THE ANGIOLOGY, ANGIOGENESIS, AND ORGANOGENESIS OF THE SUBMAXILLARY GLAND.

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WITH 14 FIGURES.

In a preliminary note[1] on the blood-vessels of the submaxillary gland and their development, the writer outlined briefly the angiogenesis of the circulation, together with its arrangement and distribution in the adult organ. At the same time, attention was called to certain researches of Thoma concerning the principles involved in the development of blood-vessels and their application to the evolution of the circulation in highly organized glands. The following extracts from this paper may emphasize these points again briefly.

"The well-known researches of Thoma on the histogenesis of the vascular system offer an explanation of some of the phenomena of vascular development, particularly to the relation between the velocity of the blood current and the size of the vessel that conducts it. The question of the ancestry of arteries and veins was solved by Thoma, who showed in chick embryos that originally they were always simple capillaries. Their subsequent transformation, according to this author, was due to their fortuitous location with reference to the primitive aortae, and the venous ostia of the heart. It has been shown that these facts apply to the vascular development in mammals as well as the chick, and for vascular systems developing in three dimensions, as well as those found in the area vasculosa where the vessels grow in two directions only. In considering the problems of angiogenesis in mammals, it is apparent that Thoma's histo-mechanical principles do not suffice to explain all the facts, nor do they even entirely accord with them. The statement that a new growth of vessels follows a rise of blood pressure in the capillary area must be considered only as an hypothesis and not a demonstrated fact, for this would make the vascular system the stimulus to the development of new cells, while there is considerable probability that it is the new cells

[1] Journal of Medical Research, Vol. VII, No. 4.

which give the stimulus for the growth of new capillaries. It must be obvious that the principal factors that govern organic growth are resident in the cells rather than in the blood-vessels, as is indicated by their behavior in the embryo before the vascular system is laid down. We have still much to learn concerning the factors that arrest the growth of organs when they reach the adult type, but there is little doubt that these phenomena are expressions of cellular rather than vascular activity, since the vascular system maintains far beyond the usual period of growth, its power of progressive development. It is, so to speak, always in a state of unstable equilibrium, in which both progressive and regressive changes are possible. Certain facts in the development of the blood-vessels of organs have already been demonstrated, the most important of which is that the intrinsic blood supply of organs usually marks out the paths along which the units of structure that compose it have developed.[2] And by following the gradual increase in complexity through a series of injected embryos, the succeeding changes from the simple embryonic to the adult form can be easily demonstrated. It is important to trace these changes not only for the light they shed on the development of the vascular system, but because many obscure features in the structure of organs are elucidated when the mechanics of their development are known.

Excepting certain radical modifications that take place at the time when the embryo ceases to receive its nourishment from the maternal blood sinuses and independently undertakes the aëration of its own blood, it has been shown that the conditions of the systemic circulation in embryos at term approximate very closely that in adult life. At the same time considerably less differentiation occurs in the intrinsic circulation of the individual organs than in the larger vessels of the general circulation. At the time of birth the structure of most organs is well developed, and the changes which take place are usually quantitative rather than qualitative. Accordingly, the material for this research was obtained from the submaxillary gland of injected embryo pigs, and the results were subsequently shown to conform to the conditions found in the glands of dogs and human beings.

METHODS.

The technique for the injection of embryos used in the study of the angiogenesis of the submaxillary has been described in detail in another

[2] Flint, Welch, Festschrift, 1900, and Reports of the Johns Hopkins Hospital, Vol. IX., 1900.

place.[3] In working up the blood supply of the submaxillary two of the simpler methods have been found especially serviceable, namely, the use of silver nitrate and a saturated aqueous solution of Prussian blue. The chief value of the silver nitrate method lies in the fact that by far a greater proportion of the silver is precipitated in the arteries, giving by a single injection a natural differentiation between them and the veins. Moreover, the endothelial lining of the blood-vessels is beautifully demonstrated by this method. A $\frac{3}{4}$ to 1 per cent solution gives good results. The only disadvantage lies in a tendency for this solution to extravasate somewhat more than the Prussian blue, but there is compensation in the fact that silver injections are usually incomplete. These give clearer pictures of the blood supply in the developing organ, because the details are not obscured by a general filling of the entire capillary system. Double injections are possible and serviceable in the embryos where it is necessary to differentiate arteries and veins, but in the submaxillary, at least, most of the differences between the arterial and venous systems can be clearly shown in the silver nitrate specimens. (Figures 2 to 8.) For the blood supply of the adult organ Prussian blue and lamp black gelatin or a carmine mass followed by a suspension of lamp black in gelatin gives very sharp pictures. The circulation in the adult organ, however, differs in no marked feature from that of the pig at birth, except quantitatively. For a study of the relationship between blood-vessels and cells, sections made by the routine methods demonstrate clearly these points. And, in following the development of the cellular elements of the ducts and alveoli, Mallory's aniline blue connective tissue stain is of great value. This stain seems to be peculiarly adapted to the use of the submaxillary because it brings out in sharp relief differences between mucous and parietal cells, and stains as well the duct epithelium. Moreover, it differentiates clearly between connective tissue fibers and cell elements.

ANGIOLOGY.

In man, the A. submaxillaris is derived from the A. maxillaris externa, which runs in a small sulcus on the surface of the glandula submaxillaris or directly through its substance as it mounts up over the lower border of the ramus of the mandible. Occasionally the A. submentalis contributes submaxillary branches that enter the organ. The Vv. submaxillares sometimes empty into the V. submentalis, but usually are tributaries of the V. facialis communis. In man the arteries do not

[3] Flint, Welch, Festschrift, and Johns Hopkins Hospital Reports, Vol. IX.

enter the hilus of the organ with the duct, but join the latter a short distance after it penetrates the gland and take up immediately the close relations which are observed throughout the developmental and adult periods of life. The veins follow the arteries throughout their course. In the pig, however, the duct is joined by the blood-vessels almost immediately after their passage through the hilus, even before branches of the first order are given off. The relationship between the duct and vascular systems is absolutely constant and dates from the earliest embryonic history of the organ.

Inasmuch as the nomenclature of the blood-vessels is taken from that of the ducts, a short account of the latter may simplify the description of the vascular system. In pigs, the distribution of the ducts is not unlike that in man, although in the former it is somewhat more regular. In man the ductus submaxillaris enters the hilus of the gland and almost immediately breaks up into branches of the first order. These run a very short distance and then terminate in a secondary system, forming interlobular ducts that ramify extensively throughout the gland. From the latter are derived a set of sublobular ducts. These divide once or twice and then terminate in lobular ducts which, entering the hilus of the ultimate lobules, at once exhaust themselves in the extensive ramifications that form the intralobular ducts and radiate from the hilus to the periphery of the lobule. They terminate in a short duct of slightly smaller caliber termed the intercalary portion connecting them directly with the secreting alveoli of the gland. The intercalary ducts are usually considered as having a much smaller caliber than the ducts of the next lower order. This, however, is not the case, as their lumen, as shown by corrosion preparations, is only slightly smaller than those just preceding. This mistaken impression probably arose from the consideration of the ducts when clothed with their epithelium. The total diameter of the intermediate ducts is much smaller, because the intralobular ducts on one side are lined with columnar epithelium and the alveoli have either high mucous or serous cells on the other, while the intercalated portions of the duct between them have only flattened epithelial cells for their walls. Running in the thick processes of fasciculated connective tissue that form the interlobular spaces, are the blood-vessels that always accompany the ducts. In one way, the interlobular spaces of the salivary glands have a certain resemblance to those of the liver except that the former have two veins instead of the single branch of the portal system found in the hepatic interspaces.

In describing the blood-vessels of the adult organ, it is convenient to divide them into three systems:

1. The glandular circulation from the A. submaxillaris to the alveolar plexus and back to the Vv. submaxillaris.
2. The circulation about the ducts.
3. Circulation in the capsule and septa.

The Glandular Circulation.

The submaxillary artery in pigs at the hilus or point of entrance is separated by a short distance from the ductus submaxillaris. The two rapidly converge, however, and, as a rule, meet just before the point where ducts of the primary order are found. Before joining the duct, the artery may give off one or two short branches that enter adjacent lobules, as well as a few branches to the large mass of connective tissue which enters the organ at the hilus. The ducts of the first order are accompanied by the Aa. principales. These now run in the connective tissue of the larger interspaces at a short distance from the lumen of the duct. There is no marked tortuosity of the main artery or its principal branches, but, at the different angles where the chief ducts are given off, the arteries sometimes wind partly around them or may take a slightly spiral course about the duct. As a rule, however, while there is a slight wavy irregularity in the course of these vessels, a complete spiral arrangement about the ducts is rarely observed. From the principal branches of the main artery the Aa. interlobulares are derived, accompanying ducts of the same order in the interlobular interspaces. From these branches the blood is distributed in radiating directions throughout the gland. They are longer than blood-vessels of any other order. In their course they may divide once or twice and finally exhaust themselves in lateral branching in the sublobular arteries which run with the sublobular ducts in the center of the primitive lobules. Arteries of this order may in thick injected specimens be easily recognized running in the center of the groups of ultimate lobules bounded by the secondary septa. They divide three or four times with the sublobular ducts and then exhaust themselves in the Aa. lobulares, each one of which enters a primitive lobule at its hilus together with the lobular duct. Once within the limiting membrane of the lobule, the ramification is more abrupt and more marked. The intralobular branches of the A. lobularis radiate from the hilus toward the periphery of the lobule, divide with and accompany the intralobular ducts. The terminal divisions of the intralobular arteries run with the intercalary ducts and divide under the clusters of alveoli into the alveolar capillary plexus. The capillaries mount up over the alveoli external to the reticulated basement membrane and anastomose with the capillary plexus

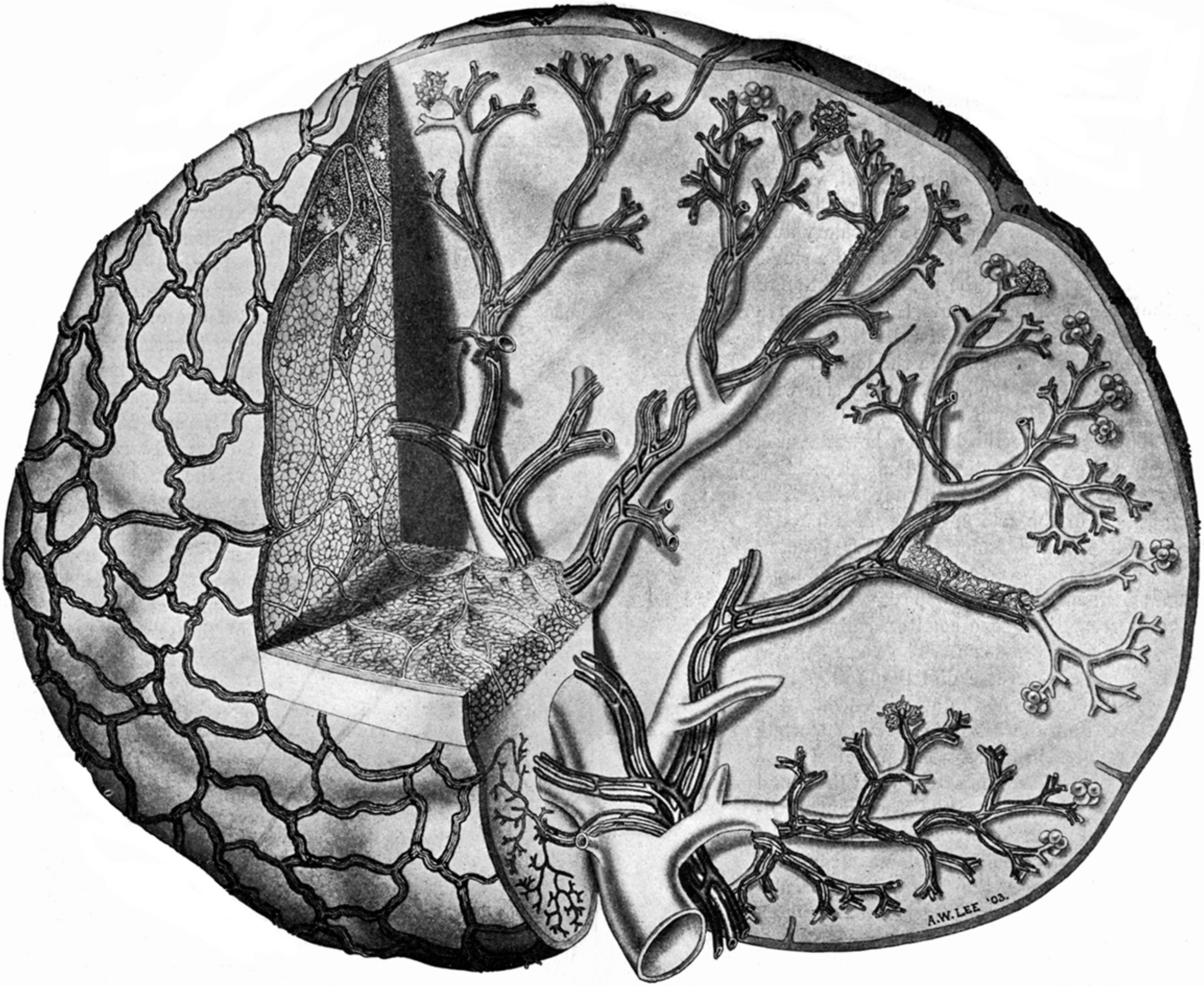

FIG. 1. Diagrammatic reconstruction of the submaxillary gland. Magnified 12 diameters. The reconstruction shows the distribution of the ducts and their termination in the alveoli, together with the arrangement of the accompanying blood-vessels. For the sake of clearness in drawing, there is some discrepancy between the relative size of the blood-vessels and ducts. The blood supply is taken from a pig at birth where the type of circulation is so developed that it differs in no way from that of the adult. The histological portion and the digested section are from the human submaxillary, while the piece digestion is from the submaxillary of the dog. The limiting membranes of these two tissues have simply been forced to meet in order to show their relationship by the different methods. Otherwise no violence has been done to the original specimens. (J. M. Flint, *Angiology of submaxillary gland.*)

of adjacent alveolar groups. The meshes are small and regular, and occupy three dimensions. This plexus has anastomoses extending throughout the lobule, but terminates on all sides at the membrana limitans. Each lobule has, therefore, with certain exceptions that will be considered later, an independent circulation.

Beginning in small radicals around the base of the alveoli, venules are formed through the coalescence of capillaries. These rapidly converge to a point near the terminal arterioles about the intercalary duct to form venae terminales. The veins are short and there is but a single one accompanying each terminal arteriole. At the point of junction of several intercalary ducts, the accompanying terminal veins through their confluence form the intralobular veins which collect the blood from different portions of the lobule and terminate in the lobular vein. This vessel makes its exit from the lobule at the hilus, side by side with the lobular artery. There is no reduplication of the veins of the intralobular system. As soon as the veins leave the lobules, however, and enter the sublobular interspaces, the venous system is doubled, yielding venae comites to each successive division of the A. submaxillaris. The sublobular veins parallel the course of the artery, giving off numerous anastomotic branches which run over and under the artery forming oblong meshes. It is not uncommon, however, to have the veins separate and pass around the duct and then join on the opposite side, or else have anastomotic branches pass from the venae comites, embrace the duct, and finally join the main veins lower down. The venæ comites with their blood current flowing in the reverse direction follow in a convergent manner the previous divergence of the arteries. Thus the sublobular veins unite to form those of the interlobular system, while these, in turn, join to make the venae principales. The principal veins part with the ducts at the same point where the artery joins them and leave the gland along with the A. submaxillaris as the Venae submaxillares. These usually empty into the vena facialis communis. In the general glandular circulation we find two vascular units, one, a complete terminal system, forming, in Ludwig's sense, the true unit of circulation, that is to say, blood-vessels supplying a group of structures which have definite relations throughout the organ with the general framework. These form, in this way, the ultimate indivisible complete unit of structure of which the organ is built up. Such a unit in the submaxillary gland would be represented by the lobule and the whole organ is simply formed of a series of these units. Another vascular unit could be formed of the terminal arteries. These break up in the alveolar capillary plexus which reunite into small venule radicals and empty into the terminal vein. Each lobule is composed of a series of such units. Even another larger unit might be constructed from the circulation embraced between the sublobular artery and the sublobular vein, supplying groups of lobules that have definite relations with the secondary septa. The ultimate lobular unit might well be considered the least, while the primitive lobule would be the greatest common structural divisor of the submaxillary gland. The smaller terminal units are comparable to the conditions of the circulation in such glands as the stomach and adrenal where cell complexes having definite relations with larger bands of connective tissue do not exist.

CIRCULATION ABOUT THE DUCTS.

The ductus submaxillaris is embraced by a rich supply of arteries derived from the Aa. principales, branches of which run in a recurrent

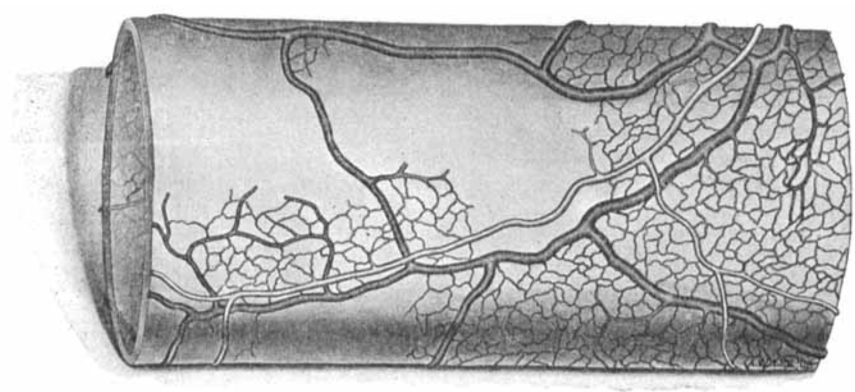

FIG. 2. Blood-vessels about the ductus submaxillaris in a pig 26 centimeters long showing the arterial, venous and capillary plexuses: arteries light, veins and capillaries dark.

direction along the walls of the ducts as far as the hilus. These arteries may anastomose with some frequency (Fig. 2), although the plexus formed by them is not a rich one. They are distributed around the surface of the duct and give off terminal branches which sink to the region just around the base of the duct epithelium and terminate in a capillary plexus formed of small, irregular, polygonal meshes. Through the confluence of the capillaries, numerous venules are derived which empty into large veins forming an irregular venous plexus about the duct. The caliber of these veins is larger than the arteries, and the meshes formed by them are irregular and polygonal. The venous plexus lies below the arterial and from a convergence of its elements larger veins are formed that terminate in the venae principales. In ducts of the interlobular order there is the same arrangement of the blood-vessels around the ducts, except that the elements of the venous plexus are not so large nor is the connection between them so frequent. As one progresses upward from the main ductus submaxillaris to the lobular ducts, there is a gradual simplifying of the duct circulation, until, in the ducts of the sublobular order, we have afferent arteries derived from the Aa. sublobulares running part way around the duct, breaking up into capillaries which reunite in small anastomosing veins, that pass around the walls of the ducts to terminate in the venae comites. Alternations of artery and veins in these instances are not uncommon and arterioles and veins are in all cases above the capillary plexus. Fig. 3, which shows the circulation in a duct of this order, gives the relations beautifully. It should be noted, however, that one of the venae comites has been re-

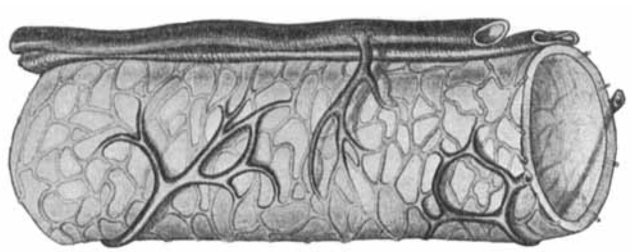

FIG. 3. Blood-vessels about a sublobular duct. The artery is the upper of the two vessels. One of the venae comites has been left out for the sake of clearness.

moved for the sake of clearness. The lobular and intralobular ducts show a still simpler form of duct circulation. Small arterioles almost immediately break up into capillaries when they are derived from the lobular or intralobular arteries. These quickly reunite again into veins that terminate into venules which empty directly into intralobular veins. This gradual simplification of the circulation about the ducts gives a characteristic demonstration of their age, and, in the angiogenesis of the submaxillary circulation, parallels can be drawn between the circulation about the ducts at different periods of embryonic life and the conditions found in the vascular supply of ducts of the different orders. In the very earliest stages the circulation of the main ductus submaxillaris is much like that about the adult lobular duct. At a somewhat later stage is approximates that of the duct of the sublobular order, while still later there is a similarity to that of the interlobular system, and finally the highest development is attained with the complete formation of the arterial and venous plexuses which embrace the main ductus submaxillaris in the adult. It is very easy, moreover, to follow in a single, well-injected gland the evolution of the duct circulation from that of the lobular type to that which embraces the main duct. The small arterioles break up into capillaries and reunite into small venules that finally terminate in the accompanying veins. These vascular elements enlarge so that the arteries branch and come to lie upon the capillary plexus and the isolated veins receive a few anastomoses from each other. With the growth of the duct and the lengthening of the artery and its ramifications, the venules which are last formed from capillaries come to lie under the arterial but over the capillary system, and thus we have the three superimposed series of vessels noted about the ducts of the larger order. Throughout the course of the successive divisions of the submaxillary arteries, branches are given off which supply the framework of the interspace. These vessels are extremely irregular and after breaking up into a capillary system that ramifies around the fascicles of connective tissue, venules are formed emptying into the venae comites at irregular intervals. The circulation to the sympathetic ganglia buried in the interspaces also has a similar derivation.

FIG. 4. Circulation about an intralobular duct. The artery is the upper vessel of the two.

CIRCULATION OF THE CAPSULE AND SEPTA.

Blood-vessels that run to the primary and secondary septa are derived from the Aa. intralobulares. Branches from vessels of the latter type perforate the limiting membrane and almost immediately break up into a loose irregular plexus, the venules from which unite into a single vein that accompanies the septal artery and flows back into the lobular circulation. The blood-vessels in the capsule are derived from two sources, in part from the arteries and veins in the periglandular connective tissue which run on the surface of the connective tissue envelope of the organ in the form of a very irregular plexus of polygonal spaces. These vessels are very small. Frequently capsular branches from the lobular arteries perforate the capsule and join the capsular plexus. These capsular arteries are accompanied by capsular veins. When septal arteries arise from lobules at a point near the capsule, they may pass from the septa and finally unite with the capsular plexus. With these two exceptions, the circulation in each lobule seems to be complete and independent, save in those cases where a lobule of the first order is not completely subdivided into ultimate lobules, so that at their bases anastomoses may occur between the alveolar capillaries of the peripheral portions of adjacent ultimate lobules.

ANGIOGENSIS.

Chievitz[4] has shown that the submaxillary gland develops as a bud from the buccal epithelium. This grows backward toward the angle of the mandible and there begins a dendronal branching that marks the anlage of the submaxillary gland. Owing to the difficulty in injecting very early embryos, a study of the relationship between vessels and cells can best be made in stained sections. The submaxillary gland is shown in a simple form in pigs represented by about 3½ centimeters, nape-breech measurement. At this time the branching column of cells is accompanied by an artery that enters with the duct at the simple hilus and lies close to the developing basement membranes. Capillaries forming an irregular plexus can be seen here and there about the ramifications of the simple tube forming the ductus submaxillaris. The arterioles, venules and capillaries at this stage are usually separated from the reticulated basement membranes by a short intervening mass of syncytium, but as the ducts increase in size this distance is diminished. These relations can be found in stained sections from the glands of pigs 4½ to 6 centimeters in length. When, however, the pig reaches an age represented by 8½ centimeters, the injection of the gland becomes a simple matter and the description can be taken up from injected organs that are cut in half and studied under the stereoscopic microscope. This gives not only the relations of the vessels throughout their course, but also enables the observer to follow them in three dimensions. At this time the gland is reniform, and the vascular supply is comparatively rich. Since the relationship between arteries, veins and ducts established in pigs of earlier age always persists, the course of the ducts accordingly may be determined by the course of the blood-vessels. Indeed, in a pig of this age the duct and its branches are represented negatively, making it possible to follow them nearly as well as though they were either stained or injected. At this period the artery enters the primitive organ at the hilus and branches with the duct. This is the simple stage of the arteria submaxillaris. In its course the artery gives off small branches which almost immediately break up into capillaries. These run around the column of cells and empty at once into the vein accompanying the afferent vessel. The meshwork formed by this capillary plexus is small

[4] Chievitz, Arch. f. Anat. u. Phys. Anat. Abth., 1885.

and irregular and the vessels composing it are often unequal in caliber. Following the branching ducts, the A. submaxillaris divides with each successive ramification, giving off still the collateral arterioles that embrace the walls of the ducts. The ramification at this time extends to about four orders and the arterioles terminate in a capillary plexus embracing the terminal buds or swellings that form the apices of the growing ducts. These vary in number from four to seven and are distinctly seen as clear spaces sharply demarcated by the embracing capillary plexus. At this age the terminal capillary system surrounding each group of primitive alveoli are entirely independent and have as yet no anastomoses with each other. The blood, derived from the terminal arterioles, passes through the capillary plexus and is gathered again into venules which accompany the terminal artery along the walls of the duct from which the buds have grown, but the alveolar plexus is finer than that around the ducts. Already at this stage, it is possible to see that the blood supply of the entire gland now looks like the vascular distribution in a single lobule of the adult organ. Attention has already been called to the analogy between the two, so the four ramifications of the A. submaxillaris; Aa. principales, Aa. interlobulares, Aa. sublobulares, Aa. lobulares are like the divisions of the intralobular arteries in the adult. Fig. 5 represents half of an injected gland at this stage, photographed so as to obtain a stereoscopic effect. The branching of the ducts is shown by the course of the blood-vessels and the irregular plexus formed by the latter upon the former is clearly visible. The alveolar plexus, however, does not stand out clearly in this specimen.

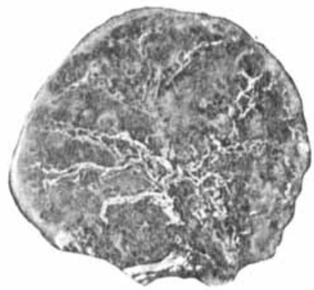

FIG. 5. Submaxillary gland of pig's embryo 8 centimeters long, injected with silver nitrate and cut in half. X 10 diameters. The simple arterioles and capillary plexus around the growing column of cells is distinctly shown. In points a few capillaries about the terminal buds may be made out.

In a pig 12 centimeters in length the ramification has proceeded to higher orders, the ducts as shown by the embracing meshwork have increased in size and the plexus embracing them is more highly differentiated. Small lateral arterioles are now given off from the main arteries which divide into capillaries. These reunite into little venules emptying into the main venae comites. In a pig 8 centimeters in length, the veins are duplicated as high as the third order, but have not yet taken up their course in such close relation to the artery. In the next stage, however, the veins follow more closely the course of the artery and the capillary plexus extends around the duct from the point where they are situated. Each successive ramification remains practically a terminal system, although occasional anastomoses are found running from the vessels accompanying one branch of the duct to those about another. These communications, however, are usually venous and not arterial, although connections between vessels of the latter type are occasionally found. The capillary plexus embracing the terminal buds is now much finer and more definitely organized than in the earlier stages. Arterioles run along with the terminal ducts and suddenly break up into an irregular, fine plexus composed of small polygonal meshes which mount up

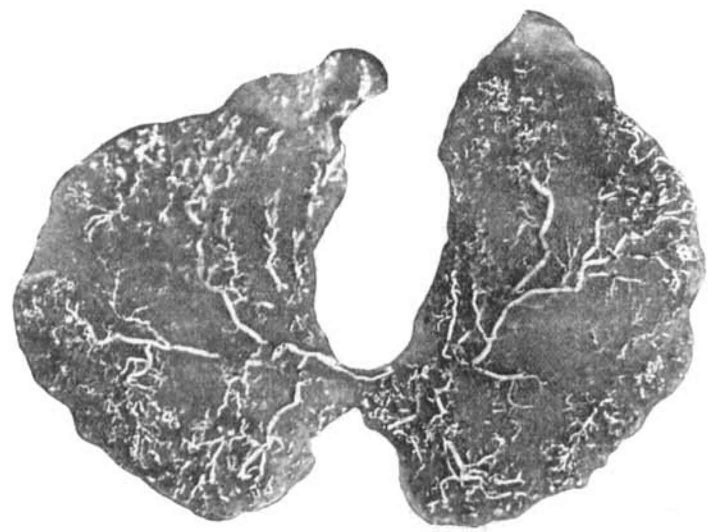

FIG. 6. Submaxillary gland of pig's embryo 12 centimeters long. Same method of preparation as Fig. 5. × 10 diameters. In this specimen only the arteries accompanying the ducts and the terminal alveolar plexus are visible.

over the summit of the alveoli and are collected into venules which return to the point of junction of the ducts and alveoli, and there unite into little terminal veins that accompany the ultimate arterioles. At this period an occasional branch from one of the terminal arteries passes out from between the buds and joins the small plexus that is being formed on the capsule of the gland. As yet septal arteries are not found. Fig. 6 shows an injected silver preparation of a pig at this stage. Except in certain points the mass has not passed over into the veins, for the most part leaving the arteries and capillary plexus around the alveoli the single visible portion of the vascular system. The greater regularity of the alveolar plexus is now clearly shown.

In a pig 18 centimeters long the main submaxillary vessels and submaxillary duct are now somewhat separated. Arteries and veins are distinctly seen in the plexus embracing the ductus submaxillaris. These are derived from its vasa comites. The ramification has not increased so much in number of orders as in the number of branches. The arteries still preserve their individuality but a duplication of veins is observed as ducts increase in size. Here and there one finds not infrequently a vein looping around the arteries and even embracing the ducts. At this period vessels of the lobular type have just been formed and the capillary plexus around the alveoli is very sharp and distinct. Anastomoses have been established between the capillary systems of adjacent alveolar groups. This forms for the first time in the history of the organ the final arrangement of the circulation in the lobule, although representing it in a very simple form. Here and there the connections between the alveolar circulation and the circulation of the capsule are seen, while, for the first time, perforating vessels leave the lobules and ramify in septa of the first and second orders. These appear best in Prussian blue specimens where the injection is complete. Compared with other organs, the amount of syncytium from which the fibrillar and cellular parts of the submaxillary framework are derived is proportionately excessive to the quantity of cells forming the primitive ducts which are destined to yield all of the epithelial elements of the gland. In all of the early stages, the blood-vessels are confined to the immediate neighborhood of the ducts, while the syncytium has none. As this syncytium is transformed into strands and septa, they receive a vascular supply of their own, which is not well shown until the pig reaches an age indicated by a nape-breech measurement of 18 centimeters. The interspaces have now attained a definite size and blood-vessels derived from the vasa comites of the main ducts leave the plexus and ramify in the substance of the connective tissue, here and there giving off arteries to supply the

FIG. 7. Submaxillary gland of pig's embryo 18 centimeters long. Same method of preparation and magnification as Fig. 5. The arteries and venae comites are distinctly seen. These may follow as far as the terminal arterioles which are now forming those of the lobular type. Little capillary clusters with their arterioles and venules represent the secondary or ultimate lobules. The plexus about the ducts is not injected.

sympathetic ganglia that are embedded in the fibrous tissue forming the main interspaces. Even at this period there is no connection between the circulation in one lobule and that of its neighbor, save occasionally at the lobular hilus where lobules of the first order have been incompletely separated by membranae limitantes into ultimate lobules. Fig. 7 shows an incomplete silver injection of the circulation at this stage. The arteries are seen as definite round tubes while the veins in the photograph appear collapsed. Owing to the lack of depth, many of the finer relationships of the blood-vessels are lost. The alveolar plexuses are clearly shown, together with the beginning of the demarcation of the ultimate lobules by the branches of the lobular arteries.

In a pig 22 centimeters long the arrangement of the blood-vessels has not been altered in any marked degree. Each of the six divisions of the branches of the arteria submaxillaris has been formed. The growth subsequent to this stage, therefore, lies more in the differentiation and complexity of the lobule rather than in the general plan of the organ, a fact which is confirmed by the study of stained specimens. The plexus about the main submaxillary duct as it enters the gland becomes more complex. Branches derived from the main artery anastomose and ramify a short distance, and then break up into a dense capillary plexus formed by irregular polygonal spaces which entirely embrace the duct, lying just external to the basement membrane. Venous radicals formed in this plexus unite and flow into larger units which form an irregular venous plexus lying on top of the capillary plexus. Emissary veins from this plexus empty into the venae comites. The double plexus can now be followed as far as the interlobular ducts, where the two layers of vessels are replaced by one. In the development of the circulation the growth of the vessels like the growth of the ducts has been entirely centrifugal.[5] If one takes a thick tangential section of the gland and views it with the stereoscopic microscope from above, the outlines of the lobules are clearly shown and the branching and radiating vessels are always found in the center looking much like the branches of a small tree viewed from above. At birth the relations of the last stage remain

[5] In another communication, Archiv für Anat. u. Phys. Anat. Abth., 1903, the writer has called attention to the centrifugal growth of the ducts of the submaxillary with reference to the formation of the lobes and lobules of the first and second orders. These structures always occupy the center of the lobes and the center of the lobules, from which point they radiate out towards the capsule or the limiting membranes. The entire arrangement of the frame-work of the submaxillary depends, in fact, upon physical factors involved in successive action of this principle of centrifugal growth upon the fibrils that compose the supporting tissue of the organ.

practically unchanged, save in the enlargement and differentiation of the lobules brought about by an increase in the ramifications of the intralobular ducts and consequent increase in the number of alveoli. *Pari passu* with these changes the Aa. intralobulares have undergone a numerical increase corresponding to the division of the intralobular ducts. The capsular plexus is now very well marked. Arteries in the connective tissue surrounding the gland, run to the capsule, forming there an irregular polygonal plexus which breaks up into capillaries that pass irregularly in the outer layer of fibrous tissue that composes it. These capillaries reunite into venules which flow into venæ comites that accompany the arteries forming a capillary plexus. As in the earlier stages, perforating branches from the lobules and septal arteries run up and join this plexus.

FIG. 8. Submaxillary gland of pig's embryo 24 centimeters long. X 10 diameters. Aa. principales, interlobulares, sublobulares, lobulares, and intralobulares are now distinctly seen. The lobules have increased somewhat in size and the lobular veins and the venae sublobulares, interlobulares, principales are well formed. The plexus about the duct is not injected, arteries appear tubular and glistening while the veins are brownish and collapsed. The photographs from Figs. 5 to 8 are given their stereoscopic effect by painting the back of the slides with India ink and focusing a strong light on the cut surface of the glands. They were then photographed with a Zeiss apparatus with the above result.

LITERATURE.

The only investigations on the blood supply of the submaxillary are those of Kowalewsky,[6] who described the blood supply and drew from the arrangement of the vessels certain conclusions concerning the secretion of the gland, depending upon the anatomical relations of the vascular system to the cells and the lymphatics. Kowalewsky worked upon the parotid and submaxillary of the cat and dog. He believed many instructive ideas could be gained from the different resistances of the vascular stream in different parts of the blood system as shown by complete and partial injections. His description is taken from the submaxillary gland of the cat. Both the arteria carotis communis and the vena jugularis externa were used for injection. An incomplete injection from the arterial side filled the capillary plexus in the walls of the ducts, while

[6] Kowalewsky, Arch. f. Anat. u. Phys. Anat. Abth., 1885.

the interalveolar capillary plexus remained completely empty as the mass reached only the arterioles running in between them. He concludes that these facts indicate "the presence in the salivary glands of two vascular systems with unequal resistances; a system of diminished resistance with capillaries in the walls of the ducts, and the system of greater resistance with capillaries in the lymph spaces between the alveoli." The arteries of the salivary glands, according to Kowalewsky, as well as the ducts and veins, run in the connective tissue between the lobules. They give, in their course, small twigs that divide twice or three times and run mostly in recurrent direction in the connective tissue wall that surrounds the ducts. Here the arteries pass over into capillaries which sink quickly to reach the neighborhood of the epithelium under which they form a comparatively thick plexus. The veins from these capillaries appear in a more superficial position, change their direction so that it is parallel to the surface of the ducts and unite to form larger trunks which, at a certain distance from the afferent arteries, terminate in the accompanying veins. Small branches are also given off from the interlobular arteries which supply the sympathetic ganglia situated in the interspaces. As the ramification proceeds there is a thinning of the connective tissue wall of the salivary ducts and the capillary plexus at these points is not so well developed. The arteries and veins accompany the interlobular connective tissue until they finally penetrate into the interior of the lobules. The intralobular ducts, like those of the extralobular system, have a capillary plexus derived from the intralobular arteries. This empties into the vein that accompanies the duct. The intralobular system divides with the ducts until they reach the surface of the lobules. Arriving at this point, the terminal arteries are some what thicker than capillaries, but in the absence of muscle elements they can scarcely be distinguished from them. As soon as the lobular surface is reached, the arteries customarily divide into several divergent branches which form recurrent arched loops and immediately break up into capillaries around the alveoli. These vessels or vascular arcades, according to Kowalewsky, are already in the lymph spaces and send from their concave portion capillary twigs into the interalveolar lymph spaces which surround the single alveoli. From these capillary plexuses between the alveoli appear numerous short venous radicals which run in the neighborhood of the salivary tubes and soon terminate in large veins which accompany the ducts in their subsequent course. In this short description Kowalewsky does not trace the exact transition from the arterial to the venous system in various parts of the gland, nor does he discuss the important relations of the vascular and anatomical units. Moreover, this author does not describe the vascular units in the different circulatory systems as such, nor does he consider the capsular and septal circulation and their relations to that within the lobules.

The alveolar capillaries are not situated in the lymph spaces, as Kowalewsky believes, but in the interalveolar spaces between the basement membranes of adjacent acini. Here they are limited by the reticulum fibrils that bind together the alveoli which they supply.

DEVELOPMENT OF THE ALVEOLAR EPITHELIUM AND THE DEMILUNES OF GIANUZZI.

In a pig 3 centimeters long (Fig. 9) the terminal buds of the branching column of cells forming the ductus submaxillaris indicate the primitive alveolus in its simplest form. It is composed of a group of irregular polygonal cells embraced and enclosed in a reticulated basement membrane. Outside of a slightly definite arrangement of the outer layer of cells, the remainder are packed irregularly within the alveolus. The cells are polygonal in shape, have a definite outline and granular cytoplasm, staining a golden brown by Mallory's method. The nuclei are vesicular or ovoid, have a distinct nucleolus and considerable chromatin deposited on the linen threads. Exclusive of the regularity of the arrangement, there is, however, no morphological difference at this stage between the cells of the central and peripheral portions of the acinus. In a pig 8 centimeters long (Fig. 10) a lumen has appeared in the center of the developing alveolus and the cells are arranging themselves in two or three fairly definite layers. No marked changes are observed in the character of the parietal group of cells, but in those of the inner layer of the lumen of the

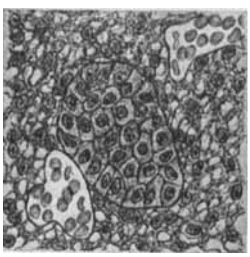

FIG. 9. Section of primitive alveolus from submaxillary of pig's embryo 3 centimeters long. Hardened in Zenker's fluid, stained by Mallory's method. × 650 diameters. This drawing shows the irregular columns of the cells forming terminal bud or apex of the growing column of cells in the developing submaxillary.

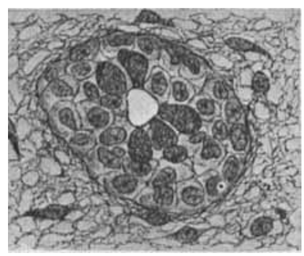

FIG. 10. Alveolus from glandula submaxillaris of pig's embryo 8 centimeters long. Hardened in Zenker's and stained by Mallory's method. × 650 diameters. The arrangement of the cells in two or three layers about the lumen is now apparent, together with the beginning of the formation of the mucous globules within the cells of the inner layer.

alveolus, one notes the formation of mucous globules within the cells which stain a deep blue with one of the elements of the Mallory stain. The mucous globules appear to be formed in the part of the cell next to the lumen, as the nucleus is pushed off to the edge nearest the basement membrane where it begins to show some signs of intracellular pressure, evidenced by its semilunar form. At the same time the nucleus takes a red stain, while the nuclei of the parietal cells remain brown in color.

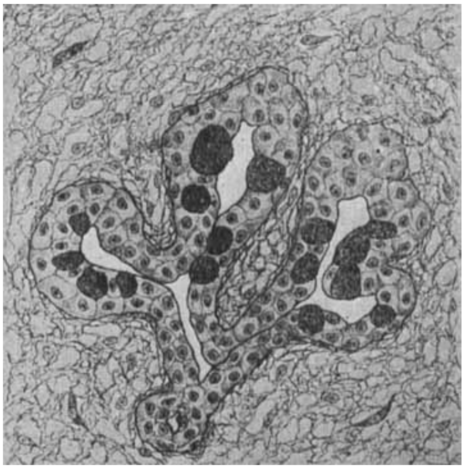

FIG. 11. Terminal cluster of alveoli from the submaxillary gland of pig's embryo 12 centimeters long. Hardened in Zenker's fluid and stained by Mallory's method. × 650 dameters. The definite arrangement of the cells of the ducts and alveoli is now apparent. Mucous cells formed from the central layer are apparent. Alveolar ampullae are also well shown.

At this time the mucous cells are not much larger than those of the parietal group and their cytoplasm looks like a reticulum of even blue lines or else as a mass of minute globules closely pressed together within the limits of the cell. At a somewhat later stage (Fig. 11) the arrangement of the cells is more definite and they are placed in two distinct layers. Mucous cells have increased in size but otherwise show the same characteristics of the cells at an earlier period. In an alveolus of a pig 18 centimeters long (Fig. 12) the mucous cells have begun to approximate laterally and, in some instances, have reached and impinged upon the reticulated membrana propria of the alveolus. The parietal cells now show evidences of pressure and are grouped off towards the reticulated membrane between adjacent mucous cells. In these instances, however, the parietal cells are not as a rule single, but occur in clumps of three or four. In many places the mucous cells are still separated from the basement membrane by an entire layer of parietal cells.

The alveoli in a pig two days old (Fig. 13) show, in general, a considerable advance in the arrangement of the mucous cells. They become larger and, as a rule, either rest upon the basement membrane or are separated from it by a very slight distance. The distended mucous cells have increased in size, but otherwise their character is not altered. The parietal cells, however, are wedge-shaped and already begin to have some of thè typical appearances of the demilune. Throughout the series of embryos there is a considerable variation in the alveoli of the same gland, but the series of illustrations represents, however, the average condition found in the alveoli at the ages mentioned. In the adult submaxillary of a pig (Fig. 14) stained by Mallory's method, there is a marked difference in the microchemical reactions of the two classes of alveolar cells. The mucous cells have increased greatly in size, the

FIG. 12.

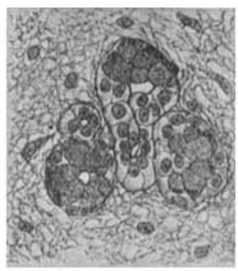

FIG. 13.

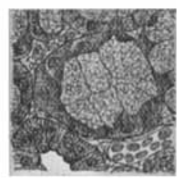

FIG. 14.

FIG. 12. Terminal alveolus from the submaxillary gland of pig's embryo 18 centimeters long. Hardened in Zenker's fluid and stained by Mallory's method. × 650 diameters. Mucous cells have now in places reached the basement membrane. Parietal cells are pushed off into the spaces left between the cells of the former group.

FIG. 13. Terminal alveolus from submaxillary gland of pig two days old. Hardened in Zenker's fluid and stained by Mallory's method. × 650 diameters. The mucous cells have in most cases reached the basement membrane. Parietal cells are now found here and there between them, already giving the final and definite relations of the demilunes of Gianuzzi.

FIG. 14. Terminal alveolus of submaxillary gland of adult pig, showing the final form and arrangement of the demilunes. Hardened in Zenker's fluid and stained by Mallory's method. X 650 diameters. The differences in the staining reactions between the cells of the central and parietal groups are indicated.

mucous globules are slightly larger, and give the body of the cell a clearer, more glairy appearance, while the nucleus still retains its crescentic shape and is pushed off to the pole of the cell nearest the membrana propria. Much more marked changes have occurred in the parietal cells; the cytoplasm has taken on a distinct bluish tinge and is now very granular, while the nuclei are less vesicular but are still brightly stained with the orange element of the dye.

Ever since the demilunes were first described by Gianuzzi they and their functions and relations have been the subject of an extensive discussion in the literature. Stöhr, who believed that the demilunes are mucous cells in various stages of activity, speaks of the false or pseudolunulae, classifying among the latter Pflüger's demilunes, which are the peripheral protoplastic portions of unfilled mucous cells and membrana propria demilunes consisting of sections of thickened basement membranes. Another point which has given rise to considerable discussion is the stratification of the alveolar epithelium, many authors holding that the cells are arranged in two layers while others maintain that only a single layer exists. The conditions probably differ in different animals. In man, apparently, both groups of cells, central and parietal, touch the basement membrane, while in pigs it is not uncommon to find even in the adult many mucous cells separated from the basement membranes by demilunes. The chief point of interest in this connection, however, is the fact that the two groups develop from a double layer of epithelium.

The significance of the demilunes has been the point of several theories that have given rise to more or less discussion. Among the prominent ones are the "Ersatztheorie" of Haidenhain, "Phasentheorie" of Stöhr and the doctrine of the specificity of the demilunes suggested by von Ebner.

The "Ersatz" theory is based on the idea that there are two groups of cells, a central group with the characteristic arrangement which consists for the most part of mucous cells and a peripheral group corresponding to the demilunes which through mitosis increase and undergo a mucous metamorphosis to replace the destroyed cells of the central group. Against this theory, however, the following objections are made by Oppel:

1. That the mucous cells are not destroyed or disintegrated during the secretion.
2. Pure mucous glands without demilunes are known to exist.
3. The demilunes never show mitotic figures.

The "Phasentheorie" is based on the assumption that the mucous and parietal cells are merely different functional stages of the same elements. Stöhr and others believe that the mucous cells are not destroyed during the secretion of the gland but persist like the cells of the stomach epithelium and that the parietal cells represent the peripheral protoplasmic part of the mucous cells which are not transformed into mucous globules. Supporting this fact are the pictures obtained during the various stages of activity of the gland, which seem to suggest, according to these authors, that the cells at first have a round nucleus with only the central portion of the cell next to the lumen transformed into mucous. As the production of this substance increases, the nucleus is pushed more and more toward the periphery of the cell, where, with the remainder of the untransformed protoplasm, it rests against the basement membrane. These with similar neighboring cells form the parietal group. In extreme cases the nuclei may be pressed flat against the base of the cell. Müller raises the following objections to Stöhr's theory:

1. The demilunes are not empty of secretion but contain secretion granules.

2. Intermediate stages between filled mucous cells and demilunes do not exist.

3. The secretion capillaries described by Stöhr with the Golgi method are simply intercellular spaces, while true demilunes have distinct intracellular secretion canaliculi.

The doctrine of the specificity of the demilunes suggested by v. Ebner is based upon the following conclusions:

1. The cells of this group contain secretion granules.

2. They contain secretion canaliculi which may be demonstrated by the Golgi method.

3. Certain substances injected into the circulation of living animals are demonstrable in the demilunes or their secretion canaliculi.

4. They react distinctly to certain microchemical tests.

From the study of the development of the demilunes in the submaxillary gland in a series of embryo pigs, it becomes patent that the doctrine of the specificity of the demilunes is the only one which is at all tenable. Aside from the various conclusions given by Müller supporting this fact, the indisputable evidence of their ancestry shows that, throughout the period of embryonic life, they are cells of an individual specific group, derived from the peripheral layer of epithelium in the embryonic alveolus. They maintain their identity throughout life and represent neither young cells which undergo, at a later period, transformation into the mucous cells of the alveolus, nor one of the functional stages of the mucous group. Embryologically and anatomically they are definite units and must be considered as cellular complexes which form definite structural elements of the alveoli of certain of the salivary glands.

Changes in the Duct Epithelium.

In a pig $4\frac{1}{2}$ centimeters long the main ductus submaxillaris is already composed of two layers of cells which are cubical in shape and not distinctly columnar. These can be followed in the main divisions of the ducts and terminate in the solid buds that form the apices of the growing ducts, which we have termed the embryonic alveoli. The cells are polygonal in shape and have deeply staining nuclei, while the cytoplasm is granular.

In a pig 8½ centimeters long the epithelial lining of the ducts of all orders from the ductus submaxillaris to the alveolus is in the form of a double row. The character of the epithelium is not changed from the simple form shown in the earliest embryos, where a similar condition also exists, but only in the larger ducts.

In a pig 12½ centimeters long, the rami principales, interlobulares and sublobulares are already formed. At this time the epithelium of the inner layer of the ducts of the lower orders shows a tendency to become columnar, the nuclei ovoid, with their long axes parallel to the long axis of the cell. The epithelium of the outer layer is more irregular and conical in shape, while the nuclei are rounded and vesicular. The portion corresponding to the intercalary ducts in the adult now joins the alveolus directly to the sublobular duct. This indicates accordingly that ducts of the lobular order have not yet been formed, but in these intercalated portions, the cells appear quite like the parietal cells of the alveoli, and are arranged in two definite strata.

At 19 centimeters there is no change in the ducts of the higher order, but, with the definite appearance of the secondary lobules, we note the formation of the lobular and intralobular ducts for the first time. The epithelium of both orders is in two layers, an inner cubical and an outer more irregular layer. The ducts connecting them with the acini show a considerable flattening with a tendency for the inner stratum to take the stain more intensely than those of the outer layer.

At 22 centimeters the ducts of the higher order show an increase in the columnar arrangement of the inner layer of cells; the central portions now stain a deep blue with a clearer peripheral portion on the side of the nucleus near the basement membrane. The ducts of the sublobular, lobular and intralobular order remain unchanged. Definite intercalary ducts have now been formed and appear to have but a single layer of epithelium with the long axis of the nuclei parallel to the axis of the duct.

In a pig 26½ centimeters long the main ducts have now a distinct columnar epithelium adjacent to the lumen. This has a bluish staining pole and a clearer peripheral pole. As the ramification proceeds, particularly in ducts of the sublobular order, there is a tendency for the epithelium to become more columnar. There is no striation in the cytoplasm of the cells of the intralobular ducts. These now appear in many places as though composed of a single layer of epithelium. Other intralobular ducts have a distinct double layer even at this stage of development.

In a pig two days old there has been scarcely any change in the character of the epithelium and the larger ducts, except that goblet cells filled with plugs of mucous stained with aniline blue are now occasionally found between the elements of the inner columnar layer. These can be observed in ducts as high as the sublobular order. Ducts of the lobular and intralobular type have in many places a double layer of epithelium but show as yet no evidences of the fibrillation observed in the intralobular ducts of the adult. Intercalary ducts in some places appear to be lined by a single layer of flattened epithelium, while in others indications of a double layer are found, but sections that pass directly through the lumen of the intercalary ducts ordinarily have only one row of epithelial cells lining them. In the adult, the height of the columnar epithelial cells forming the inner stratum of the larger ducts is considerably increased as well as the number of goblet cells found between them. In a two-day pig the goblet cells are rounded, while in the adult, unless greatly distended, they are elliptical in form. The intralobular ducts in the adult have but a single layer of epithelium, and the cell pole away from the lumen of the duct is dictinctly striated. Intercalary ducts which are extremely difficult to find owing to the increase in size and the thickness of the alveolar groups, now show usually but a single layer of flattened epithelium. In each of the lobules there are a few groups of serous alveoli embedded among those of the mucous type. These are provided with intercalary ducts not dissimilar from those that enter the mucous alveoli. The serous alveoli are extremely few in number and are difficult to find in sections of the pig's submaxillary at the time of birth. But they may occasionally be noted in pigs 26½ centimeters long coming off from intercalary ducts adjacent to a group of the regular mucous alveoli. Whether they represent a special differentiated form of alveolus concerned with the production of special elements of the submaxillary secretion is not certain, but the method of their development is obvious. They represent simply an alveolus in which the cells of the inner layer have not been differentiated into the cells of the mucous type. It does not follow, of course, that they would then be analogous to the parietal cells of the mucous alveoli, although this hypothesis must be considered. It is interesting to note, however, that in pigs of this age one finds these alveoli with a double layer of cells. It should be remembered, moreover, that in pigs

22 centimeters long it is not uncommon to meet with alveoli without mucous cells. These may be, in part, alveoli of the serous type which we find in the adult, but probably also represent a group in which mucous cells have not yet developed.

RÉSUMÉ.

1. The blood-vessels of the submaxillary gland form practically three circulatory systems:

(a) The glandular system in which the main artery enters the gland at the hilus rapidly approaches the ducts and runs with them in the interlobular spaces until the lobules are penetrated where the arteries terminate in a capillary plexus around the alveoli. From these capillaries venules are formed which follow the course of the arteries, leave the lobule at the hilus where they become duplicated into the venae comites of the main arteries. They now run with the arteries, giving off frequent anastomoses which pass over and under them, and finally leave the gland at the hilus to empty into the V. facialis communis.

(b) A system around the ducts, the arteries of which are derived from the ramifications of the main arteries of the submaxillary gland, the branches of which course in the connective tissue about the ducts forming around those of the higher orders a simple indefinite arterial plexus. The ultimate terminals pass downward and divide into a capillary network just beneath the epithelium lining the ducts. Small veins originating from the union of capillaries pass upward and unite into larger venous elements to form an irregular plexus of veins just beneath the arteries. Larger emissary veins leave this plexus and flow as tributaries into the venae comites accompanying the main arteries. In the interlobular system both the arterial and venous plexuses become less definite, but the scheme of the duct circulation is the same. In ducts of the sublobular order there is no definite arterial or venous plexus, the capillary plexus still persists and the arteries and veins lie above it. The same thing is true of the lobular and intralobular ducts except that the circulation about them is much simpler.

(c) The circulation in the framework. A well-marked capsular plexus is derived from vessels in the periglandular connective tissue. These run on the surface of the submaxillary gland and break up into an irregular arterial plexus formed of polygonal spaces. Venae comites accompany the arteries. Derivatives of this plexus give off the capillaries to supply the capsule which unite into venous radicals and flow into the accompanying veins. Occasional branches from the intralobular arteries

penetrate the membranæ limitantes and then join the plexus in the capsule. These arteries are accompanied by a single vein. Similarly, arteries are derived from the intralobular system which perforate the limiting membrane of the lobule and break up in the septum. Occasionally septal arteries will pass out through the primary or secondary septa and communicate with the capsular plexus. With the single exception of this connection between the vessels of the framework and the glandular system, the circulation within the lobules is absolutely independent. The capillaries of adjacent lobules do not anastomose. Limiting membranes are not bridged by blood-vessels.

2. The rôle played by the circulation about the ducts in the secretion of the submaxillary is uncertain. Obviously they nourish the duct epithelium and therefore any part that the latter takes in the production of saliva must be traceable to this portion of the vascular system.

3. The vascular system of the submaxillary develops *pari passu* with the ducts. The latter form the stimulus for the production of new blood-vessels. In the earliest stages the simple branching column of cells forming the submaxillary receives an arteriole which breaks up into a capillary plexus about the columns and finally empties into the vein accompanying it. The terminal buds of the cell columns are embraced by an irregular capillary plexus, the prototype of the future alveolar plexus. The circulation around each separate division of the main duct is independent, anastomoses between them occurring with great rarity. As the ramification of the ducts proceeds, they are followed by an extension of this simple vascular system. Venae comites are formed that accompany the main arteries from the sublobular interspaces to the hilus, and the simple capillary plexus about the main ducts develops into an irregular arterial, capillary and venous plexus. Finally, in a pig 18 or 19 centimeters long, the division of the ducts has increased to those of the lobular order and, as a result, a lobular circulation of simple type is finally produced. From this point the further development of the circulation is simply one of degree as the general plan is now completely established. A little later branches of the intralobular arteries perforate the limiting membrane and join the circulation developing in the capsule and the septa.

4. Like the blood-vessels of the adrenal, those of the submaxillary gland mark out the paths of development taken by the cell groups of the organ, forming, in a measure, a record of the ontogeny of its parts. This is known to be generally true of the systemic circulation and now holds for the submaxillary as well as the adrenal gland. It may then be

assumed with safety that " the angiology of an organ is in a measure the recapitulation of its ontogeny."

5. The epithelium of the ducts in early embryos consists of a solid column of cells. At an early period the lumen is formed and the cells arrange themselves in two fairly definite layers. As the ramification of the cell columns proceed, the penetration of the lumen extends upward until all the ducts as far as the small terminal buds have a double layer of cells. In a pig 8 centimeters long the lumen appears within the alveoli, the first formation of the ampullae. The size and definition of the duct epithelium increase up to the time of the adult, the cells increasing chiefly in size. At the period just before birth mucous goblet cells appear in among the columnar epithelium and the inner layer of the larger ducts. The fibrillation in the external portion of the cells lining the intralobular ducts is not manifest in sections stained by Mallory's method until after birth. Usually the ducts of the intralobular system appear to have but a single layer of cells in the adult, although in some cases, particularly in the intercalary ducts, one finds an occasional double row.

6. The alveolar epithelium consists in the pig 4 centimeters long of a solid group of polygonal cells. At a little later period these cells arrange themselves in two or three indefinite layers about the lumen or ampulla of the alveolus. In the cells of the inner layer mucous globules begin to appear. These increase in size until they finally reach the basement membrane, leaving the cells of the outer layer in the interstices between the bases of the mucous cells. In this way the mucous elements of the alveoli are formed from the cells of the inner layer, while the demilunes of Gianuzzi are derived from the parietal cells. In following so definitely the ancestry of the demilunes, it become obvious that they are definite elements in the alveolus and are neither mucous cells in one or another stage of activity, nor do they represent young mucous cells.

In conclusion I wish to express by thanks to Dr. A. W. Lee, of this department, for the painstaking care he has taken in the production of these drawings.