythmical movements of the ureters, due to the passive hyperaemia. (*e*) With increased frequency of the drops of fluid which trickle into the ureter its contractions are accelerated, more or less, according to the nature of the fluid. (*f*) Ligation of the upper part of the ureter immediately above the pelvis produces a marked slowing, followed by complete arrest, of its movements. (*g*) Atropine at first produces acceleration, afterwards retardation, and finally arrest of the contractions of the ureter. (*h*) Some diuretics, *i.e.* diuretine and adonidine, do not modify the frequency of the movements of the ureters; caffeine, on the contrary, accelerates them in small doses, delays them in large.

The latest work on the movement of the ureters, carried out by Lina Stern in Prévost's laboratory (1903), confirms the above conclusions as a whole. Unlike Protopopow's results, however, section of the splanchnic in the dog produced acceleration, and stimulation of its peripheral end, inhibition of the movements. According to this author the splanchnic contains both accelerator and inhibitory fibres; the action of the latter is favoured by atropine. According to Fagge (1902), on the contrary, stimulation of the hypogastrics accelerates the movements of the ureters, while stimulation of the splanchnics produces no effect.

IX. The ureters open into the bladder by two oblique orifices that function as valves, and close by the positive intravesical pressure. While this impedes reflux into the ureters, the flow of urine into the bladder, caused by the rhythmical peristaltic movements of the ureters, which drives the fluid forward, and opens the orifices, is not prevented.

The Bladder has an external serous or peritoneal coat which lines only the posterior and upper half, an internal mucous membrane which is covered with stratified epithelium similar to

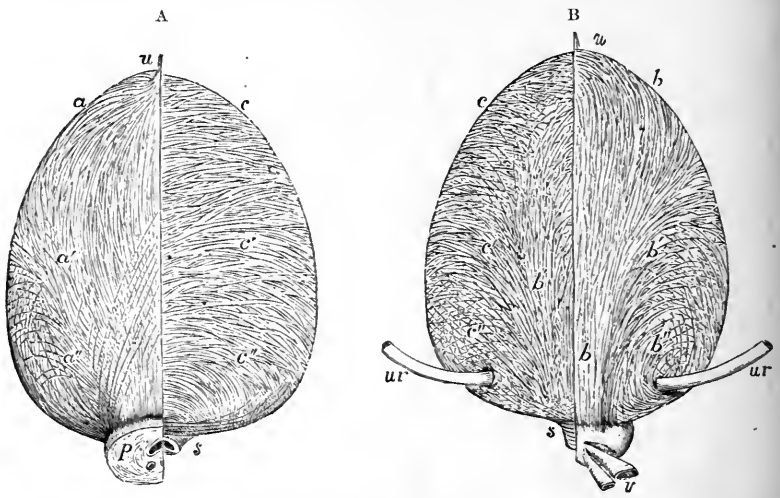


FIG. 126.—Course of the muscular fibres of the bladder (Allen Thomson after Pettigrew, and from nature), ½. A. *From the front.* On the right side the superficial fibres are shown; on the left, the deep or circular fibres; *a*, on the right side the median and most superficial bands of the longitudinal fibres, showing slight decussation of the fibres; *a'*, those diverging somewhat; *a''*, the lowest, which pass much more obliquely; the attachment of the longitudinal fibres to the prostate is shown. On the left side, *c* the upper, *c'* the middle, *c''*, the lowest set of circular or deeper fibres; *s*, the thickest and most transverse sets of three fibres forming the sphincter; *p*, right half of the prostate, the left half having been removed; *u*, urachus into which some of the longitudinal fibres are prolonged. B. *From the back.* Right side shows superficial fibres; left, the deeper fibres of the same kind, or intermediate fibres; and some of the circular fibres; *b*, *b*, median, most superficial and strongest bands of longitudinal fibres on right side; *b'*, more diverging fibres near middle of bladder; *b''*, the most divergent which surround entrance of ureters. On left side, *c*, *c'*, and *c''* indicate the deeper circular fibres passing round at various levels, and crossing with the deeper diverging fibres posteriorly; *s*, the most transverse fibres at the neck forming the sphincter; *u*, the urachus; *ur*, the ureters; the left half of the prostate has been removed to show the sphincter; *v*, part of right vas deferens and vesicula seminalis.

that of the ureters, and an intermediate muscular coat, which calls for special consideration.

The muscular coat has an outer layer, the fibres of which are mainly longitudinal, and are most distinct upon the anterior and posterior surfaces of the bladder, and an inner layer of which the fibres are mostly circular, which is thinner and irregularly reticulated (Fig. 126). This distinction into two or three layers is, however, only an anatomical device, since the fibres of which they

are composed pass from one layer to another, and are united by connective tissue. It is also an artificial distinction to regard the longitudinal fibres collectively as one muscle, the *detrusor urinae*, because the layer in which the fibres are mostly circular must also contribute to the compression of the vesicular cavity and increase of pressure within it, and thus to the expulsion of the urine. The term "musculus detrusor" should comprise the entire muscular coat of the bladder, which, as a whole, constitutes a hollow muscle consisting of a tissue of plain fibres.

Anatomists are not agreed as to whether there is an *internal sphincter* of plain muscle at the neck or urethral orifice of the bladder, independent of the layer of circular fibres described above, and of the external sphincter of striated muscle (*Wilson's* or *Guthrie's muscle*) which is certainly under direct voluntary control. Griffiths in England (1891), and Versari in Italy (1897), devoted themselves to this subject. The former denied the existence, not only for man, but for mammals and vertebrates in general, of an internal *sphincter vesicae* independent of the circular muscle fibres of the bladder. According to Griffiths, there is no thickening of the muscular fibres near the urethral orifice to justify the term "sphincter." But the question whether there is or is not a sphincter in the bundle of circular fibres that surrounds the neck of the bladder, ought not to depend on whether this bundle is thicker than the circular layer of the bladder or not, but on whether it has any special structure and distinct physiological function. In regard to structure Versari's researches seem to us exhaustive. He admits the existence of an internal sphincter in both sexes, in adults as well as in infants and children, for man as well as other mammals. According to Versari there is a distinct formation shown by the peculiar arrangement of the fibres, the greater compactness of the bundles and their smaller size, and lastly by the smaller quantity of interstitial connective tissue (Fig. 127). As regards specific function, it is evident that while contraction of the muscular coat of the bladder drives out the contents, and acts as a *musculus detrusor urinae*, the tonic contraction of the internal sphincter prevents incontinence of the bladder, *i.e.* escape of urine in the intervals between one micturition and another. The function of the sphincter is therefore diametrically opposed to that of the detrusor.

Some authors (Wittich, Lesser, Rosenthal) have concluded from the fact that urine can be retained in the bladder even in a dead body, that no tonic contraction of the sphincters is required, but that the simple elasticity of the tissues is enough to prevent incontinence. Retention of the urine in a dead subject, however, depends on the contracture which appears in the plain muscles after the death of the nerve centres, and persists until the advent of *rigor mortis* (S. Mayer), during which the bladder of the dead

body can support the pressure of a column of about 900 mm. of water before it empties. Heidenhain and Colberg tried to demonstrate the tonic action of the *sphincter vesicae* by introducing a sound into the ureter as far as the neck of the bladder, and measuring the pressure necessary to overcome the resistance of the sphincter and to permit the penetration of fluid into the bladder, which pressure is reduced after the death of the animal. But it may be objected that the external pressure which is required

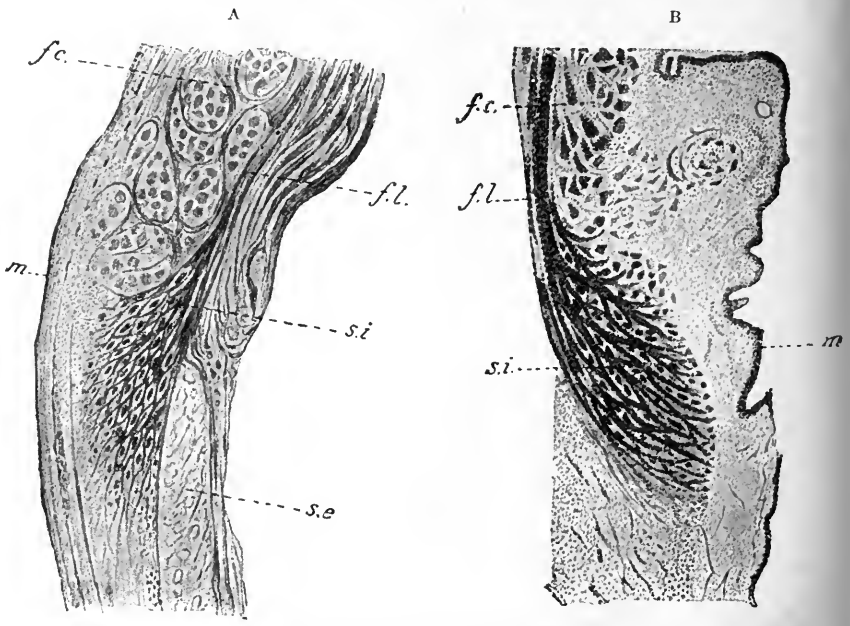


FIG. 127.—A. Section through bladder of young woman near the posterior wall of the curve. (Versari.) *Si*, internal sphincter; the bundle of circular fibres as seen in cross-section, with longitudinal fibres from the detrusor urinae showing between. *Se*, external sphincter of striated muscle; *fl.*, *fc.*, longitudinal and circular fibres, of which the muscular coat of the bladder is composed, and which unite in forming the detrusor urinae. B. Section through bladder of girl near the posterior wall of the cervix. (Versari.) Lettering as in A. Here the external sphincter is not visible. It is nearly always incomplete and ill-developed in females, and is probably absent in infancy.

in order to force the fluid into the bladder, sets up a reflex which causes the sphincter to contract, or at least increases its tonicity. The better demonstration of this normal tonic activity seems to us to lie in the fact of the incontinence of urine which is not uncommon in cases of disease of the brain or spinal cord.

Since even in sleep, when the action of all voluntary muscles is relaxed, the urine is normally retained in the bladder, it is clear that the tonic activity to which the retention is due depends on the *internal* sphincter of plain muscle, and not on the *external*

sphincter of striated fibres, which is thrown into activity by voluntary impulses only when it is necessary to delay evacuation of the bladder, on feeling a desire to pass urine.

We must accordingly conclude that the urethral orifice of the bladder is provided with an internal sphincter of plain muscle (morphologically distinct from the circular layer of the bladder), on the tonic contraction of which depends the retention, on its paralysis the incontinence of urine.

While it is difficult to give experimental proof, we regard it as probable that the tone of the internal sphincter of the bladder is not constant, but varies with the tension of the bladder, and that it is not *automatic* but *reflex* in character, *i.e.* determined by the presence of the urine and the pressure which the latter exerts upon the urethral orifice. The same opinion was clearly set forth by Haller (1778) in the following words:—"Videtur urinae modicam copiam in convexo vesicae fundo versus rectum intestinum, sub urethra producto, facile et absque sensu colligi; deinde sphincterem incipere stringi, quando major nunc lotii copia ad urethrae ostium adscendit, et eo majorem ejus musculi laborem esse, quo altior super urethram nunc urinae columna est, suo pondere urethrae ostium nitentis."

Experimental evidence for the theory of the retention of urine by the tone of the internal sphincter of plain muscle has recently been given by Rehfisch in I. Munk's laboratory (1897). In five dogs which for over three months survived the severe operation of removal of the prostate, including Wilson's muscle (external striated sphincter), he saw that the urine was perfectly retained in the bladder without a trace of incontinence. The same fact was demonstrated on man by a very elegant experiment. By means of a rigid catheter, he injected into the bladder of a man as much boric acid solution as was required to fill it completely. On then drawing the catheter back as far as the prostatic portion of the urethra, so as to inhibit the contraction both of Wilson's muscle which surrounds it, and of the compressor urethrae which surrounds the membranous part of the urethra, he observed that the subject was able not only to pass urine at will, but also to interrupt the evacuation at any moment, by relaxation or contraction of the internal sphincter (the only one he could control), so as to open or close the urethral orifice.

Again: by other experiments on dogs Rehfisch was able to show that, under ordinary conditions of closure of the urinary canal, the external sphincter and the compressor urethrae play only a subordinate part, the retention of the urine being specifically the task of the internal sphincter. After opening the peritoneal cavity and exposing the bladder, he connected one of the ureters with a manometer by a cannula which penetrated into the bladder, and introduced into the other ureter the cannula of a syringe by

which fluid could be injected as required into the bladder. He then ascertained the height to which the internal pressure of the bladder must be raised in order to see the first drop of fluid flow from the catheter introduced into the urethra at different depths. He found that this pressure was approximately the same, either when the catheter was pushed as far as the prostate, so as to hinder the action of Wilson's muscle, or when it was in the free part of the urethra, on which the action neither of this muscle nor of the compressor urethrae was hindered.

While Versari restored to the internal sphincter its anatomical function as distinct from that of the detrusor muscle, these important experiments of Rehfisch prove it to be the chief physiological factor in the closure of the urethra, and therefore in the normal retention of urine.

X. The *mechanism of micturition* or *urinary excretion* is certainly more complex than that of *retention*. It should be stated at the outset that three different kinds of Micturition can be distinguished and must be considered separately:—(*a*) wholly involuntary micturition, (*b*) micturition produced by a desire to pass urine; (*c*) voluntary micturition, *i.e.* independent of desire.

Involuntary micturition is a constant physiological phenomenon in infants at the breast, both in sleeping and waking; it is often observed in young children during teething, particularly when tedious and painful; it sometimes occurs with older children in sleep, up to the age of puberty. In all these cases micturition is a purely reflex, unconscious phenomenon, discharged by the great excitability of the efferent and afferent nerves to the bladder, by which the tone of the detrusor muscle, and therefore the tension of the bladder walls, is reflexly exaggerated. It is probable that in these cases the tone of the internal sphincter increases simultaneously, so that there is a conflict between the two antagonist muscles, the *sphincter* which closes the urethral orifice, and the *detrusor* which tends to open it by an outward pull (as assumed by Kohlrausch), which is due more particularly to the contraction of the fibres inserted radially between the muscular bundles of the sphincter, to which Versari has lately called attention. Since the struggle ends with emission of the urine contained in the bladder, the expulsive force of the detrusor ultimately prevails over the retentive force of the sphincter.

Experimental confirmation of this very simple mechanism of involuntary micturition is afforded by an experiment of Mosso and Pellacani (1882) on chloroformed and curarised dogs. They divided the ureter close to the neck of the bladder, opened the abdominal cavity, introduced a cannula into one of the ureters joined up with a Mariotte's bottle, and determined the pressure necessary to obtain a flow from the urethra. The tone of the detrusor muscle was then artificially raised by mechanical,

electrical, or thermal stimulation of the bladder walls, after which the pressure necessary to produce incontinence was again determined. They found that increase of tone in the detrusor was always under these conditions associated with increase of tone in the sphincter, so that more pressure was necessary to force the urine through it.

The involuntary micturition of fright, formerly interpreted as the effect of a sudden paralysis of the sphincters, may result from an analogous process. Mosso and Pellacani noted in support of this view that when a dog is frightened by shouts, or sudden pain, there is an increase of tone in the sphincters, expressed in the fact that a much higher pressure than the normal is required to force fluid through the urethra. This result can, however, be explained by a reflex contraction of the sphincter, due to the injection through the urethra; it does not seem to us to prove the contention of the authors.

In the adult also, owing to the preponderance of the detrusor activity over that of the internal sphincter, involuntary micturition would take place each time that excessive accumulation of urine, or increased activity of the nerves to the bladder, raised the vesical tension beyond a certain point, if the sphincter were not (in order to retain the urine within the bladder for a certain time longer) reinforced by the active voluntary intervention of Wilson's muscle, and of the compressor urethrae, as well as of the musculi bulbo-cavernosi, to which is associated the action of the sphincter ani. When these coadjuvants are inadequate, involuntary micturition takes place, as not infrequently occurs in young children.

The mechanism of the micturition which is aroused by consciousness of distension in the bladder and irritation in the region of the vesical orifice, leading to an imperative desire for relief, is more complex. The origin of these sensations must first be examined.

They are certainly not due directly to the tension of the bladder, because the amount of urine passed under different conditions is very variable, and is not in ratio with the strength of the desire. There may often be an urgent need to micturate, when very little urine is present in the bladder. This leads to the conclusion that the tone of the bladder wall is very variable, and that the need to micturate depends less on the passive distension of the bladder than on its active reaction to the contents, *i.e.* the pressure of the urine within the bladder.

In this connection the researches of Mosso and Pellacani on the great *reflex excitability* and *variable tone* of the muscular coat of the bladder are interesting. It is susceptible to mental influences, whether these are accompanied by changes in arterial pressure or not. At constant pressure the bladder may contain

a very different volume of fluid, and the need of micturition always arises under the same pressure (in a dog at a pressure of 20 cm., in a girl at a pressure of 18 cm. water) whatever may be the volume of fluid contained in the bladder. These authors concluded that micturition is excited by the pressure to which the walls of the bladder are subjected, and not by the varying degree of their distension.

If when the desire to micturate arises, the act of evacuation is delayed by the voluntary mechanism above described, the desire may lessen, or even disappear after a certain time. This phenomenon depends on a lowering of tone in the bladder and the consequent reduction of vesical pressure, although the quantity of urine has not been diminished, but even increases,—which confirms the variability of the tone of the bladder and the dependence of the desire to micturate upon vesical pressure, *i.e.* on a certain active reaction of the muscles of the bladder to its contents.

When, on the contrary, the need to micturate increases and becomes imperative, the flow of urine must be given free vent, and may in this case be termed *voluntary*, but only because it commences with the relaxation of Wilson's muscle (external sphincter), *i.e.* with the removal of the obstacle opposed by the will to the action of the detrusor urinae. It is true that in order to reinforce the expulsory effort of the latter, and to empty the bladder as completely as possible, abdominal compression, *i.e.* the repeated voluntary contraction of the abdominal muscles and diaphragm, plays an active part. This intervention, however, is not necessary, because the detrusor is in itself capable (after the animal's body has been opened) of developing sufficient force to hold up a column of water 1·5-2 m. in height (as observed by Mosso and Pellacani), and micturition normally takes place easily, even if more slowly, without any intervention of abdominal compression, *i.e.* with no perceptible modification of respiratory rhythm.

The mechanism of micturition aroused by consciousness of tension in the bladder accordingly differs from that of involuntary micturition only in the previous, voluntary relaxation of the external sphincter. On this assumption both involuntary micturition and that preceded by the desire to micturate would be essentially reflex acts, independent of the direct exercise of the will.

This theory, which at first sight appears simple and satisfactory, was overthrown by an ingenious experiment of Rehfisch.

By perfecting a method already employed by v. Zeissl in the study of vesical innervation (*infra*), Rehfisch introduced a catheter into the human bladder, provided with a two-way tap by which boracic acid solution could be injected in order to increase the content and distension of the bladder. By a turn of the tap he

established communication between the bladder and a Gad's metal manometer which recorded the intravesical pressure on a revolving drum. The subject was then invited to micturate, and the urine which flowed from the urethra down the side of the catheter was run into a filter communicating with a bottle connected at atmospheric pressure with a Gad's plethysmograph, which recorded the flow of urine on the same drum. The arrangement is shown in Fig. 128. By this ingenious method Rehfisch was able

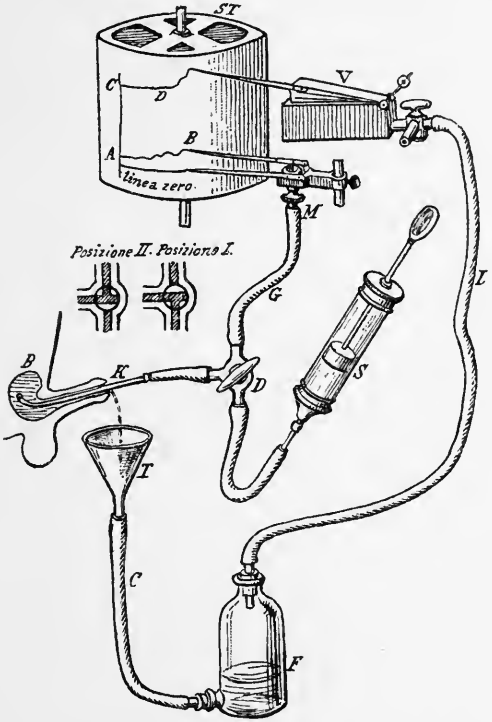


FIG. 128.—Apparatus used by Rehfisch to study micturition in man. The catheter *K*, introduced into the bladder *B*, communicates either with the syringe *S* or the manometer *M*, according as the two-way tap *D* is set in position *I.* or *II.* The funnel *T* receives the urine which flows from the urethra down the side of the catheter, and leads it through tube *C* to flask *F*, whence the pressure is transmitted by tube *L* to the plethysmograph *V*. The manometer records the curve of vesical pressure *A*, *B*, on the revolving cylinder, and the plethysmograph the volume curve of the urine *C*, *D*.

to compare the pressure curve with that of vesical evacuation, during voluntary micturition.

If the opening of the sphincter, as expressed in the rise of the lever, always coincided with the moment at which pressure in the bladder became maximal, this would show it to be the passive effect of the increased tension in the bladder, and would be an experimental demonstration of the theory by which micturition

is made to depend on the predominance of the detrusor over the sphincter. But in nine experiments Rehfisch was able to show that the opening of the urethra occurred five times when the curve of vesical pressure was on the down-grade, three times when on the up-grade, and once when it had reached its summit. He also saw that the pressure in the bladder was not maintained at a constant level during the time of evacuation, but almost constantly diminished.

These results contradict the hypothesis that it is the preponderating force of the detrusor which opens the sphincter and keeps it open for the entire period of micturition. They show, on the contrary, that the moment of opening the urethra or relaxing the sphincter is independent of the contraction of the detrusor, although the latter precedes the former by a shorter or longer period. We may therefore conclude that in the mechanism of micturition as incited by desire, the lowering of tone or active voluntary relaxation of the internal sphincter of smooth muscle is a main factor in the process, and that instead of opposing, it promotes the contraction of the detrusor.

Hanc (1899) obtained confirmation of this theory by experimenting with curarised dogs, on which he simultaneously recorded the pressure in the bladder and the amount of flow from the urethra during the reflex excited by stimulating the sciatic. At the beginning of each experiment the bladder was filled with a constant quantity of tepid water. He concluded from the ratio between intravesical pressure and the flow of urine in thirty-two experiments that they are independent of each other, *i.e.* that the contraction of the detrusor and the expansion of the sphincter are two distinct phenomena due to the activity of two separate nerves. The animals being curarised, all active intervention of the will is excluded in this kind of reflex micturition.

If the animal be put under morphine before stimulating the sciatic, the contraction of the detrusor persists, but there is no longer dilatation of the sphincter, so that the evacuation of the bladder is premature. This is probably due to the fact that the two muscles are under the tonic influence of two distinct spinal centres of antagonistic action. Chloral hydrate also acts like morphine, but weakens the reflex of the detrusor as well. Atropine and cocaine weaken both reflexes. Strychnine produces the opposite effect, but in a variable degree. The same holds good for muscarine.

It is also possible, as we stated above, to perform the act of micturition perfectly, independent of any more or less urgent desire, *i.e.* without the bladder being in such a tonic or contracted state as to arouse the sense of repletion or tension. For instance, micturition can be repeated a few moments after evacuation of the bladder.

This form of micturition is purely *voluntary*, and quite distinct

from what we have been considering. Few physiologists since Kohlrausch (1854) have taken it into serious consideration.

Kohlrausch, in order to explain micturition without, or previous to, desire, assumes that active intervention of the diaphragm and abdominal muscles is necessary, in order by compression of the intestines to lower and flatten the top of the bladder, and to produce the contraction of the detrusor. This muscle, by the fibres inserted between the bundles of the sphincter, would act in a less oblique direction, almost vertical to the fibres of the antagonist muscle, and would thus succeed in overcoming the resistance and opening the orifice of the urethra. Such an interpretation, however, appears to us to be totally erroneous, since it subordinates the phenomenon to the active intervention of abdominal compression. We have frequently convinced ourselves that it is easy to micturate a few minutes after emptying the bladder, without any modification of respiratory rhythm by which compression could be exerted. Moreover, in this case the urine is evacuated by a process which differs somewhat from that above. The micturition caused by desire takes place directly the obstacles (voluntary contraction of external sphincter, and reflex tonic contraction of internal sphincter) which prevent the escape of the urine are removed. Micturition without desire is, on the contrary, preceded by an obscure sense of slow relaxation of the internal sphincter, followed by a very long pause before the flow of urine commences, during which a not unpleasant sensation of titillation is felt near the orifice and the upper part of the urethra. That Valentin is in almost complete agreement with this description of micturition without desire is shown by the following passage:—"Si mingendi consilium coepimus, musculum clausorium vesicae relaxatum esse primo sentimus, tum vero intervallum longius breviusque intrat, quo lotium nondum defluit, denique lotium ipsum ejicitur." Nothing is omitted here except the sense of titillation previous to the passing of the urine.

The only possible interpretation of the phenomena which accompany micturition without desire appears to us to be as follows:—By the cerebral motor centres we voluntarily inhibit the action of a spinal centre which exerts a tonic action upon the internal sphincter of the bladder; the relaxation or expansion of this muscle permits a few drops of urine to trickle into the first part of the urethra, which act on the sensory endings of the urethral mucosa, and arouse the sense of titillation; this sensation then produces reflex contraction of the detrusor, which is followed by evacuation.

So that in this case also (if our interpretation be justified) micturition is not entirely voluntary, but is a process which, although initiated by the will, develops as a reflex act, independent of the influence of the higher centres.

Micturition without desire, therefore, differs from that caused by desire only in the fact that the dilatation of the urethral orifice by voluntary relaxation of the internal sphincter precedes instead of following the reflex contraction of the detrusor.

XI. It is very important that we should complete the study of micturition by reviewing the experimental evidence for the *innervation of the bladder*, since it substantially confirms our theory as to the mechanism of micturition in the above three different cases.

From a number of experiments on dogs, cats, and rabbits, we may assume positively that the bladder is supplied by two sets of nerves. The first set are derived from the lumbar nerve-roots, particularly from the third and fourth pairs, the fibres of which run in the rami communicantes to the lumbar part of the sympathetic chain, where with the mesenteric nerves (upper, middle, and lower) they join the inferior mesenteric ganglion, and finally, by the hypogastric nerves, reach the hypogastric plexus and the bladder.

The second set of nerves to the bladder originate in the roots (both anterior and posterior) of the sacral nerves, especially of the first to the second pair, from which two branches are given off, known as the *nervi erigentes* of Eckhard, which run straight to the hypogastric plexus, and thence to the bladder and the corpora cavernosa of the penis (see Fig. 106, p. 371). So that all the nerves which run from the cerebrospinal axis to the bladder pass in two distinct nerve-trunks, the hypogastric and the nervus erigens. Both, as we shall see, innervate the detrusor, and also the internal sphincter of plain muscle. The external sphincter and other striated muscles of the urethra are innervated by the nervus pudendus (Griffiths).

The vesical nerves are particularly abundant at the neck of the bladder, where they form plexuses in which ganglion cells are included (R. Mayer): they terminate partly in the blood-vessels (vasomotor nerves), partly in the muscle cells (motor nerves to muscles), and partly penetrate between the layers of the epithelium (sensory nerves).

Budge (1864) was one of the first to investigate the motor and sensory nerve-paths to the bladder. He saw that the nerves coming from the anterior sacral roots are able to excite contraction of the bladder directly, and also reflexly (by stimulation of corresponding posterior roots). Stimulation of the lumbar sympathetic also produced contraction of the bladder, but this was always accompanied by signs of pain in the animal. Stimulation of the central cord of this nerve produced the same effect. Section of the rami communicantes so as to interrupt all connection with the cord, but not with the hypogastric nerves and plexus, had, according to Budge, no effect on the bladder. From this he

concluded that the sympathetic contains sensory fibres to the bladder which reach the cord by the rami communicantes. Having noted that other nerves (trigeminus, splanchnic) which cause pain do not increase intravesical pressure, he concluded too hastily that only the sensory nerves coming from the bladder are capable of acting reflexly upon it.

Oehl (1865-69) obtained contraction of the bladder (as deduced from the increase of intravesical pressure) in dogs by exciting the intact vagus in the neck, or the central end of the cut nerve, or even its peripheral end, although in the last instance the effect is minimal. From this he concluded that the vagus contains sensory as well as motor fibres in direct or indirect connection with the bladder. Kehrer (1867), however, on repeating Oehl's experiments, with the peritoneum opened so that he could observe the bladder directly, saw that the stimulation of the vagus produced no effect even when transmission of all other movements was prevented. He, therefore, denies the connection of the vagus with the bladder, a negative conclusion which was also reached later by Sokowin, Nussbaum, Nawrocki.

Bert (1869) amended Budge's conclusion that only the sensory nerves arising from the bladder were capable of acting upon it reflexly. According to him, centripetal excitation of the sciatic, median, and infraorbital nerves constantly produces a contraction of the bladder.

Sokowin confirmed this result, and found the same for other sensory nerves (crural, splanchnic), but he added that all the reflexes ceased after ablation of the cerebral hemispheres of the animal. He concluded that sensory nerves which do not arise in the bladder act reflexly upon it, inasmuch as they arouse pain. The vagus was the only exception, since he was unable to confirm Oehl's results.

In a second series of experiments Sokowin found that stimulation of the centripetal fibres of the hypogastric nerve acts reflexly upon the motor fibres of the hypogastric on the other side, by means of the inferior mesenteric ganglion, which in this case functions as a reflex centre. He further saw that centripetal stimulation of the posterior sacral roots produces reflex contraction of the bladder, which ceases in the cat after division of the cord at the level of the fourth lumbar vertebra. Nussbaum (1879), in Nawrocki's laboratory, confirmed these important results of Sokowin as to the direct and reflex innervation of the detrusor muscle. Subsequently Nawrocki and Skabitschewsky (1891) adduced fresh proofs from a more extensive series of accurate researches, and came to the following conclusions:—

(*a*) Every sensory nerve of the body produces contraction of the bladder by the mediation of the brain. (*b*) Excitation of the sensory spinal nerves to the bladder is carried across the cord to

the corresponding motor nerves to the bladder. (*c*) In the transmission of excitation from the sensory sympathetic nerves to the motor nerves of the bladder, the inferior mesenteric ganglion acts as the reflex centre.

All these investigations concern the innervation of the detrusor muscle exclusively, because they were carried out by the introduction into the bladder of a cannula or catheter connected with a water manometer, which threw the sphincter of the bladder out of play. Further, the motor nerves to the bladder were almost always stimulated reflexly, from the central end of the divided sensory nerves. The effects on the detrusor and sphincter of direct excitation of the motor paths to the bladder had next to be studied, to see if they are identical or antagonistic, in accordance with the function of the two muscles.

This most important problem was ingeniously solved by von Zeissl (1893). He confined his experiments on curarised dogs to studying the effects of excitation of the hypogastric nerves and the nervi erigentes on the detrusor and on the sphincter. With this object he employed a method similar to that which Rehfisch subsequently modified so as to render it applicable to man (see Fig. 128, p. 467). After laying open the peritoneum, he tied one ureter, and connected the other with a pressure-bottle by means of which the bladder could be filled. He then interrupted the communication of the bladder with the bottle and brought it into relation with a mercury manometer, which recorded variations in tone (contraction or expansion) of the detrusor on a revolving cylinder. Lastly, he tied a tube into the urethra, and connected it with a plethysmograph, by which the amount of flow from the bladder is recorded on the drum. On comparing the two curves obtained from stimulation of the hypogastric or the erector nerve, the action of these nerves on the two antagonistic muscles of the bladder can be computed.

The following conclusions appear from von Zeissl's work:—

(*a*) The nervus erigens contains motor fibres to the detrusor and inhibitory fibres to the sphincter, because its peripheral stimulation causes contraction of the former, and expansion (relaxation) of the latter. (*b*) The first effect is quite independent of the second, since it always precedes it by a greater or less interval, so that the escape of fluid from the bladder cannot be regarded as a direct effect of vesical contraction. (*c*) If the contraction of the detrusor is hindered by substituting a glass bell-jar for the wall of the bladder, stimulation of the nervus erigens only produces dilatation of the sphincter, showing that this effect is not passive, but depends on specific inhibitory or diastolic fibres contained in the excited nerve. (*d*) The hypogastric nerves contain motor fibres to the sphincter, and moderator nerves to the detrusor, since their peripheral stimulation arrests the continuous flow of urine

from the urethra, produced artificially by surcharging the bladder with fluid, while a pressor effect upon the bladder walls seldom makes its appearance.

In a second set of experiments (1894), von Zeissl, experimenting not with curarised dogs, but on such as were merely under morphine, obtained results which were wholly in agreement with the preceding. He also performed a new series of experiments to determine the reflexes of the sphincter and detrusor, by excitation of the central end of certain sensory nerves (sciatic, ulnar, median, phrenic, splanchnic, and vagus). The method employed was simpler than the above. In curarised male dogs he introduced a glass tube right into the bladder, or to the end of the membranous urethra, according as he wished to bring out the effect on the detrusor, or the sphincter.

This tube was brought into direct connection with a water manometer, which recorded on a revolving cylinder the flow from the bladder consequent on excitation of the nerve. The peritoneum was not opened.

Stimulation of the central end of the above nerves always produced contraction of the detrusor and expansion of the sphincter. The sole exception is the stimulation of the central end of the vagus, which has no effect on the bladder, while, like the other nerves, it causes a rise of arterial pressure. From this we may conclude that the vesical reflexes produced by excitation of the sensory nerves are transmitted by the motor paths in the anterior sacral roots, which make up the nervi erigentes.

The later work of Courtade and Guyon (1896), while it mainly confirms von Zeissl's results, has little intrinsic value, since it was carried out by a less perfect method, and under conditions farther removed from the physiological.

The more extensive researches of Langley and Anderson (1896), on the innervation of the viscera, do, on the contrary, confirm both the results of Nawrocki and Skabitschewsky, and those of von Zeissl, which are also sustained by the later experiments of Rehfisch and Wlassoff (1900).

Von Zeissl afterwards (1902) continued his researches on the innervation of the bladder, using the same method as before. He found that central stimulation of the sciatic (even when all increase of pressure in the bladder was excluded) induced partial evacuation by opening the sphincter, which, however, might be due solely to the nervi erigentes. If water is made to flow continuously through the urethra central stimulation interrupts the flow, even after the hypogastrics have been divided. This, however, is due, not to the erigentes, but to the nerves which supply the striated sphincters (external sphincter, compressor urethrae), the endings of which, like those in the sphincter ani, are only paralysed by an excess dose of curare.

As regards the central organs on which the movements of the bladder depend, it can be gathered from the above that there must be *cerebral, spinal,* and *sympathetic centres*: the first come into play in voluntary micturition and that excited by the feeling of vesical tension; the second in involuntary and purely reflex micturition; the third in the micturition which can be experimentally produced after cutting off all connections of the two former with the bladder.

With what part of the cerebrum do we act in voluntary retention of urine, when the tone of the vesical sphincter is increased, and in micturition, when that muscle is voluntarily relaxed? To this we are unable to give any adequate reply. We only know from Budge's early work that it is possible by electrical stimulation of the cord to follow the spinal paths from the bladder to the brain, as far as the cerebral peduncles. We also know from the early work of Valentin that excitation of different parts of the brain, especially of the cerebral peduncles, the corpora striata, and the optic thalami, provoke movements of the bladder. Certain experiments of Mosso and Pellacani indicate that the cerebro-vesical paths run in the posterior segment of the cord. Lastly we know from Bechterew and Mislawski that electrical excitation of the sygmoid gyrus of the cerebral cortex of dogs, behind the external extremity of the sulcus cruciatus, produces contraction of the detrusor vesicae. Sherrington also found a cortical centre for the bladder in monkeys.

In man, according to the observations of Friedmann (1904), who saw in a child that a circumscribed cortical lesion produced an almost isolated disorder of the voluntary innervation of the bladder, the cortical centre for the latter lies at the limit of the upper third of the posterior central convolution, in the direct contiguity of the upper parietal lobe. The centre for the arm is located immediately in front of it. The same conclusion appears also from the work of Czyhlarz and Marburg.

As regards the localisation of the spinal centres for the bladder, Budge (1858) discovered in the spinal cord of rabbits a spot a few millimetres in extent, which he termed *the genito-spinal centre*; this controls the contractions of the bladder, lowest part of the intestine, and the vasa deferentia. In dogs, on the contrary, Giannuzzi (1863) found two points in the lumbar cord which, if mechanically excited by a deep puncture, react by contractions of the bladder; the first point corresponds with the level of the third, the second with that of the fifth lumbar vertebra. There is no doubt that the lumbar-sacral cord contains all the central mechanisms both for the periodic emission and the retention of urine. This is proved by the experiments of Goltz (1874) on dogs whose cord was divided between the last dorsal and the first

lumbar vertebrae. The immediate effect of this operation is paralysis of the bladder, which, however, ceases in a few days, while the operative sequelae disappear, and purely reflex micturition takes place, owing to the tension of the bladder which acts on the centripetal nerves. Micturition can also be caused by holding the animal in a vertical posture, and exciting the skin of the perineum with slight mechanical stimuli.

Even when the spinal centres are occluded, the paralysis of the bladder, although it lasts longer, gradually dies out, until the normal function of the bladder is completely re-established. This appears from the marvellous results obtained by Goltz and Ewald (1896) on dogs deprived of the lumbo-sacral cord, which long survived this serious operation. The bladder was much distended at first by accumulation of urine, and had to be emptied artificially by pressure on the peritoneal walls; but the paralysis of the detrusor slowly disappeared, until a few months after the operation it was found that the bladder emptied itself periodically without adventitious aid. The animal passed long periods without urinating, during which time the urine accumulated, and was evacuated when the stimulus to the bladder walls became sufficient to induce reflex micturition.

A very simple proof of this fact, showing that the bladder is able to function normally without the help of the cerebrospinal centres, by co-ordinated reflexes from the intravesicular ganglion plexus, was obtained by von Zeissl (1896). He divided on a dog all the nerves that run to the bladder, and found that after this operation (which is much simpler than that of Goltz and Ewald) the animal was able both to retain the urine and to expel it periodically in a normal manner.

That in this case also the intravesicular ganglia function as reflex centres appears very probable from the experimental demonstration of Sokowin, Nussbaum, Nawrocki and Skabitschewsky, which show that the inferior mesenteric ganglion is capable of functioning as a reflex centre for the bladder.

But the reflex action of the ganglion plexus of the bladder does not cut out the rhythmical automatic activity of its own muscle cells, independent of the ganglia. Rhythmic contractions are seen in fact in the frog's bladder when it is excised from the animal, as also in fragments of bladder which are subsequently found under the microscope to show a total absence of ganglion cells (Pfalz).

The question has been much discussed as to whether the mucous membrane of the bladder has any capacity for absorption, and whether the urine accumulated in the bladder becomes concentrated from absorption of water or any of the soluble substances. The capacity of the bladder for absorption is readily shown by the injection into it of toxic substances; these take effect after a certain time. The fact that the urine collected

during sleep is more concentrated than that of waking (Posner) seems to indicate that the bladder does absorb some of the water of the urine and concentrates it. But according to Kaupp, who examined the composition of the urine in the bladder at different times with a constant diet, no absorption of water takes place, but only of urea, with excretion of sodium chloride. According to Wundt, the concentration which the urine undergoes in the bladder is greatest when the loss from the skin in the form of sweat is also maximal.

Gerota (1897) showed by his accurate work on absorption in the bladder that the mucous membrane of the bladder, unlike that of the urethra, contains no lymphatics, which, on the contrary, are plentiful in the muscular coat, and probably communicate with the lymph sinuses of the mucosa. On injecting various substances by puncture into the bladder, he arrived at the following results:—

(*a*) The permeability of the mucous membrane of the bladder is low owing to the multiple layers of the epithelium.

(*b*) Substances which have large molecules, such as the alkaloids, do not diffuse: those with small molecules diffuse, but very slowly and in very concentrated solutions.

(*c*) The diffusion of urea is too small to have any practical importance.

The later work of O. Cohnheim (1901), who, after tying the ureters, introduced into the bladder different solutions, the concentration of which was determined before and after the experiment, shows, in accordance with the previous conclusions of Lusini, Boyer and Guinard, Pousson and Ligalas, that the normal bladder has no capacity of absorption. The walls of the bladder are impermeable both to salts and pigments and to water. The fluids introduced are preserved as unaltered as if they were in a glass vessel. It is only when the walls are necrosed or profoundly injured by the action of caustic or toxic substances (*e.g.* sodium fluoride) that they become permeable and assume the character of an ordinary diffusion membrane.

Similar work, but with somewhat different results, was undertaken by Galeotti and Fasola (1903). After previous ligation of the ureters, they injected various solutions of sodium chloride or saccharose into the bladder, which were hypo-, iso-, or hypertonic to the blood, and of which the quantity and concentration were exactly determined before and after the experiment. They made two sets of experiments, one series being on the normal bladder, the other on the bladder of which the walls were altered by chloroform. The following were their results:—

(*a*) The epithelium of the bladder injured by chloroform behaves like a semi-permeable membrane, through which osmotic equilibrium is immediately established, with increase of volume if

the fluid was hypotonic. (*b*) Normal epithelium, on the other hand, does not as a rule set up osmotic equilibrium, but reacts differently according to the requirements of the organism. (*c*) With hypotonic solutions there is no change in quantity or concentration. (*d*) The same holds good for isotonic solutions if the animal had been well supplied with food and drink, but if it were suffering from hunger or thirst, partial absorption followed. (*e*) With hypertonic solutions there was a marked absorption of salt.

Both the reabsorption of water in case of need, and that of the salt from hypertonic solutions (the excessive elimination of which in a too-concentrated urine would under normal conditions involve too great a loss of this useful substance), must, according to these authors, be interpreted as useful reactions in the animal economy, requirements to which the variable capacities of the epithelial cells of the bladder can adapt themselves.

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CHAPTER IX

THE SKIN AND CUTANEOUS GLANDS

CONTENTS.—1. Structure of the skin and continuous desquamation of the stratum corneum. 2. Coiled sweat glands and sensible and insensible cutaneous secretion. 3. Chemical substances excreted in perspiration. 4. Innervation of sweat glands. 5. Sebaceous glands and specific formation of sebum. 6. Mammary glands. 7. Chemical composition of milk. 8. Influence of diet on the secretion of milk. Origin of secretory products. 9. Histological and chemical processes of milk formation. 10. Influence of nervous system on the milk secretion. 11. Absorption by the skin. Bibliography.

THE body suffers considerable loss of material by the skin, as well as from the lungs, intestine, and kidneys. But this loss consists only to a minimal extent in katabolic products. As an *excretory organ* and *blood purifier*, the skin (by the glandular secretions which it pours out) is therefore of secondary importance. Its functions as a *protective organ* are far more significant. It not only regulates the internal heat and adapts it to the external environment, lubricates the stratum corneum of the epidermis and the hair, and renders them elastic, but it further provides the fittest nutriment for the new-born animal, which is the most fundamental form of protection of the species.

In this chapter we shall deal with the skin, not as the seat of the sense-organs (which will be fully discussed in Vol. IV.), but only as an external integument, provided with innumerable glands by which the body suffers loss, either in the form of gas and vapour (perspiration), of water (sweat), of adipose and horny substances (sebaceous and ceruminous secretions, epidermoid desquamation), or of an alimentary fluid (milk secretion). Each of these products has a distinct physiological significance and special character which it must be our task to determine. Lastly, we shall discuss the question whether, and how far, the skin may be regarded as an absorbing surface.

I. Without entering into details of the minute structure of the skin, the interest of which is mainly morphological, we shall confine ourselves to stating that two principal layers can be distinguished, the *epidermis* (or cuticle), and the *derma* (cutis

vera, or corium); the former corresponds with the epithelium, the latter with the areolar substrate of the mucous membranes, which are an invagination of the skin.

Both in the epidermis and in the derma several layers can be distinguished: in the first, the harder, horny layer (stratum corneum), and the softer, mucous or Malpighian layer (rete mucosum); in the second, the corium proper, and the panniculus adiposus (Fig. 129).

From the physiological point of view it is an important fact that the many layers of cells which make up the epidermis, from

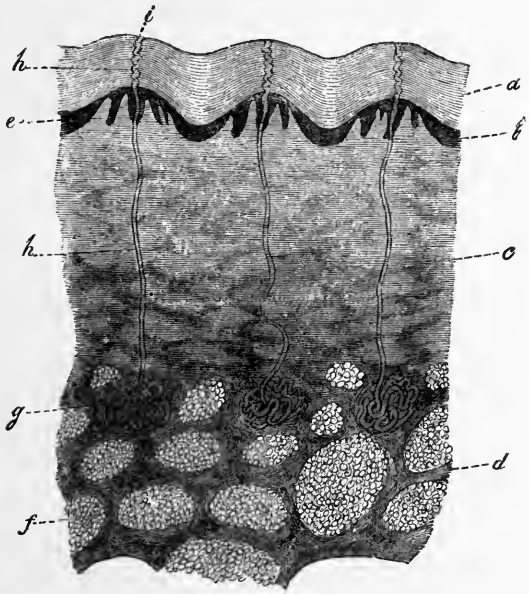


FIG. 129.—Vertical section of skin and subcutaneous tissue, from the end of the thumb, across the ridges and furrows. (Kölliker.) 20 diameters. *a*, horny; *b*, Malpighian layer of epidermis; *c*, corium; *d*, panniculus adiposus; *e*, papillae on the ridges; *f*, fat clusters; *g*, sweat glands; *h*, sweat ducts; *i*, their openings on the surface.

the deepest stratum of the Malpighian layer (which fit into the surface of the corium) to the most superficial of the horny layer, undergo perpetual modifications in their form and physico-chemical characters, corresponding with so many alternating phases of their existence. The deepest layer is the youngest, and consists of cells vertical to the surface of the corium, to which they are attached by denticulations at their lower ends (Fig. 130). The next and older layers consist of rounded or polyhedral cells, and become more flattened as they approach the surface. All these cells have fine intercellular processes or bridges, which, if viewed separately, give an effect of spines (the so-called "spiny cells").

Between the connecting bridges there is a system of intercellular channels (Bizzozero) which may become dilated with excess of fluid, on which the bridges between the cells are more apparent. These spiny cells contain pigment granules, which are more abundant in proportion as the skin is darker. The colour of the skin in the black races is due to this pigment, which is particularly plentiful in the deeper cells of the Malpighian layer (Fig. 131).

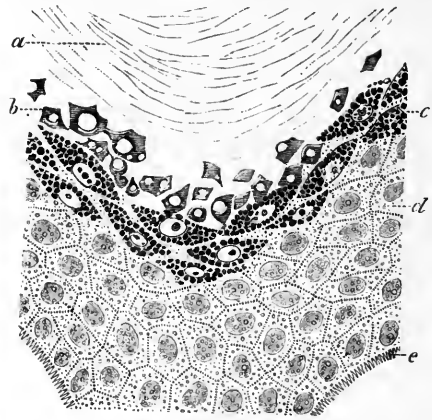


Fig. 130.—Section of epidermis from skin of finger, coloured by picro-carmine. (Ranvier.) *a*, stratum corneum; *b*, stratum lucidum, with scales of eleidin; *c*, stratum granulosum full of eleidin granules; *d*, deep cells and intercellular canals of rete mucosum; *e*, dentations of deepest cells, for attachment to cutis vera.

The more superficial cells of this layer are spindle-shaped, and contain a number of granules of a substance (eleidin) that stains deeply with carmine (stratum granulosum of Langerhans).

Between this and the horny superficial stratum there is in some parts of the skin an intermediate layer which looks clear, and is formed of cells with indistinct outlines; this is probably a transition between the cells of the granular and those of the horny layers (stratum lucidum of Oehl).

The cells of the stratum corneum, which are nearly all destitute of a nucleus, may be regarded as senile cells, degenerated into horny substance, which, in proportion as they approach the surface, lose all their vital character and are finally reduced to hard, dry, transparent scales, perpetually cast off from the surface of the skin by desquamation (*scurf*). So that by this continual shedding of the superficial lamellae, which are replaced by those of the subjacent layers, the body suffers a constant loss of horny substance, comparable with any other loss of substance by excretion.

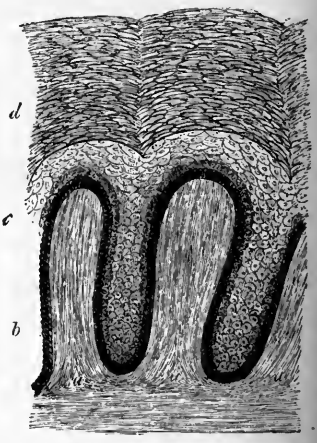


Fig. 131.—Skin of the negro. Vertical section, 250 diameters. (Kölliker.) *a*, *a*, cutaneous papillae; *b*, undermost and dark-coloured layer of vertical epidermis cells; *c*, mucous or Malpighian layer; *d*, horny layer.

The horny scales give no protein reaction, but contain a

derivative, belonging to the group of sclero-proteins, which is known as *keratin*. The constitution of this is unknown; it has the same percentage composition as the proteins, but contains a considerable amount of sulphur, partly in loose combination with other elements, from which it separates on boiling in alkaline solution.

It is difficult to estimate the amount of horny substance detached from the surface of the body in the form of epidermoid scales. According to Funke, the loss of lamellae in the sweat amounts to 6 grms. in 24 hours. Moleschott (1878), on the strength of a fact observed on himself (viz. that a scrap of epidermis sloughed off in a boil was regenerated in 34 days), calculated ingeniously that an individual of average body-weight must lose 14·35 grms. epidermis daily, containing 12·20 grms. horny substance, and 2·10 grms. nitrogen. These figures are exaggerated and incredible, and are based on improbable hypotheses, particularly on the assumption that the epidermis of any cutaneous area (from which it has been removed) is regenerated in the same time in which it is renewed by successive desquamations over the whole remainder of the normal cutaneous surface.

Moleschott again (on the strength of data furnished him by Berthold as to the growth of hairs in the beard, and those noted by himself as to the growth of hair and nails, which are horny tissues essentially analogous to the epidermis) computed the mean daily product of these structures at 0·26 grms. *i.e.*, far less than he calculated for the epidermis alone. It is also remarkable that the production of horny tissues is much diminished by age, that it is greater in summer than in autumn, and is accelerated by frequent removal. By leaving less time between one cutting of the hair and the next, says Moleschott, the growth of the hair is accelerated. To us, therefore, it appears logical to conclude that on removing the skin from a cutaneous surface, *e.g.* by application of blisters, it should be regenerated in a much shorter time than is required for the complete renewal of the epidermis over the whole area of the intact skin.

The regeneration of the stratum corneum is effected by mitotic division of the cells in the Malpighian layer. The karyokinetic figures are seen only in the spiny cells, not merely in the deepest stratum contiguous to the papillae of the corium, but in the less profound strata as well. While these cells are multiplying, the more superficial are changing into cells of the granular layer. It is probable that the granules of these cells are those which form the keratin, or become converted into it. The more superficial cells of the stratum granulosum are simultaneously converted into those of the stratum lucidum, and these lastly into the scales of the stratum corneum.

We shall consider the structure of the corium, and more

particularly of the papillary layer, when we come to study the skin as the seat of the special senses. Here it is enough to say that the depressions between the papillae are filled by cells of the Malpighian layer, which is therefore thicker at these points. The

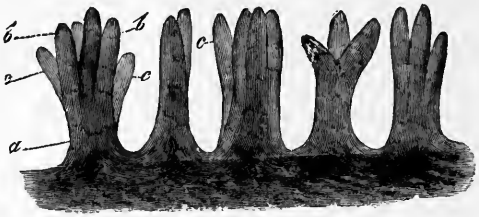


FIG. 132.—Compound papillae from the palm of the hand. (Kölliker.) 60 diameters. *a*, basis of a papilla; *b*, *b*, divisions or branches of the same; *c*, *c*, branches belonging to papillae of which the bases are hidden from view.

surface of the epidermis is also uneven, and presents prominences and depressions at a number of places, corresponding with the position of the papillae or interpapillary spaces. These prominences are termed the *papillary ridges* of the epidermis.

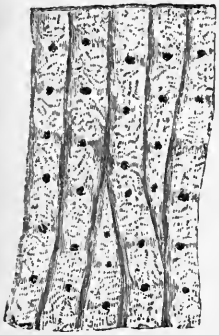
In many parts of the skin, particularly on the palmar surface

FIG. 133.—Linear sweat prints from palmar surface of finger (Aubert's photographic method). The white line marks the papillary ridges, forming a vortex at the tip; the black lines are the furrows which lie between the crests.

of the hand and fingers, the papillae of the corium are compound, *i.e.* cleft at the summit into two or more secondary points, which are ranged in lines separated by superficial furrows (Fig. 132). The surface of the cuticle which covers these papillae shows ridges separated by characteristic curved lines, which form a sort of vortex at the culminating point of the digit (Fig. 133). Under a

high power, these ridges are divided not only by longitudinal furrows, but also at short and fairly regular intervals by less profound transverse furrows with a minute funnel-shaped orifice in the middle of each, which is the mouth of a sweat-gland (Fig. 134).

II. The Sudiferous or Sweat-Glands, already known to Stensen, Malpighi, Boerhaave and others, and more exactly located as regards their orifices by Eichhorn (1826), were first described accurately and almost simultaneously by Purkinje, Wendt, Breschet (1834), and Gurtl (1835), not only for man but also for



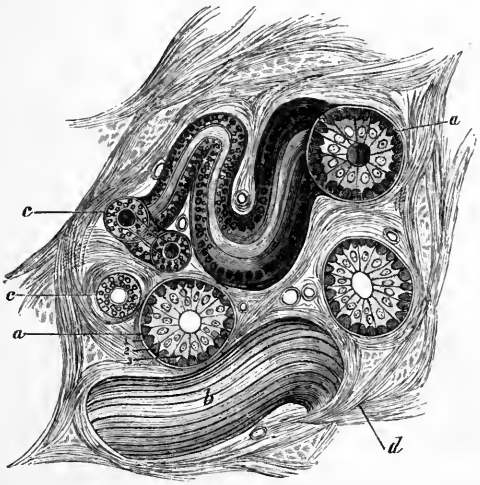


FIG. 134.—(Left.) Four ridges of the epidermis, with short furrows across them, and the orifices of the sudoriferous ducts. (Breschet.)

FIG. 135.—(Right.) Section of a sweat gland in the human skin. (Schäfer.) *a*, *a*, secreting tube in transverse section; *b*, part of secreting tube seen from above (surface focus); *c*, *c*, efferent tube (commencing duct); *d*, intertubular connective tissue with blood-vessels. In the section across the secreting tube, 1 is the basement membrane; 2, the muscular fibres cut across; 3, the secreting epithelium lining the tube.

the domestic animals. They consist of long tubes in which the secreting part is coiled up into a ball, seated at varying depths of the corium and in the first layers of the subcutaneous adipose tissue (Fig. 129). The excretory duct or conducting tube is continued from the coiled gland through the corium, and in a spiral course through the epidermis, opening between two adjacent papillae with the widened orifice described above. The secreting tube is considerably larger than the duct, and has a wider lumen (Fig. 135). It has a basement membrane, plain muscular fibres, and one or two layers of columnar cells characterised by a very distinct cuticular lining. The excretory duct is covered with a single layer of cells, which are smaller and have no true cuticle. Although direct evidence is wanting, it is probable on analogy

that the secretion of these glands is principally, if not exclusively, the work of the cells in the coiled glands. The muscle-cells which surround the basement membrane, and are interposed between it and the epithelium, apparently serve by their contraction to accelerate the flow of the secretion along the duct.

Man has the capacity of sweating diffusely over the whole of the surface of the skin, but perspires more easily and copiously by the face, particularly the forehead, the palm of the hand, the sole of the foot, the axilla, and the groins. The monkey sweats more from the top of its nose, and very little from the palm of the hand and sole of the foot, although these parts are hairless. The horse and sheep sweat freely from all parts of the body, although hairy; the calf less readily; the goat, rabbit, mouse, and rat not at all. Carnivora, generally speaking, sweat only from the ball of the foot, and even there the dog sweats little or not at all, while the cat on the other hand (the chosen subject for physiological investigation into sweat-secretion) perspires readily and copiously in that part. The pig sweats almost incessantly at the flat surface of the snout, where Gurtl found a large development of sweat glands. In the ox the nasal pinnae (alae) are continually moist with sweat.

The power of sweating mainly or exclusively from certain definite areas of the skin is in proportion not so much with the number of sudoriferous glands in those regions and their total absence in others, as with the varying secretory activity of these glands. In fact, the coiled form of gland is not inseparably associated with the function of sweating. There are highly developed coiled glands which never secrete sweat during the whole life-time. Such, *e.g.*, are the glands existing in animals that never sweat from any part of the skin, or those in regions where sweat is never secreted. Obviously, these glands must have another function, distinct from that of sweat secretion. We shall see in effect that they probably have the same function as the sebaceous glands. The coiled glands which abound in the skin of the external auditory meatus are a typical example of glands which, with the complete structure of sudoriferous glands, have no other office than that of secreting the cerumen which covers and protects this passage.

Krause (1844) made a laborious investigation of the distribution of the sweat glands in the different regions of the skin in man, and determined the number that could be counted in a square inch of surface. On reducing the unit of measurement to square centimetres the results were approximately as follows:—

In the forehead	140
„ cheeks	60
„ chest, abdomen, forearm . .	225
„ neck, back, rump . . .	50

In the upper arm and leg . . .	55-70
„ palm of hand	310
„ back of hand	170
„ sole of foot	300
„ dorsum of foot . . .	100

They are more numerous in the axilla than elsewhere, but hard to count, because the excretory tubes of several glands converge into one single excreting duct.

Aubert (Lyons) invented a very elegant method for the exact calculation of the enormous number of sweat glands in the skin. A sheet of ordinary white paper is closely applied to any area of perfectly dry skin surface, for a period of 30-80 minutes. On then plunging it into a 0·25 per cent silver nitrate solution, and exposing it to sunshine, the ground of the paper turns black, but every point at which it came in contact with the mouth of a sweat gland remains white, so that a photograph is obtained in which the orifices of the glands appear as ducts (Fig. 136). The explanation is very simple. Sweat is continually given off from the mouths of the sudoriferous glands in the form of invisible perspiration. The sweat contains chlorides which are deposited on the paper only at the points corresponding with the glandular orifices, so that these points only react to the silver nitrate by forming silver chloride. If the paper is applied, on the contrary, to a surface that is visibly perspiring, the sweat with its chlorides will cover the whole surface of the papillary ridges, and instead of dots, an exact impression of the outline of the ridges is seen as a white line, the furrows that bound them coming out black (Fig. 133).

So long as the secretion of sweat from the coiled glands is below a certain narrow limit, the water excreted (with the volatile substances of the sweat) evaporates from the surface of the skin, which remains dry (*perspiratio insensibilis*); but when the secretion increases, or evaporation is hindered by the state of the atmosphere, sweat appears on the surface of the skin. First minute droplets form at the orifices of the coiled glands, next these run together and form larger drops, finally by gravity they flow over the skin, or saturate the clothing (*perspiratio sensibilis*).

The loss of substance, particularly of water, from the human body by the skin is undoubtedly enormous, but it varies considerably with different circumstances. The first experimental attempts to determine this loss were made by Santorio (1614). He weighed the intake of food and drink, as well as the ponderable excreta of his own body, and found (after remaining whole days on the balance) that $\frac{5}{8}$ of the weight of the *ingesta* are eliminated by the skin and lungs. Dodart (1725) made similar experiments. The question was subsequently taken up by Lavoisier and Seguin (1790), who estimated the water excreted from the human skin at one litre in 24 hours. In his later work on the total excretion by the skin and lungs, W. F. Edwards (1824) found that it varied quantitatively in different animals in ratio with their weight. But he erred in differentiating between *sudoratio* and *perspiratio*, as if there were two different secretions, instead of two different

phases of a single secretory process. It cannot be absolutely denied that a minimal degree of aqueous evaporation may take place over the entire surface of the skin independent of any process of secretion, but there can be no doubt that almost the whole of the insensible loss of water suffered by the skin is due to the secretion of sweat, which evaporates as fast as it creeps from the orifices of the glands. Evidence for this has recently been given by Aubert in his photographs of the sweat-drops during insensible perspiration (Fig. 136).

It is also important to note from recent work on general metabolism (that of Pettenkofer and Voit in particular) on calculating the average results obtained by the evaporation of

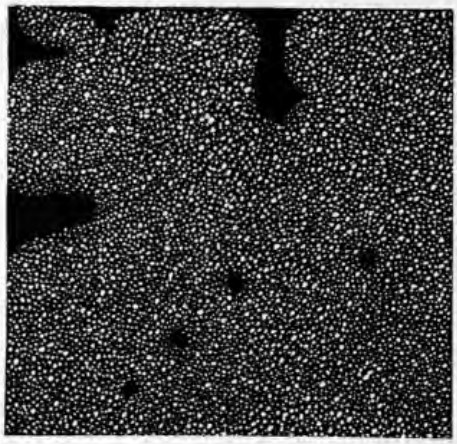


FIG. 136.—Sweat prints from back of hand. (Aubert.) The pores or mouths of the sweat glands are shown as white dots on a black ground.

water in cutaneous and pulmonary respiration jointly, as compared with the water eliminated in the urine, that

the dog excretes	70 %	H_2O in	the urine,	30 %	in cutaneous secretion.
„ man	„ 60 %		„	40 %	„
„ horse	„ 30 %		„	70 %	„

In carnivora, therefore, the loss of water by the kidneys greatly exceeds that by sweating; in herbivora, the contrary is the case; in man, excretion by the kidneys is slightly in excess of that by the sudoriferous glands, approximating to the carnivora rather than to the herbivora. The daily loss of water by the skin amounts in man on an average to $6\frac{1}{4}$ the body-weight, and is almost double that by pulmonary excretion.

As every one knows, there is a marked antagonism between the loss of water by the kidneys and intestines, and that given off

by the skin and lungs. On perspiring freely, as in summer, micturition is scanty; in winter, on the contrary, when visible perspiration is suspended, micturition is frequent and copious. But apart from the influence of season and temperature in general, clinical observation shows that in all cases in which there is excessive loss by the kidneys and intestines (diabetes, diarrhoea) this is compensated by a marked dryness of the skin; with the opposite conditions the contrary is observed (nephritis, anuria).

A good many fallacies prevail as to the intensity of cutaneous perspiration. It is often stated, *e.g.*, that not only the temperature, but also the humidity of the surrounding atmosphere, increase cutaneous secretion, whereas in reality the latter reduces evaporation, or insensible perspiration, by increasing sweat, or sensible perspiration. Frequent renewal of the air in contact with the skin acts in the opposite sense: natural or artificial ventilation of the atmosphere, within certain limits, does not perceptibly diminish the cutaneous secretion, but it reduces sensible perspiration by increasing evaporation.

There is no constant relation between height of external temperature and intensity of cutaneous secretion, the capacity for sweating being very different for different individuals of the same species. *Caeteris paribus*, however, perspiration in one and the same individual increases in proportion with the external temperature. In order to rouse the skin to a more active secretion of sweat the external temperature must approximate to 33° C. (Schierbeck, 1893).

Besides *external conditions*, cutaneous secretion may be considerably affected by alterations in the *internal conditions*, among which are:—(*a*) amount and quality of the food ingested, and particularly what is drunk; (*b*) muscular activity or rest, which respectively increase or diminish cardio-vascular activity; (*c*) use of certain drugs known as *diaphoretics*, *e.g.* pilocarpine, muscarine, partially also nicotine and physostigmine (or the drugs which have an opposite, *antidiaphoretic* action, *e.g.* atropine and daturine); (*d*) sudden or violent mental emotions (anguish, anger, joy) which increase the cutaneous secretion, independently of dilatation of the cutaneous vessels (blushing), or their contraction (pallor).

III. Since the external or internal conditions that promote or hinder sweat secretion are so variable, it is easy to see why the data collected by different observers as to the amount of sweat secreted in the time-unit are of little general value.

When collected in large quantities for purposes of analysis, the sweat is a slightly turbid, almost colourless fluid, salt in taste, with a more or less powerful rancid smell, due to the volatile fatty acids.

In some regions, *e.g.* the axilla, groins, and pubis, the sweat has a more penetrating odour, which may be highly unpleasant, and is due to the special fatty acids mingled with the secretion.

When examined under the microscope, the sweat shows a number of epidermoid scales detached from the surface of the skin, as well as fat-granules.

Human sweat gives an acid reaction under ordinary conditions; in the horse and cat it is almost always alkaline (Luchsinger). The acidity of human sweat is due to the fatty acids. Some authors hold that this depends on the admixture of the secretion from the sebaceous glands, and state that in parts where the latter are absent, *e.g.* the palm of the hand after well washing, the sweat has an alkaline reaction (Tourton); others again contradict this observation (François-Franck, Albini). Since we know (*supra*) that many coiled glands have throughout life a function that differs in no way from that of the sebaceous glands, it seems logical to assume that the coiled glands which do serve the sudorific function also secrete along with the sweat a small amount of *sebum*, which (*infra*) is rich in fatty substances of various kinds, and gives to the whole secretion its acid reaction. Trümpy and Luchsinger (1878) established the important fact that during profuse sweating the acidity of human sweat gradually diminishes till it becomes neutral, and is eventually alkaline like that of the horse. This phenomenon is easily explained on the assumption that the acid sebum of the secretion, which is a slowly formed product of the secretory cells, is easily exhausted, while the watery sweat, which has the alkaline reaction of the blood and lymph from which it is derived, persists.

Various methods have been tried for collecting the products of cutaneous secretion from the whole surface of the body or from any part of it. If the forearm is enclosed in a rubber bag, with a glass bottle at one end, evaporation from the skin is checked, and the whole of the exudate runs into the bottle in the form of sweat (Anselmino, 1844). The subject may be enclosed in a Pettenkofer and Voit's respiration chamber, breathing through a rubber mask applied to the mouth and nostrils, with tubes attached. Comparison of the water and carbon dioxide of the air that enters and leaves the chamber gives the sum of the products evaporated from the entire cutaneous surface (Schierbeck, 1893). If the subject is enclosed in a receptacle (with the exception of the head), and the temperature of the surrounding air is raised, a copious secretion of sweat is induced from the whole cutaneous surface, and collects at the bottom of the receiver (Favre, 1852). By the simpler method of the so-called vapour-bath, which is produced by raising the temperature of the surrounding atmosphere, it is possible to collect the greater part of the sweat that runs off the skin, so as to determine its content of organic substances (Argutinsky, 1890).

Quantitative analyses of the principal organic and mineral constituents of the sweat led to widely dissimilar results, according to Schottin (1851), Favre (1852), Funke (1858). All the analyses, however, point to the fact that sweat is the most watery of all the secretions, since it contains not more than 0·5-1·5 per cent solids, of which about $\frac{1}{3}$ consists of mineral substances, mainly sodium chloride. The following table, drawn up by Harnack, gives

the composition of the sweat in a patient suffering from rheumatism, who was made to sweat 1-2 hours in a bath:—

Specific gravity	1003-1006	
Water	99·09-99·16	per cent.
Solids	0·91- 0·85	„
Organic substances	0·42- 0·85	„
Inorganic substances	0·67- 0·65	„
Sodium chloride	0·52	„
Earthy phosphates	0·03	„
Sulphuric acid	0 05	„
Potassium	0·04	„
Urea	0·12	„

This table does not include either the lactic acid or the sudoric or hidrotic acid (a nitrogenous acid with the empirical formula $C_{10}H_{16}N_2O_{13}$) of Favre, which were not found by any other observers.

The chlorides, and still more the phosphates and sulphates of sweat, are less abundant than those of urine, as shown by Kast (1887).

There is now no doubt as to the presence of urea in normal sweat. The different amounts found by different observers may partly depend on the dissimilar interval between the secretion and its analysis, in which a certain variable proportion of the urea undergoes conversion by ammoniacal fermentation.

According to Argutinsky's experiments on himself, by the vapour-bath, as to the total nitrogen eliminated from the skin, 68·5-74·9 per cent is present in the sweat in the form of urea, and 31·5-25·1 per cent in the form of ammonia. The same observer estimated the amount of nitrogen eliminated in the sweat during severe walking or climbing exercise. With this object he wore a special suit of cotton clothes, which were extracted, when saturated with sweat, at the end of the excursion, the extract being analysed by Kjeldahl's method. The following were the results of three experiments:—

Excursion of about	20-22 kilos.	in 7 hrs.	(July).	N excretion =	704·4 mgrms.
„	18-20 „	partly climbing	(Aug.)	„ =	753·5 „
„	18-20 „	„	(Oct.)	„ =	219·3 „

According to Argutinsky the nitrogen excreted by the skin may amount to 4·7 per cent of that eliminated by the urine, which should be taken into account in making exact calculations of the total products of metabolism.

Besides urea and ammonia, other urinary constituents have been found in human sweat. Capranica detected creatinine in the proportion of ·04 per cent. In uraemic conditions the cutaneous excretion of these products may be enormously increased. Schottin and others found urea crystals in the skin of uraemics.

The small quantity of fatty acids which causes the character-

istic odour of sweat are made up of formic, acetic, butyric, propionic, and capronic acid. Ethereal sulphates of phenol and scatole are also present, but only in small amounts (Kast). The perspiration from the armpit sometimes stains the underclothing blue, from the indican present in the sweat. It is, however, doubtful whether this indican comes from indoxyl secreted in the sweat, or from indoxyl developed by chromogenic bacteria.

Lastly, human sweat nearly always contains a small amount of protein (0·045 per cent, which is a normal constituent in the sweat of horses, and causes the characteristic foam of their perspiration), as well as two enzymes, one diastatic or saccharifying, the other tryptic or proteoclastic.

Reference should be made, in reviewing the more recent work on the chemical constitution of the sweat, to the researches of W. Camerer, jun. (1901), who collected the perspiration from healthy subjects in light-, hot-air, or vapour-baths, and analysed it accurately with the following results:—

TABLE I.

	100 c.c. Sweat contain								
	Water.	Dry Residue.	Ethereal Extract.	Total Nitrogen.	Urea Nitrogen.	Ammonia Nitrogen.	Ash.	NaCl.	Proteins.
1. Light-Bath .	97·9	2·1	0·17	0·188	—	—	1·040	—	—
2. Light-Bath .	—	—	—	0·150	0·051	0·012	0·866	0·66	Trace
3. Hot-air Bath	98·3	1·7	0·02	0·137	—	0·011	1·042	0·78	—
4. Vapour-Bath	99·24	0·76	0·085	0·091	0·031	0·006	0·465	0·34	Trace

TABLE II.

	100 Parts Dry Residue contain			100 Parts Total Nitrogen contain			100 Parts Ash contain
	Ethereal Extract.	Total Nitrogen.	Ash.	Urea Nitrogen.	Ammonia Nitrogen.	Ash.	
1. Light-Bath . .	8·4	9·3	57·2	—	—	55·3	—
2. Light-Bath . .	—	—	—	34	8·0	57·7	76
3. Hot-air Bath .	11·8	8·1	61·3	—	8·0	75·3	75
4. Vapour-Bath .	11·2	12·0	61·2	34	6·6	51·1	73
Average . .	10·5	9·8	57·9	34	7·5	59·8	75

The much lower concentration of the sweat obtained by vapour baths is evidently due to its dilution by the water condensed from the steam.

There is a marked difference between these results and those obtained by Argutinsky, since 34 per cent of the total nitrogen consists of urea-nitrogen and 7·5 of ammonia-nitrogen. The rest is accounted for by traces of protein and other nitrogenous substances, including uric acid, which was demonstrated by the murexide test in experiments 1, 2, 4 of the table.

Just as the nature of the solid substances eliminated by the sudoriferous glands in the form of sweat shows the function of the skin to be subsidiary to, and in a certain measure vicarious of, that of the kidneys, so the insensible output of water and carbonic acid with simultaneous absorption of oxygen, indicates that the skin is a *respiratory surface*, aiding and partly supplementing the function of the lungs. In man and mammals, however, the gaseous exchanges by the skin are insignificant in comparison with those of the lungs. According to Aubert and Lange, the total excretion of carbonic acid by the human skin is only 3-4 grms. per diem, but this figure was doubled in the later work of Schierbeck.

The small amount of CO_2 given off by the skin is not, as some hold, due to the thickness of the epidermis. In all probability there is no sensible respiratory gas exchange through the stratum corneum, but this, like the excretion of water, is entirely accomplished by the ducts of the cutaneous glands. The scanty secretion of CO_2 is more likely due to the fact that the skin is irrigated by arterial blood, in which the carbonic acid is at low tension. In certain amphibia, on the contrary, *e.g.* frogs, the gaseous exchange that takes place by the skin is (in consequence of the limited pulmonary surface, the habitual moisture of the skin, and above all the fact that, like the lungs, it is supplied with mixed blood from the single ventricle of the heart) in excess of that by the lungs, so that these animals live for a long time after the lungs have been cut out.

In man it is doubtful whether the excretion of carbonic acid by the skin and the (usually smaller) absorption of oxygen occur, as in the lungs, principally by a process of diffusion. The former (as was rightly observed by Foster) might not be derived directly from the blood, but from decomposition of the carbonates contained in the sweat; in the same way the oxygen that disappears may not be absorbed by the blood circulating in the skin, but may be utilised to oxidise some of the organic constituents of the sweat.

From this point of view the results of Schierbeck's experiments (1893) are interesting. He studied the effect on human cutaneous secretion of different degrees of external temperature, varying from 29° to 39° C., and found that the excretion of CO_2 does not vary

perceptibly until the external temperature rises from 29° to 33° C. Between these limits no formation of sweat drops on the skin is apparent, perspiration maintains its *insensible* character, and not more than 35 c.c. carbonic acid are given off per hour (= 9 grms. per diem). When, on the contrary, the external temperature rises above 33° and reaches 39° C. there is a rapid and progressive increase in CO_2 excretion by the skin. Above 33° perspiration suddenly becomes *sensible, i.e.* it assumes the form of sweat, and simultaneously with this the amount of CO_2 excreted is suddenly doubled, and increases with the further increase of temperature and secretion of sweat (0·87-1·23 grms. per hour = 20·9-29·5 grms. in 24 hours). These results of Schierbeck indicate that the amount of carbonic acid given off by the skin depends not upon the quantity of blood circulating in it, but rather upon the secretory work of the cutaneous glands; this rises abruptly at the critical temperature of 33° C. to an output of twice the amount of carbonic acid, which thus comes not from the blood directly, but from the sudoriferous glands of which it is a secretion product.

W. Barratt (1897-99) made a careful study of cutaneous secretion in man under different experimental conditions, by the following method. As in the plethysmograph, the arm was introduced into a metal cylinder made impervious by a rubber sleeve through which air, free from carbonic acid and aqueous vapour, was circulated, and subsequently passed into vessels containing sulphuric acid and caustic soda. The metal cylinder was surrounded by a water-bath, which could be heated to various temperatures. Experiments on the normal arm showed that the elimination of carbonic acid is very small in comparison with that of water. The former at a temperature of 35° C. only amounts to 0·02 grm. per hour, while that of water = 3-4 grms. The ratio is thus 1-200; but it varies from hour to hour and more noticeably from day to day. A ligature applied to the arm produced increased elimination of carbonic acid (up to 40 per cent) and diminution in the elimination of water (up to 20 per cent), which was more pronounced in proportion as the ligature was tighter.

Varnishing the skin with collodion, by which the orifices of the sweat glands are blocked, causes marked diminution in the elimination of water (to 78·1 per cent) without entirely abolishing it. These results, in conjunction with the direct experiments on the diffusion of water vapour and carbonic acid through thin plates of horn, led Barratt to conclude that the horny layer also played an important part in the elimination of water, and that the discharge of carbonic acid through the skin is a process of simple physical diffusion, which takes place through the whole stratum corneum independent of the sweat glands.

V. Willebrand's researches (1902), on the other hand, agree

perfectly with Schierbeck's results. The subject of experiment was enclosed in a metal box, so that only the head was outside. The cutaneous transpiration of the rest of the body was determined at a temperature of 12-34° C. by estimating the content of water and carbonic acid in the air that circulated through the apparatus, and was entirely renewed every five minutes, the quantity being measured by gasometers, before and after its passage through the box. He found that when the body was completely at rest the elimination of water increased slowly, and in proportion with the temperature of the external air, which rose from 12° C. to the point at which perspiration broke out, which occurs between 30° and 33° C.

The elimination of carbonic acid by the skin at a temperature fluctuating between 20° and 33° C. is unaltered, provided the body is completely at rest, and amounts to 7-8 grms. in 24 hours. But when the temperature rises to the point at which sweat breaks out (*i.e.* 33° C.) a rapid three- or four-fold rise in the discharge of CO_2 appears suddenly.

The molecular concentration of human sweat was first studied by Ardin-Delteil (1900) with the cryoscopic method. He found that the freezing-point of sweat was always higher than that of blood, on an average $\Delta = 0{\cdot}237°$ C. It varies considerably with the individual and the time of year: in the summer, when the sudoriferous glands secrete much water for the purpose of regulating the temperature, the molecular concentration of the sweat falls to $\Delta = 0{\cdot}08°$; its maximum, on the contrary, may be $\Delta = 0{\cdot}46°$. These oscillations are principally due to the varying content of sodium chloride. The fact that sweat has a lower molecular concentration than the blood was also confirmed by Strauss (1901) for the sweat collected from sick people and that obtained by hot-air baths. The normal hypotonia of the secretion of the sudoriferous glands, as compared with the normal hypertonia of the renal secretion, witnesses to the different functions of the two secretory processes, the former being mainly concerned with excretion of water, the latter with excretion of the solid products of metabolism.

Experiments have been made to determine whether the sweat has any *toxic properties* (Röhrig, Queirolo, Capitan and Gley, Cabitto, Arloing, Charrin and Mavrojannis, Mairet and Ardin-Delteil), but have not led to any consensus of results. Some authors assert that there is a toxic action, but the majority entirely deny the toxicity of normal sweat.

IV. When the secretory activity of the sudoriferous glands rises to the point at which it is manifested in the sensible form of sweat, it is usually accompanied (as occurs with many other secretions) by dilatation of the cutaneous vessels. The thermoregulatory function of the skin depends fundamentally on this

association of the two phenomena. In the summer, or in an overheated atmosphere, the vessels dilate, and cutaneous perspiration increases, after which the body is liable to a chill either from increased irradiation of heat into the atmosphere, or by increased evaporation of sweat. In the winter, or in too cold an atmosphere, on the contrary, the skin becomes pale from vascular constriction, cutaneous perspiration is diminished, and the internal heat is stored up owing to the lessened dispersion at the surface of the body.

One of the earliest experiments which unmistakably shows the coincidence of cutaneous hyperaemia and sweating was that of Dupuy on the horse (1816), repeated and confirmed by Mayer (1826), which seems to have inspired Cl. Bernard with the discovery of the vaso-constrictor nerves in 1851. Division of the cervical sympathetic in the horse produces a marked and persistent secretion of sweat in the same half of the animal's head, accompanied with neuro-paralytic hyperaemia. According to Mayer, galvanisation of the skin of the neck in man, which excites the sympathetic, reduces cutaneous transpiration when it causes pallor, and increases it on the contrary, both in the neck and arm, when the skin is flushed.

This correlation of the two phenomena is, however, neither constant nor necessary, and countless observations and experimental data show that the secretion of the sweat glands is directly influenced by *secretory nerves*, which are quite independent of the *vasomotor innervation*. The sweat, *e.g.* of anguish, the "cold sweat" of the death-agony, and of many illnesses, particularly of consumption, are associated with anaemia and not with hyperaemia of the skin.

In his fine researches on the vaso-dilator fibres that run in the sciatic to the lower limb, Goltz (1875) noted that excitation of the peripheral end of this nerve, besides hyperaemia, determined the appearance of sweat drops on the pad of the cat's foot. This fact was confirmed by Kendall and Luchsinger (1876), who also found that peripheral stimulation of the brachial plexus excited sweat drops on the pad of the cat's front paw. They found, however, that this secretion is not necessarily connected with flushing of the skin or increased temperature of the foot. With currents that are not unduly strong the secretion of sweat can be observed even when the cutaneous surface (which has no hair) becomes pale and cold. They further saw that sweat can be excited on the pad of the cat's foot by stimulation of the sciatic 20 minutes after amputation of the limb, showing absolutely the independence of the secretion from blood pressure and circulation.

No less important were the results of Ostrumow (1877). He saw that stimulation of the abdominal sympathetic produced the same effect on the cat's paw as that of the sciatic, that the effect

was not inhibited by ligation of the aorta, but did cease, as in other glands, after atropinisation of the animal.

Luchsinger (1877) and Nawrocki (1878) confirmed the existence of sudoriferous fibres in the abdominal sympathetic for the production of sweat in the cat's hind-foot, and also found sudoriferous fibres in the thoracic-sympathetic to the front paw of this animal, and in the cervical sympathetic to the head of the pig and horse.

The spinal origin of these fibres has been worked out by a number of observers—Luchsinger, Nawrocki, Vulpian, Ott, and more recently by Langley (1891). According to Langley, the sudorific fibres for the cat's hind paw run from the cord to the sympathetic through the rami communicantes of the last two thoracic roots and the first three or four lumbar roots. They connect with the last lumbar and first sacral ganglia, and run in the grey rami of these ganglia to the spinal nerves which unite to form the sciatic.

The sudorific fibres to the front paw, according to Langley, reach the sympathetic by the rami communicantes of the 6th, 7th, and 8th thoracic nerves; then ascend to the stellate ganglion, and reach the brachial plexus *via* the grey fibres of this ganglion, and pass thence to the median and ulnar nerves.

Besides the *secretory* fibres for sweat, some authors admit the existence of antagonistic fibres, *i.e. inhibitory* to the sweat glands (Vulpian, Ott, Arloing). But the experimental data adduced are ambiguous, and do not prove the existence of a double order of nerves for the regulation of cutaneous secretion. The sudorific fibres can be excited, and the secretion of sweat promoted, by exciting the centres from which they emanate. The centres for the secretory sweat fibres to the hind limbs of the cat are in the lumbar cord; those for the anterior limbs in the cervical cord.

On separating the dorsal from the lumbar cord in the cat by a cross-section, and then placing the animal for a few minutes in a temperature of 40-45° C., sweating is provoked not only in the pad of the anterior foot, but in the posterior as well (Luchsinger). This secretion depends not only on a direct action of the superheated air upon the sudoriferous glands, but upon the activity of the central nervous system. In fact, when the sciatic is previously divided on one side, no sweat is secreted at the pad of the corresponding foot, although the sweat glands here are exposed to the action of heat as much as in the three other limbs.

The sweat excited by an asphyxial condition of the blood (as is probably the case with the sweat of the death-agony) depends on excitation of the nerve centres, and not on that of the peripheral apparatus. In fact, if a cat in which the sciatic is divided on one side is asphyxiated, sweat appears only in the three paws connected with the centres, and not in that which has been cut off.

Both in warmed and in asphyxial blood sweating may be

conceived of as a *reflex* or as a *direct excitation* of the spinal centres of sweat secretion. Luchsinger showed that sweating occurs in the hind paw of a cat in which the cord has been divided in the middle of the thorax, both with rise of temperature and in asphyxia, if all the posterior roots below the cross-section are divided. In this case the sweating must be explained by *direct excitation* of the lumbar centres.

Reflex sweating is more easily demonstrated. It is only necessary to stimulate the central end of the cut sciatic or ulnar or median nerve to promote perspiration in the three other paws. The mere sight of a dog makes a cat sweat from all four feet.

Many interesting phenomena can be observed when poisons are used to excite or hinder sweat secretion. Certain poisons, particularly strychnine and picrotoxin, apparently promote sweating merely by their action on the spinal cord, since they have no effect on the paw of which the nerves have been divided. Other poisons, on the contrary, *e.g.* nicotine and eserine, produce slight sweating even in the paw of which the nerves are cut; so that these drugs stimulate not only the centres, but also the peripheral apparatus (Luchsinger, Högyes). Pilocarpine excites a marked secretion of sweat even when the nerves have been divided, so it must act upon the nerve-endings in the glands (Luchsinger, Nawrocki, Vulpian), or on the secretory cells (Max Levy). Even after degeneration of the cut nerve, the limb can be excited to perspire by a sufficient dose of pilocarpine. A similar but less pronounced effect is produced by muscarine (Trümpy and Luchsinger).

Atropine and duboisine are poisons which have an antagonistic action to that of pilocarpine and muscarine. Intravenous injection of 3 mgrms. atropine in the cat will inhibit the secretory effect of exciting the sciatic. If 10 mgrms. pilocarpine are then injected, sweating takes place, although excitation of the nerve still has no effect. In this case it must be assumed that atropine paralyses the nerve-endings, while pilocarpine excites the secretory cells. But if 20-30 mgrms. atropine are injected, the paralysis extends to the secretory cells also, so that local application of pilocarpine has no effect (Rossbach). That atropine acts not only on the nerves, but also on the gland cells, by a temporary paralysis of the secretory function, was elegantly demonstrated by Aubert in his method of photographing the sweat-prints (Fig. 137).

V. The Sebaceous Glands are distinguished from the Sudoriferous, not only by their morphological structure, but still more by the nature and process of their secretion. They are no less plentifully distributed in the skin than the former. They are compound tubular glands, the excretory duct of which runs along the canal of a hair follicle (Fig. 138). They are therefore most

plentiful in the regions beset with hairs or down, and are few in the parts destitute of hair, and entirely absent from the palm of the hand and sole of the foot.

Externally the sebaceous glands are pear-shaped or acinar. They are of unequal size, and are not in proportion with the thickness of the hair to which they are attached. Those of the

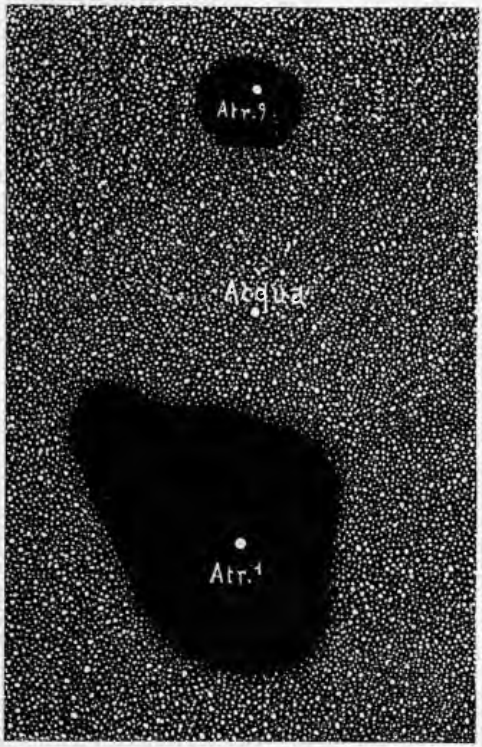


FIG. 137.—Sweat-prints showing suspension of secretion by local application of atropine. (Aubert. The area *Atr.*1, to which a sponge soaked in atropine was applied, shows no sweat-prints *Atr.*9, which was covered with belladonna plaster, also shows none. The centre, on which a sponge soaked in plain water was laid, remained unaltered.

alae of the nose and the cheeks are larger than elsewhere, though connected only with the fine, downy hairs of those parts (Fig. 139).

The epithelial cells which line them are polygonal, and charged with fat-granules. The cavity of the gland is filled by a granular mass, the *sebum*, which lubricates the hairs and the stratum corneum.

Sebaceous glands are also found in the mucous membrane of the labia majora and minora of the vulva, in the clitoris, the glands and prepuce, and in the eyelid (Meibowmian glands). The

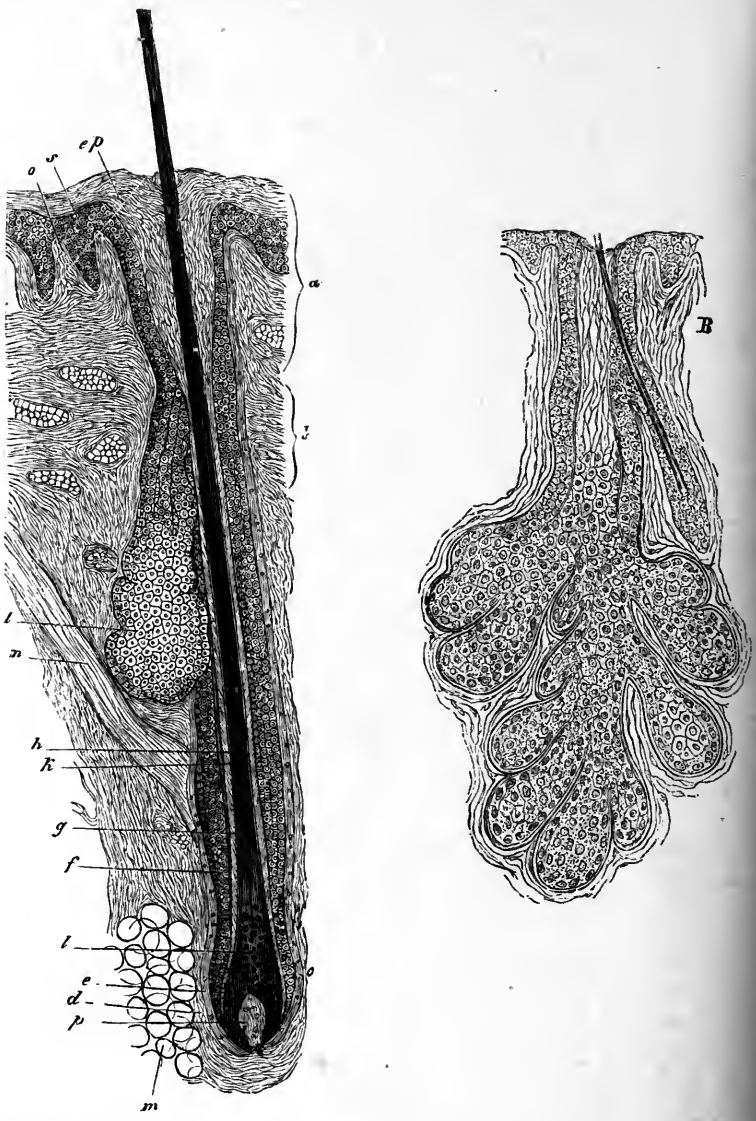


FIG. 138.—(Left.) Hair follicle, longitudinal section. (Biesiadecki.) *a*, mouth of follicle; *b*, neck of follicle; *c*, lower bulbar swelling; *d*, *e*, dermic coat (outer and middle layer; the inner or hyaline layer is not seen); *f*, *g*, epidermic coat (inner and outer root-sheath); *h*, cuticle of root-sheath; *k*, medulla; *l*, hair-bulb; *m*, fat of subcutaneous tissue; *n*, arrector pili; *o*, papilla of skin; *p*, papilla of hair-bulb; *st*, Malpighian layer of epidermis; *ep*, stratum corneum, erroneously represented in figure as continuation of inner root-sheath; *t*, sebaceous gland.

FIG. 139.—(Right.) Longitudinal section of a sebaceous gland from the cheek, with a small hair growing through its duct. Human. (Toldt.)

largest are in the alae of the nose and the red margin of the lips near the angle of the mouth.

The sebaceous content of the glandular spaces is fluid, and consolidates into a semi-soft yellowish mass during its passage through the duct, so that it can sometimes be squeezed out, particularly at the nasal pinnae, in the shape of a vermiculus. The ceruminous glands of the external auditory meatus are coiled glands. But there are also true sebaceous glands in connection with the hairs of the auditory meatus, to which, exclusively, some authors attribute the secretion which lubricates this duct.

Under the microscope the sebaceous secretion shows innumerable fat-granules, cells in fatty degeneration, crystals of cholesterol, and almost invariably microscopic acari (*demodex folliculorum*). Chemical examination shows the presence more particularly of neutral fats, soaps, fatty acids, cholesterol, a small quantity of protein, casein, and extractives of an undetermined character. In the minerals insoluble earthy phosphates, chlorides, and alkaline phosphates predominate.

The *vernix caseosa* which covers the skin of the foetus comes from the accumulation of the sebaceous substance secreted during intra-uterine life, mixed with detritus of macerated epidermal and epitrichial cells. According to Liebreich and Ruppel it contains cholesterol, oleic and palmitic acid, and their respective glycerides. It facilitates the progress of the foetus along the vagina in delivery.

The *smegma preputii* is analogous to the foetal vernix caseosa, and contains a specific compound of ammonia, on which the odour peculiar to this secretion depends. The substance known as *castoreum* is the secretion from the sacculated prepuce of the beaver; it has a characteristic odour, and is employed as a sedative in medicine. It contains resinous substances, benzoic acid, and other aromatic compounds.

The *wax* or *cerumen* of the auditory meatus, in addition to specific fats of a waxy consistency, contains a specific bitter extractive. The secretion of the Meibowmian glands does not differ from that of the cutaneous sebum, and lubricates the eyelashes. It tends to collect along with the tears in the inner angle of the eye, where it is entirely or partly absorbed, and is carried off with the former by the lachrymal duct.

All these secretions have a *protective* function which is quite distinct from that of perspiration. Their mechanism is also very simple, and quite different from that of other secretions. The ordinary secreting cells elaborate the material of their secretion without being destroyed in the process; the young cells of the sebaceous glands, on the contrary, multiply incessantly by karyokinesis (Bizzozero and Vassale), while the older cells undergo fatty degeneration, until they drop off and mingle with the sebaceous substance collected in the cavity of the gland.

The formation of sebum is therefore not so much the result of a true secretory process as of the perpetual renewal and fatty degeneration of epithelial cells,—perfectly analogous to the renewal of the stratum corneum of the epidermis, in consequence of the keratinous degeneration of the cells of the Malpighian layer.

Nothing definite is known as to the influence of the nervous system on the sebaceous glands. It would not be surprising if, like the glands of plants, they function independent of any regulatory nervous influence. Yet certain observations of Arloing (1899) suggest they are probably no exception to the general rule. After dividing the cervico-sympathetic in the donkey, he saw that a quantity of wax collected in the sebaceous glands of the skin of the ear, which reached its maximum 15 hours after section, and ceased about 64 hours after. Excitation of the peripheral end of the nerve also seems to cause a perceptible increase in the secretion of these glands.

VI. The Mammary Glands, from which the highest class of vertebrates has been named, belong to the skin no less than the sudoriferous and sebaceous glands.

They are compound acinar glands which may be regarded as a collection of enlarged sebaceous glands with modified functions. In man there are only two, in the region of the breast; in the mare and the goat two, and four in the cow, in the lower abdominal region; multiparous animals have ten, twelve, or even more along the abdominal wall. From the phylogenetic point of view it is an important fact that in many of the lower mammals of the *Monotreme* group the mammary glands consist of a large number of small cutaneous glands without a nipple, which resemble enlarged sebaceous glands. The new-born offspring are nourished by licking the region of the maternal abdomen in which these glands are situated. For the rest we have seen that the secretion of even the ordinary sebaceous glands contains a small amount of caseinogen, which confirms the phylogenetic homology between sebaceous and mammary glands (Neumeister).

The development of the mammary glands commences in both sexes in the third month of intra-uterine life. At birth the glandular tissue consists of tubes which branch two or three times and terminate in a blind sac. At the twelfth year these tubes subdivide into more branches, but the glandular alveoli at the extremity are not developed till the approach of puberty in the female.

In males the mammary gland is only a rudimentary, vestigial organ, witnessing to an original hermaphroditism. In the adult they are no more developed than in the foetus. At the age of puberty they may develop to a certain extent and harden, but immediately undergo a process of degenerative involution. New-born animals of both sexes constantly secrete a small quantity of

milk for a few days, which is popularly known as "witches' milk." The mammary secretion may occur (though very rarely) in adult males, in virgins, and in females who have not conceived, are not pregnant, and not in labour. Talmud, Cardano (1556), Fiorentino (1553), A. V. Humboldt, Haeser, all cite authentic cases in which the male gland secreted. Degeneration or involution of the gland takes place in women after the menopause.

During its maximal development, which coincides with the period of suckling, the glandular mass of the female breast consists of some twenty distinct lobes, held together by fibrous and areolar tissue, interpenetrated by accumulations of adipose tissues. Each lobe is a distinct gland, with a *galactophorous* or milk duct opening by a separate orifice on to the summit of the mammilla. Before branching, each milk duct dilates considerably to form an ampulla or sinus, which serves as a temporary reservoir for the milk. Each lobe divides into smaller lobes, and these again into lobules, consisting of a collection of alveoli or terminal acini, into which the minute lactiferous ductules open. The alveoli often present lateral enlargements and sometimes (as in the pulmonary alveoli) communicate *inter se* by the breaking-down of the septa, so that larger cavities are formed.

The walls of the alveoli consist of a basement membrane, having on its inner surface a layer of flattened stellate cells, which embrace the gland cells like a basket. The glandular epithelium is a single layer of cells, which vary considerably in form according as they are at rest or active, whether the alveolus is dilated or contracted, and so on. We shall subsequently return to the significance of these differences.

The secretory ducts have longitudinal fibres of plain muscle continuous with those present in the skin of the nipple. For the greater part of their course the ducts are lined with a single layer of columnar cells, except the principal ducts which run to the nipple, and are lined with scaly, stratified epithelium.

The arterial vessels enter at different points and form a capillary network round each alveolus; this is continued into veins which surround the base of the nipple in Haller's *circulus venosus*. The lymphatic vessels also, which directly convey the materials of the lacteal secretion, surround the alveoli, and communicate with numerous intra-alveolar lymph sinuses containing a number of leucocytes, some of which penetrate through the basement membrane to the interior of the alveoli. The nerves running to the mammary gland are branches of the intercostal and supra-clavicular nerves. They proceed partly to the skin of the nipple, partly to the muscular fibres of the ducts, the blood-vessels, and the glandular acini where their endings have not yet been determined.

VII. Human Milk is a white or yellowish fluid, opaque, without

odour, and with a peculiar, sweetish taste. Its specific gravity varies from 1·025 to 1·034. In the fresh state it gives the same reaction as cow's or goat's milk, *i.e.* slightly alkaline or amphoteric, while the milk of carnivora is faintly acid. If left to stand, a yellowish layer, the *cream*, forms on the surface. In time it turns sour or clots, by lactic fermentation.

The percentage composition of human milk is very variable. From the average of a great number of analyses carried out by Pfeiffer and Leed, it contains 10·8-13 per cent solid constituents. These are organic and inorganic. The organic are represented by the three principal groups of food-stuffs—proteins, fats, and carbohydrates.

The proteins are present to an amount of 1·6-2·5 per cent. The chief protein is *caseinogen*, a phosphorated substance belonging to the nucleo-proteins, which has the property of clotting when acted on by chymosin or rennin (Chapter II. p. 118). There is further a *lact-albumin* which closely resembles serum-albumin, as well as other proteins, *e.g. lacto-globulin, lacto-mucin*, etc.

Some authors claim also to have detected a small amount of *proteose* and *peptone* in human milk, which has been disputed by Dogiel and Hofmeister. If milk is filtered at high pressure through a porous filter, the caseinogen is held back, while the albumin passes, and can be precipitated by heating the filtrate. It is not definitely known whether the skin which forms on the surface of milk on boiling really represents protein contained in the milk. It forms again as often as the first skin is removed. It is probably an albumin or globulin formed during heating by alteration of the caseinogen.

The fat of milk forms a perfect emulsion, the droplets as seen under the microscope being 2-5 μ in diameter, the so-called *milk globules*. The stability of this natural emulsion depends on the fact that each fat-globule is surrounded by a layer of caseinogen solution which prevents the drops from fusing. If milk is treated with caustic soda, and then with ether, the caseinogen is precipitated, and the fat runs into large drops.

When milk is allowed to stand, the fat-globules, which are lighter, mount to the surface and form the cream, and if this be skimmed off the milk loses a large amount of its butter. The opacity of milk is due to the fatty globules. When the cream is removed, the milk that remains has a higher specific gravity than the natural milk. By centrifuging, milk can be almost entirely deprived of its fat and becomes semi-transparent.

Milk-fat is a mixture of all the animal fats. Palmitin, stearin, and olein preponderate; but they are always accompanied by small quantities of butyrin and other glycerides. Generally speaking, it may be said that the fat of milk resembles that of adipose tissue; its composition varies like the latter in different

animals, particularly in the proportion in which the olein, palmitin, and stearin are present. Human milk contains twice as much olein as it does palmitin and stearin; in cow's milk the three glycerides are present in approximately equal amounts. In human milk the fat content varies from 2·5-4·3 per cent, while in cow's milk it may amount to 6 per cent.

The carbohydrates of milk are *lactose* or *milk sugar*, which is a disaccharide, and splits on absorption of water into two monosaccharides, *dextrose* and *galactose*. By means of an enzyme which is apparently pre-formed in the milk or forms in it on standing, or by the bacteria from the air, lactose undergoes lactic acid fermentation, by which milk turns sour and clots, the lactic acid which is formed neutralising the alkali which holds the caseinogen in solution. Lactose does not ferment like glucose on merely adding yeast. But there are special bacteria which produce an alcoholic fermentation with formation of a small amount of lactic acid. This is utilised for the preparation of *kumis* from the milk of mares, and *kefir* from that of cows, which are much used in Russia. According to bacteriologists these fermented milks are due to the symbiotic action of two different microbes, a *blastomycete* (*saccharomycete*) which produces alcoholic fermentation, and a *schizomycete* which causes the lactic fermentation of lactose (Gorini).

Lactose is more plentiful in human milk than in cow's milk; in the former it oscillates between 5·5 and 6·9 per cent, while in cow's milk the average is 4·8 per cent (König). Another difference between the two kinds of milk is that human milk is richer in lecithin, and poorer in mineral constituents, especially in lime and phosphoric acid—it contains about $\frac{1}{6}$ the lime and $\frac{1}{4}$ the phosphoric acid of cow's milk.

Of the inorganic salts it is remarkable that potash and phosphoric acid preponderate over sodium or chlorine, as is also the case in the blood corpuscles and the muscles.

A copious literature in regard to the constituents and physiological properties of milk has recently sprung up; it is chiefly concerned with the study of milk by new methods learned from physical chemistry and bacteriology. Milk serum has been investigated on the same lines as the various blood serums with regard to its bactericidal, haemolytic, and other properties. No final or even general conclusions have been arrived at, but the specific character of each kind of milk has been demonstrated, confirming the old adage, that "mother's milk is a treasure impossible to replace" (Seiffert).

This rapid survey of the chemical composition of milk brings out the fundamental fact that this secretion is a chemical elaboration by the secretory cells of the mammary gland, and not a mere transudate of the blood or lymph circulating through it, as was formerly held. Caseinogen is rarely present in the blood;

fats are there in minute quantities only, whereas they are abundant in milk; lactose is not found at all in blood; lastly, the inorganic constituents of milk and blood are quantitatively different.

The yield of milk from the body in 24 hours is generally considerable. During well-established lactation a good wet-nurse will produce a litre or a litre and a half per diem. This amount may be greatly increased since it depends on a number of factors, the principal of which is the degree of development of the mammary gland. Interesting observations on this subject have been made on the cow. Two cows of the same breed and approximately the same weight produce very different quantities of milk, in proportion with the development of the udder. According to Fleischmann the maximal yield from a milch cow is 24 litres = 25 kilos. milk per diem, with about 3 kilos. solid substances.

Since the maximal weight of the udder is about 5 kilos. with 1·5 kilos. solid substances, it follows that in these extreme cases the udder secretes five times its own weight in the day.

The development of the gland, which is maximal during the first weeks after parturition, diminishes with the duration of lactation, and the yield of milk decreases in proportion. The influence of race upon the development of the udder and consequently of its yield of milk is great. The best milch cows are those of the Swiss, Dutch, and Oldenburg breeds. According to Fleischmann muscular work, within certain limits, conspicuously diminishes the lacteal secretion, and in time determines a certain amount of glandular involution. This is why the race of cattle employed in heavy agricultural labour give little milk.

VIII. In order to form an idea of the process by which the mammary gland forms the specific constituents of milk, which do not pre-exist in blood and lymph, we must examine the effect of nutrition in general, and of specific diets in particular, upon lacteal secretion.

It is only necessary to compare the amount of organic substances contained in milk with a scanty and an abundant diet, to see the great influence of alimentation in general upon the functional activity of the mammary gland. Every one knows that a wet nurse must be well fed in order to have good milk, which in physiological language means that the crude materials furnished by the blood and lymph to the mammary gland for the production of milk come for the most part directly from the food. It is, however, far more important to see how the chemical composition of milk alters with a preponderance in the diet of protein, fat, or carbohydrate. *A priori* one would suppose that there would be a ratio between the quantity of protein, fat, and carbohydrate ingested and the amount of the same in the milk. Experiment shows, on the contrary, that a diet rich in protein not

only improves the yield of milk as a whole, but also the amount of its principal constituents, particularly the fat content.

This fact was established in 1846 by Franz Simon, for nursing women, and confirmed by Decaisne in 1873. Still more striking results were obtained by Ssubotin (1866), on comparing the chemical composition of the milk of a bitch fed on meat with one fed on potatoes only.

The fact that a full flesh diet largely increases the fat content of milk supplied a valid argument in favour of the theory specially sustained by Voit, that animal fat is mainly derived from protein. The secretory cells of the mammary gland principally employ protein as the material from which they elaborate the organic constituents of milk. A full protein diet first develops or increases the secreting cells and the size of the gland, and then the total quantity of the secretion and its fat content increase also. The effect is not seen at once, but after a few days, and it is more pronounced in the early months of suckling than in the later, when the gland begins to undergo a slow process of involution. Once the gland has been developed, a smaller amount of alimentary protein suffices to maintain its increased function.

The effect of a protein diet upon the sugar content of milk has been much disputed. According to the experiments of Ssubotin on bitches, and of Kühn on cows, the lactose is somewhat diminished; but according to I. Munk's later experiments (1881), full protein feeding augments not only the fat and protein content of milk, but the amount of sugar also.

A full diet of fats not only does not increase the fat content of milk but even diminishes it, if the food does not contain a sufficient amount of protein at the same time. In the latter case there is an increase of butter such as occurs on a richly nitrogenous diet. From this it may be deduced that the ingested fat does not tend to increase the fat of the milk, but, by sparing the nitrogenous consumption, makes it possible for the protein to be utilised more largely for the formation of butter, as shown by the admirable work of Pettenkofer and Voit, to which we shall have to refer below in speaking of general metabolism. That increase of alimentary fat, with a constant amount of alimentary protein, does not increase the amount of butter in the milk, is directly proved by Kühn's investigations with cows.

The amount of carbohydrate fed has no appreciable effect on the amount of lactose secreted by carnivora. But even in herbivora no relation can be observed between the quantity of ingested starch and the sugar content of the milk. Since, as a rule, a starchy diet coincides with scarcity of protein food, it follows that the secretory cells of the gland find little material to hand for the formation of the milk as a whole. That not only the fat but also the lactose (for the most part at any rate) come from the protein

circulating with the lymph in the gland, is seen from the fact that bitches fed with an exclusively flesh diet excrete large quantities of sugar in their milk (Ssubotin). It is therefore a mistake to feed wet nurses on thick soups and farinaceous foods, with the object of increasing the supply of milk. Protein substances should be the basis of a rational diet for nursing women.

Starting from the hypothesis that the lactose of the milk originates in a process of conversion by the secretory gland-cells of the dextrose of the blood, P. Bert (1884) excised the udder of a goat, after which she became pregnant and gave birth. For three days after parturition, the urine contained sugar, since it reduced cupric oxide. To account for this transitory glycosuria he assumed that after parturition glucose was normally formed more abundantly than usual, and was converted into lactose in the mammary gland. As the udder had been excised in the goat experimented on, the puerperal hyperglycaemia gave rise to glycosuria. But it seems to us far simpler to account for the fact observed by Bert, by referring the temporary glycosuria to injuries of parturition. In any case it would be advisable to check the fact, by determining what kind of sugar was present, and otherwise extending and varying the experiment. We know from Hofmeister (1878) that the urine of women and mammals in general often contains lactose immediately before and after parturition, which is due presumably to reabsorption of the lactose formed by the cells of the mammary glands.

Paul Bert's experiments were repeated by Porcher in 1905 with the same results. He further found that cows, goats, and bitches into which glucose is injected in small doses subcutaneously, or by the peritoneum or mammary gland, are capable of excreting it during lactation as lactose in the urine, which lends support to the view that the mammary glands really effect a conversion of glucose into lactose. Piantoni (1908) came to the same conclusion, on studying the effect on the lacteal secretion of a milch goat of the subcutaneous injection of various sugars (lactose, galactose, glucose, saccharose, raffinose, and dextrin).

According to C. Foà and Andreoni (1908) there is no percentage difference in the content of the substances (glucose, glucoproteins, glycogen) from which lactose originates, in the blood of women who are suckling and not suckling. On comparing the content of these substances in the carotid blood with that of the blood that has traversed the gland, he finds a marked diminution in the latter of free glucose and of that which is combined with the proteins, while the glycogen is not diminished.

IX. The exact cytological and chemical mechanism by which the milk is secreted from the epithelial cells which line the alveoli of the mammary gland, is still a matter of dispute.

It was formerly held that the milk is discharged, on analogy

with the secretion of the sebaceous glands, by the disintegration and liquefaction of the older cells, in proportion as new cells replace those destroyed and converted into milk. This view rests on the common origin and homology of the two kinds of glands. It also finds support in the theory that prevailed as to the origin of the *colostrum corpuscles* found in the first milk, which is secreted in the last days of pregnancy and the first 3-4 days after parturition. The colostrum corpuscles are true cells, mostly nucleated, round, and very granular. By some they have been regarded as modified gland cells, which become detached and pass into the secretion previous to complete disintegration, which they undergo later, when colostrum corpuscles are no longer present in the milk. As soon as the mammary glands are excited to activity, the alveolar cells fill with granules and globules of fat, and the alveolar spaces with a clear fluid in which fat globules and occasional colostrum corpuscles are seen to float.

The colostrum corpuscles, however, have not the appearance of epithelial cells, and on the warm stage of the microscope they exhibit amoeboid movements similar to those shown by leucocytes. They are therefore supposed by many to be leucocytes that have wandered from the lymph sinuses of the perialveolar tissue into the lumen of the alveoli, and not cast-off epithelial cells.

The theory that milk is formed by regeneration of the epithelial cells is discounted by the fact that no such rapid and persistent cell-multiplication can be detected in the mammary gland as would account for the organic constituents of the milk, on the theory of detritus from disintegrated cells. Heidenhain, indeed, calculated that the gland-cells would have to be renewed at least five times in every 24 hours, if they are to provide the solid materials of the milk.

Partsch (1880) advocated another view, which was accepted by Heidenhain. According to this, the secretion products formed in the gland become gradually accumulated at the free ends of the cells, which lengthen out and become columnar, projecting unequally into the lumen of the alveolus. The enlarged free end is supposed to become detached, and discharge the accumulated products, while the outer part of the cell (with the nuclei) remains intact, and repeats the same process.

In support of this hypothesis they adduce certain histological researches carried out on the mammary gland of the bitch in different phases of secretory activity (Fig. 140). At the commencement of lactation the alveoli were distended by a clear secretion, in which fat globules and a few colostrum corpuscles floated. The epithelium was flattened against the basement membrane, and contained fatty globules of various sizes. During full secretory activity, on the other hand, *i.e.* when lactation was fully developed, the cells became first cubical and then columnar, and vary in size;

they projected irregularly into the lumen of the alveolus, had usually two or three nuclei, and contained fatty globules similar to those of the milk, at the end which projected into the lumen.

Later work on the mammary gland in full secretion did not confirm these observations. Generally speaking, the epithelial cells are uniformly flat or at most cubical, as shown by Fig. 141. Schäfer regards it as probable that the columnar appearance described by Partsch and Heidenhain is found only in collapsed alveoli, due to the deformation of the basement membrane. On the other hand, the same argument which Heidenhain urged against the first view can with slight modifications be adduced

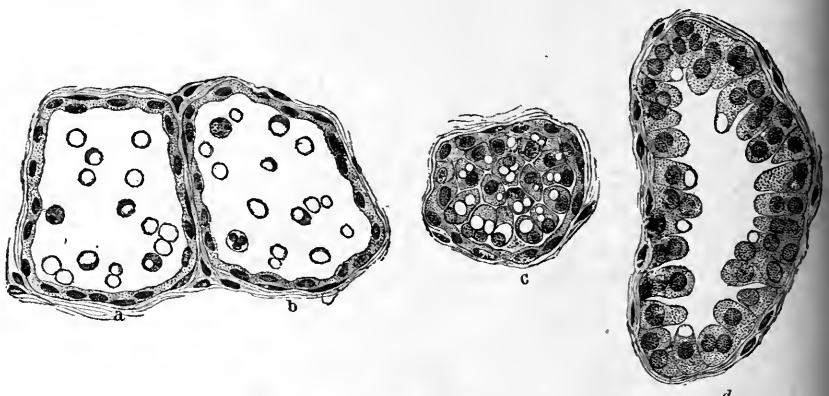


FIG. 140.—Alveoli of mammary gland of bitch under different conditions of activity. (Heidenhain.) *a*, *b*, section through the middle of two alveoli at the commencement of lactation, the epithelium cells being seen in profile; *c*, part of the wall of an alveolus in a similar condition, with epithelium cells seen flat; *d*, alveolus in full secretory activity.

against his own, which assumes the formation of the milk to depend upon disintegration of the projecting, non-nucleated part of the cell protoplasm. The regeneration of the protoplasm lost by secretion would have to be so rapid that we know of no analogous phenomena to give countenance to it.

Since in all the other glands we have been studying the secretory process takes place without any cellular destruction or regeneration (except in the case of the sebaceous glands, the function of which is no true secretion), it is difficult to see why the simplest hypothesis should not also be accepted for the lacteal secretion. According to this the epithelial cells of the mammary gland have the power of forming the specific organic constituents of milk from conversion of the crude materials drawn from the lymph, not by any cytological process that involves the disintegration of the protoplasm, but by an essentially chemical method, the exact nature of which is unknown to us,—as in the

case of all the other secretions. This does not preclude the multiplication of cells during the active secretory work of the mammary gland to an extent in excess of the normal, but at present we know nothing as to the exact manner in which this is accomplished. According to Steinhaus (1892) there is frequent mitotic division of the cell nuclei without subsequent cellular division, accompanied by transformation of the nuclear substance into fat—which would explain the origin of the fat of milk. Szabò (1896), on the

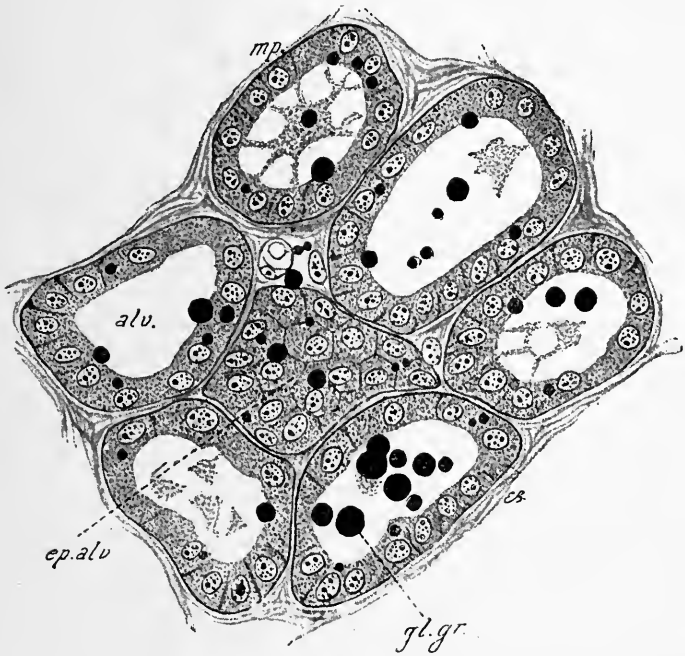


FIG. 141.—Section of lobule of mammary gland of guinea-pig during lactation. (Szymonowicz.) *alv*, lumen of alveolus; *mp*, membrana propria; *ep. alv*, alveolar epithelium, tangential section; *gl*, *gr*, fat drops stained osmic acid.

contrary, observed no mitosis during lactation, but an a-mitosic multiplication of nuclei, so that each cell contained two or three. He also found a great accumulation of protein granules in the cell protoplasm, which gradually pass into the secretion and become dissolved.

In all probability these granules are the *nucleo-gluco-protein* which Hammarsten (1894) found in the protoplasm of the mammary gland, and which probably represents the mother substance of the caseinogen and lactose. In fact, Thierfelder (1883) saw that on grinding up fresh mammary gland in physiological saline, and leaving it to digest for some time at body

temperature, caseinogen and lactose were formed. The latter is preceded by the formation of a colloidal carbohydrate which is identical not with glycogen, but, according to Landwehr, with animal gum. These observations agree with what we have stated in regard to the preponderating importance of alimentary protein for milk production, and the amount of the respective organic constituents of milk. We may reasonably conclude that the mammary gland obtains from the serum-albumin of the lymph, more particularly, the material for the synthetic formation of the nucleo-protein and gluco-protein of which its protoplasmic granules are composed. The different specific constituents of the milk are derived from the decomposition of these and of the nuclear substance.

Arnold's subsequent work (1905) on the formation of the fat of milk also gave results that entirely agree with the above view. On studying the mammary gland of woman, cow, and rat under the microscope, he saw that a copious secretion of fat could occur without cellular degeneration; that the fat always appeared first inside the cell, in place of the granules of the cytoplasm (particularly in the basal part opposite the lumen), while fat was never seen round the cells. The mother substance of the fat must therefore be supplied to the cells in a dissolved form, which is afterwards converted into fatty granules by the protoplasm.

As regards the colostrum corpuscles, on the contrary, Popper (1904) fell back on the conclusion that they are epithelial cells detached from the alveoli or ducts, which on reaching the lumen of the gland are still capable for a certain time of showing vital phenomena, before they undergo fatty degeneration. Their origin as gland cells is shown more particularly by the aspect of their nuclei, which exactly resemble those of the gland cells, and are clearly distinguished from those of the leucocytes by the reticular arrangement of the chromatin. These and other data militate against the foregoing view by which the colostrum corpuscles are taken to be leucocytes.

X. The evidence as to whether the secretion of milk is *directly* or *indirectly influenced by the nervous system*, is of a conflicting nature. Generally speaking, it may be said that a number of everyday observations demonstrate the intervention of the nervous system both in the development and in the secretory activity of the mammary gland.

The correlation between the genital apparatus and the mammary glands is familiar to every one. The latter develop gradually during gestation; immediately after parturition the milk secretion becomes very abundant, and persists throughout the period of suckling. Moreover, during this period menstruation usually ceases. These facts witness to a special trophic and functional relation (a sympathy as was formerly said) between

the genital organs and the mammae, due in all probability to a reflex nervous influence between the two organs.

Nothing but a reflex nervous excitation can explain the fact that periodic suckling or milking is necessary to keep up the lacteal secretion. In order to stop it, either in the first days after parturition or at any subsequent period of suckling, it is only necessary to interrupt the periodic evacuation of the gland.

When the gland spaces have been emptied they gradually fill up again, rapidly at first, and afterwards more slowly, until at a certain degree of tension the secretion ceases entirely, and the milk is gradually reabsorbed. It is certain that sucking at the pap or milking the udder does not merely empty the gland of the milk already secreted, but also reflexly promotes the further secretion. According to Heidenhain, the glandular spaces of the udder of a good milch cow have a capacity of about 3000 c.c., this being the difference in volume before and after evacuation. A Swiss cow is known to yield a quantity of milk far in excess of 3 litres at a single milking. It is therefore clear that the milking not merely empties the udder, but also activates the secretion of new milk. This is also proved by the fact that frequent milking considerably increases the yield of milk in a cow, but it is not advisable to trade upon this fact, since the animal's general nutrition would deteriorate.

Lehmann (1887) injected a solution of indigo-carmine (sodium sulphindigotate) into a milch goat, and at once began to milk her. The first milk kept its colour, then it became slightly tinged, and (after the lapse of an hour or an hour and a half) it became a definite blue. This proves that the secretion is promoted by milking.

Another proof of nervous influence on the milk secretion is seen in the fact that milking causes considerable alteration in the composition of the secretion. While the glands are emptying the fat content increases, and that of caseinogen diminishes. According to Reiset the difference between the first and second milk is greater in proportion with the interval between the two milkings. This phenomenon seems to us inexplicable, unless it be admitted that the mechanical stimulation of the teat exerts a reflex trophic action on the secretory cells.

Certain observations of Baglioni (1907) agree with the above. In a nursing woman he saw that when the child was put to one of the breasts and began to suck greedily (especially when the breasts were very full), a copious gush of milk came spontaneously from the other breast. Evidently this is a reflex, in which the stimulation of one breast excites secretion in the opposite breast also, either by increasing the secretory activity, or by producing a contraction of the plain muscular fibres of the milk ducts, on which the milk is ejected. That such a phenomenon really takes

place conspicuously in the breast, and may effectively co-operate in the efforts of the child to suck by jerking the milk out of the ducts, especially when the breast is full, can be seen by removing the infant shortly after it has begun to suck greedily. The orifice of the nipple will continue for some time to excrete the maternal milk.

Sudden mental emotions readily produce an inhibitory effect on the secretion of milk. In anger or fear it is soon suppressed.

Mental suffering may diminish the secretion, or alter its composition to such an extent that it is insufficient, or even becomes harmful to the infant.

It is thus a matter of common experience that the nervous system regulates the milk secretion, and promotes or moderates it, not by any simple vasomotor action, but by a trophic or secretory influence.

Nevertheless, the physiological experiments undertaken in the hope of confirming these empirical observations by the discovery of the nerve paths and centres of lacteal secretion have so far led only to negative or contradictory results.

Eckhard (1858) was the first who experimented in this direction. He saw in goats that neither division nor excitation of the external spermatic nerve which innervates the udder of these animals produced any sensible effect on the milk secretion; it was unaltered in the udder both on the side operated on and on that which was left intact. His observations have been repeated by others with positive, but often contradictory results.

Röhrig (1876), in order to study the rate of the lacteal flow in the goat, introduced into the excretory duct (which is solitary in this animal) a fine catheter, pushing it up beyond the milk sinus, and connecting it at the free end with an aspirating vessel. By this means he obtained a regular flow of milk at a rate of about 2 drops per minute, if the goat kept still, while 8-10 drops per minute escaped if the animal was restless. To obviate the disturbing effect of moving, he curarised the animal, which did not alter the rate of secretion. On cutting or faradising the separate branches of the external spermatic nerve under these experimental conditions, he obtained results which led him to admit the existence of:—

(*a*) Sensory nerves capable of inducing reflex movements (*b*) motor nerves, which cause erection of the nipple and tonic contraction of the muscular fibres of the lactiferous ducts; (*c*) vasomotor nerves, section of which produces acceleration of the secretion, peripheral stimulation its delay.

He held the presence of *specific secretory nerves* in the mammary gland to be improbable. But in Heidenhain's opinion the experiments described by Röhrig are not sufficiently numerous or conclusive to make his evidence irrefutable.

Laffont (1879), on repeating Röhrig's experiments on curarised goats, came to the opposite conclusion, viz. that the milk secretion, like many other secretions, is under the simultaneous control of *secretory* and of *vaso-dilator nerves.*

Hammerbacher (1884) studied the effect of pilocarpine and atropine injection on the lacteal secretion of the goat. In animals kept on a constant diet, he found that subcutaneous injection of 3-15 cgrms. pilocarpine caused no perceptible increase in the milk secretion, while a few hours after injection of large doses of this drug the secretion was reduced, and the milk also contained fewer solids.

Atropine, on the contrary, even in small doses diminishes the secretion of milk, while the content of solids, particularly the percentage of fat, was much increased. This effect of atropine is borne out by the clinical fact that it is successfully used to stop the secretion of milk in nursing women.

Valentowicz (1888), who continued Röhrig's experiments on goats, found that the stimulation of the peripheral end of the external spermatic diminished the secretion instead of increasing it. But after dividing this nerve on one side, the difference in the amount of secretion, and also in the composition of the milk on the two sides, is not very marked. He noted, however, that after some time there was a certain increase in the amount of milk secreted and the fat content, on the operated side (*paralytic secretion*). If milking was discontinued in both udders for several days and then resumed, the secretion was found to be much less in the normal mamma than in that of which the nerve had been cut out. He concluded that the external spermatic nerve (as a whole) is an inhibitory nerve for the milk secretion.

To us the experiments of Mironow (1894), also on goats, seem more important. He wished to confirm the clinical fact that sudden excitation of the nervous system and sharp mental emotions diminish or temporarily suppress the function of the mammary gland in nursing women. The milch goat was kept on a constant diet, and milked twice a day so as to reach a certain maximum of secretion. On the day before the experiment and after obtaining this result, the goat was milked every 2-3 hours from the morning till night. The same 2-3 hours' milking was repeated on the day of the experiment, but on that day a sensory nerve to the hind leg (the saphenous nerve) was exposed, raised by a thread, and excited with an induced current of increasing strength for 30-60 minutes, on which the animal showed symptoms of acute pain, agitation, tachypnoea, etc.

In twenty-four experiments of the same kind, on different goats, Mironow invariably obtained a considerable diminution in the secretion of the milk, for a longer or shorter time, in direct relation with the intensity and duration of the pain.

This result cannot be explained as a simple modification of the blood circulation in the mammary gland, not only on account of the time the pain lasts (which may be six hours), but also because not only the quantity but also the quality of the milk is altered: it becomes thicker and contains a larger amount of solids, due particularly to increase of fat.

Mironow further confirms Eckhard's observation that unilateral section of the external spermatic nerve at the point at which it leaves the pelvis has no appreciable influence on the total yield of milk, nor upon the amount of milk secreted by the gland operated on.

But he adds two important observations, as follows: (*a*) bilateral section of the external spermatic reduces the total yield of milk by more than half (57 per cent); (*b*) the depressing action of the pain after the bilateral division of these nerves continues, showing that it is transmitted to the mammary gland by other nerve paths.

These nerve paths, according to Mironow, are represented by nerve fibres that enter the mammae along with the branches of the inferior epigastric vein and artery, and which he terms the inferior epigastric nerves; and further by a branch of a nerve that accompanies a vein which ascends in the symphysis of the pubes, and then divides into two branches to the two udders, which he terms the azygos nerve.

In excising these nerves as well as the external spermatics, so as completely to isolate the mammary gland from the central nervous system, Mironow did not succeed in suppressing the lacteal secretion, but only in reducing it to about 35-45 per cent. He also noted that after thus isolating the glands from the central nervous system, the pain provoked by protracted sensory excitation no longer affected either the quantity or the quality of the milk. The inference is that the mammary gland must have peripheral nervous centres which control the secretory activity independent of the higher centres.

A goat in which all the nerves to the udder had been cut became pregnant and gave birth to two kids. The secretion of milk increased during pregnancy, and after parturition gradually regained almost the normal quotum obtained before the operation. This led Mironow to think that the effect of pregnancy and parturition on the development and secretion of the mammary gland was not exerted reflexly by the brain and spinal cord, but by the peripheral intermammary centres, possibly by modifications in chemical composition of the circulating fluids, due to a special internal secretion of the uterus.

Later physiological experiments confirmed the correlation between the mammary gland and the genital organs. Halban and Knauer (1900) saw that excision of the ovary was followed by

arrested development or atrophy of the uterus; Foges (1905) showed by experiments on young rabbits and kittens, that the development of the mammary gland is connected with the presence of ovaries capable of functioning, while the presence or absence of the uterus was immaterial. On the other hand, Pfister (1901) observed a reflex influence of the mammary glands upon the genital apparatus, excitation of the former causing secretion in the genital organs, return of menstruation, and so on.

All these investigations into the innervation of the mammary gland await confirmation and development by further research.

Ribbert (1898) made a number of experiments with the object of investigating the development of the mammary gland during pregnancy.

According to this author the development of the gland is not controlled by the nervous system, because in a case of transplantation of a mamma from a virgin rabbit into a pregnant one, the transplanted gland developed mammary functions.

These results, according to most authors, prove definitely that glandular development occurs by a chemical stimulus or *hormone* carried in the blood. But it must be remembered that Ribbert alone, and in one single case, obtained a positive result; all the control researches have so far proved negative.

By another method Lane-Claypon and Starling arrived at a theory in accordance with that of Ribbert, in which they not only assume generally, with him, that the blood during pregnancy contains the hormone or stimulating substance for the development of the mammary gland, but claim to have located the origin of this substance. They state that the foetus itself produces specific hormones which stimulate the development of the mammary gland. They find that repeated injections of extract from the foetus (a large number, over 100, being employed) lead to development of the mammary gland in virgin rabbits. C. Foà (1908) repeated these experiments, using foetal extract from different species, particularly bovine, and arrived at the same results. The hormones which develop the mammary gland are not specific for the species to which the foetus belongs; their action, as was noted by Camus, Gley (1902), and others, is similar to that of the hormones of the pancreatic and enteric secretion (*secretin*).

We cannot, however, admit that these results have the decisive importance attributed to them in favour of the theory of chemical co-ordination. Even admitting that extract of foetus, injected artificially in very large amounts, is able to activate the development of the mammary gland, we are still far from any direct proof that the foetus really gives off the supposed specific hormones to the maternal blood, during physiological pregnancy.

We have already pointed out (p. 90) in regard to the pancreatic and intestinal secretions that the theory of *secretin* as a specific

excitant of those glands, and the English authors' theory of "chemical co-ordination," generally speaking, are ill-founded. Certain experiments in our own laboratory deserve mention, in relation to the point we are now discussing, because the method of experiment lends itself to the solution of this problem. U. Lombroso in collaboration with Bolaffio employed the method of *parabiosis* (*supra*, p. 102) between virgin and pregnant rabbits. The animals experimented on only survived at most for nine days; but no trace of modification was ever detected in the mammary gland of virgin rabbits, although the iodine test proved that active exchanges took place between the two animals. It should be remembered in judging the negative value of these results in regard to the hormone problem, that in the virgin rabbit the mamma is reduced to six or seven simple tubules, and that it exhibits profound modifications even by the third day of pregnancy.

In rats, which longer survive the effects of parabiosis, no appreciable modifications could be seen in the virgin mamma, although the time was greatly extended.

An observation of Morpurgo's on a parabiotic couple of mixed sex supports these negative results. The female became pregnant after four months' parabiosis, was delivered at term, and suckled her young, but there was no sign of lactation in the male.

All these observations (while still insufficient) militate not merely against the theory that the foetus discharges a specific substance into the maternal blood by which the development of the mammary gland is stimulated, but, generally speaking, against the theory that development is activated by any chemical stimulus circulating in the blood.

XI. The much-debated question of whether the human skin is capable of *absorption* must not be omitted from this chapter. While apparently lending itself to easy solution by experiment, it is on the contrary a difficult problem, judging from the amount of literature on the subject, and the contradictory results arrived at by different workers.

With the exception, as we have seen, of the palms of the hands and soles of the feet, which have no sebaceous glands, the whole surface of the body is lubricated with the sebum secreted by these glands, owing to which the horny layer of the epidermis is rendered highly impermeable to water even with prolonged immersion. After a hot bath of 30-60 minutes, the epidermis of the palm and sole alone is visibly softened, showing that the skin is unsuited for absorption of water or substances dissolved in it.

The method of weighing the subject before and after total immersion in a bath is obviously inadequate evidence for this statement. In fact, the experiments by this method of Jamin and De Laurés (1872) gave conflicting results; sometimes there was

increase, sometimes decrease, sometimes no variation in weight. These differences are readily explained by the numerous sources of error inherent in the method :—

(*a*) Imperfect sensibility of the balance used for weighing the subject; (*b*) difficulty of avoiding absorption by small accidental lesions of the epidermis and by the mucous surfaces of the genital organs; (*c*) practical impossibility of estimating the amount of fluid which is not absorbed but imbibed by the superficial layers of the epidermis, particularly the skin of the palm and sole, which is not protected by sebum; (*d*) impossibility of estimating the losses from the body during the bath, by respiratory gas-exchanges and cutaneous transpiration, and by drying after the bath from the rubbing off of the epidermis.

More probable results, which approximate better with the facts, are obtained if, instead of weighing, the method of changes in the volume of the water is adopted, as shown by the displacement of the level in a capillary tube, communicating with the closed vessel in which a part only of the body is immersed. Fleischer (1877) employed the glass cylinder of Mosso's plethysmograph (which has a capillary manometer), and kept his forearm immersed in the water for three hours, but found no absorption by the skin.

In order to test whether substances soluble in water were absorbed by the skin, compounds which could be chemically detected in small quantities in the urine were employed.

This chemical method is certainly the most delicate and the most easily applied in the study of absorption, but integrity of the epidermis in the part of the body experimented on is essential, and substances which have an alterative effect on the skin must be excluded.

The majority of the experiments by this method prove definitely that when the epidermis is intact it lets through neither water nor substances dissolved in it, provided these really have no chemical action on the epidermis. Braune (1856), on steeping his feet in solutions of potassium iodide, potassium iodate, iodic acid, was unable subsequently to detect iodine in the urine. Parisot (1863), besides baths of potassium iodide and ferrocyanide solution, also tried infusions of belladonna, digitalis, and rhubarb, repeating the experiment twice a day for three to eight days, without finding any absorption. Hüfner (1880), after soaking his feet in solution of lithium chloride, looked for lithium without success in the urine by the spectroscopic method. These negative results were confirmed by Winternitz (1891), who used aqueous solutions of 10-15 per cent lithium chloride. Lastly, Fubini and Pierini (1893) found no absorption by the skin with aqueous solutions of 3 per cent potassium ferrocyanide, 2 per cent sodium santonate, 5 per cent sodium salicylate, 5 per cent potassium iodide, 2 per cent lithium benzoate.

If, instead of aqueous solutions, fluids capable of softening and dissolving the sebum of the epidermis, *e.g.* ether and alcohol (not chloroform which irritates the skin), are employed, a certain amount of absorption can easily be detected, more with ether which is a better solvent of fat, less with alcohol which dissolves fat less easily. Winternitz (1891) demonstrated the presence of lithium in urine by the spectroscope, after steeping the skin of the forearm for three and a half hours in an ethereal solution of lithium chloride, to which a little alcohol had been added; with purely alcoholic solutions the results were negative. After previously smearing the skin with ether, he found a slight absorption of lithium, after keeping the forearm nine hours in a watery solution of lithium salts. This experiment proves that it is the cutaneous sebum which makes the skin refractory to absorption.

By means of the *cataphoretic* action of the galvanic current (also known as *electrical endosmosis*), it is possible to drive the aqueous solutions through the skin, and to produce absorption by the blood and lymph paths (Pascheles, 1895). The amount of substance absorbed increases with the strength of current, but beyond a few milliamperes the galvanic current damages the skin. This method is therefore of little use in therapeutics.

It has often been debated whether volatile substances, *e.g.* tincture of iodine, applied to the skin can be absorbed by it. The positive data of Röhrig are contradicted by the negative results of Fleischer, who took every precaution to exclude absorption of iodine by the respiratory passages. Mesnil (1894), on keeping his arm for thirty-two hours in a glass cylinder filled with iodine vapour, observed no absorption. On the other hand, Sciolla (1893), Linossier and Lannois (1894), Guinard and Stoorbe (1894), obtained absorption of guaiacol when applied to the skin.

Oily substances and unguents applied to the skin are not absorbed (Baschkis, Obermayer, Fleischer, Fubini and Pierini). But if the skin be rubbed hard for a long time with these unguents, so that they are mechanically pressed into the hair follicles, gland ducts and intercellular spaces of the epidermis, absorption not only of the dissolved substances but also of the suspended corpuscles can be obtained. From a therapeutic point of view the most important fact is the absorption of mercurial salves with friction (Kulzer, Neumann, Fürbringer, and others). Voit demonstrated that mercury in the form of metal spherules can be forced into the human corpse, by energetic rubbing, not only between the layers of the epidermis, but also into the corium. But in the living subject, the mercury on coming in contact with the sodium chloride of the sweat is probably converted into calomel, and partially into sublimate, and absorbed in that form.

The results of experiments on cutaneous absorption in mammals

are conflicting. Generally speaking, it may be said that the thinner, less horny, and more vascular their skin, the better it is adapted to absorption. Forlanini (1868) succeeded in poisoning rabbits by simply treating the skin with aqueous solutions of strychnine acidified with acetic acid. Other workers, however, obtained negative results on rats and guinea-pigs (Wittich, Fubini and Pierini).

Signora Traube-Mengarini (1890) made a series of experiments on the skin of dogs and man by painting the skin of the abdomen (which is almost hairless) and the mammae with solutions of borax carmine, of potassium ferrocyanide, and with medicinal iodine for several days in succession. For human skin, a boy was painted, once only, between the shoulders with tincture of iodine. The animals were killed, and a bit of the boy's skin removed, after 45 minutes, when the solutions applied to the skin were sought for under the microscope—the carmine being fixed with sublimate, the ferrocyanide with ferric chloride (with which it forms Berlin blue), and fresh sections being made of the skin treated with iodine by the freezing microtome.

The following results were obtained: (*a*) the carmine had only stained the superficial layer of the epidermis; (*b*) the potassium ferrocyanide had penetrated beyond the stratum corneum into the superficial cells of the stratum granulosum; (*c*) the iodine, on the contrary, had penetrated all the layers of the epidermis and corium, and had been absorbed by the lymph.

To interpret this penetration of iodine Signora Traube-Mengarini concluded that it alters the skin chemically by formation of undefined compounds, particularly with the cutaneous fat. It is known from previous experiments by Fleischer, Waller, and Winternitz, that the absorption of various soluble substances, in solutions of ether or chloroform, takes place more readily and constantly in the skin of certain mammals than in that of man.

Cataphoresis of soluble substances also occurs more easily in these animals than in man.

In the skin of frogs the conditions for absorption are still more favourable, because there is no sebum. It is constantly moist, and highly vascular. The fact observed by Reid (1890) is interesting to the effect that diffusion through living frog's skin takes place more easily from without inwards, while in dead skin the exchanges occur more readily in the opposite direction. This proves that the absorption of which frog's skin is normally capable is not a purely osmotic phenomenon, independent of the vitality of the cells of which it is composed.

According to Pesci and Andres (1901-2), both the living skin of the frog and that of the higher vertebrates and of man behaves as a semi-permeable membrane, which permits water to leave or enter, according to the hyper- or hypo-tonicity of the solutions,

but not the substances which are dissolved in it. The skin of the frog when altered chemically or by necrobiosis is, on the contrary, more or less permeable to them.

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