THE PHYLOGENETIC RELATIONS OF THE LYMPHATIC AND BLOOD VASCULAR SYSTEMS IN VERTEBRATES

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At a time when the ontogenesis of the vertebrate, and especially of the mammalian, lymphatic system has called forth general interest and considerable activity in research, it seems advisable to regard the mutual relations of the hæmal and lymphatic divisions of the vertebrate vascular system from the standpoint of their phylogeny, in as far as material for such observations is to date available, and in turn to fit the facts ascertained by the study of mammalian lymphatic ontogenesis into the framework obtained by these generalized comparisons.

This appears all the more advisable when we consider that any valid theory of lymphatic development must, on the one hand, agree in its postulates with the phylogenetic facts, as far as they are definitely established, and that, on the other hand, a review of the ascertained comparative conditions of the two systems in their mutual bearing on the general question will serve to direct attention to the problems of vascular morphology as yet imperfectly known, and thus guide the inquiries in the right direction.

In the earliest zoölogical conditions in multicellular organisms a simple circulation suffices to supply all the metabolic demands of the tissues. Such a circulation is attained when a system of intercellular canals develops in which a clear plasmatic fluid, without free cellular elements moves in response to the pulsations of contractile areas included within the system.

In general terms a circulation of this kind is, from the phylogenetic standpoint, a primary formation and represents the primitive lymphatic type of vascular organization, from which in higher forms the hæmal system develops as a secondary vascular

acquisition. In the physiological sense this establishment of a hæmal circulation, as a graft on the earlier circulation of non-cellular plasma, is to be interpreted as the expression of the increased rate of tissue combustion and the resulting growing demands of the organism for oxygen, required in the ascent to higher animal types. The biochemical agent which makes this elevation from the lower to the next higher rung of the zoölogical ladder possible, is the hæmoglobin, and the morphological expression of its employment is found in the genesis of the modified mesodermal cell entering the circulation as the free red blood cell.

The first circulation of this type contains in the plasma-stream cells which enable the organism to establish a very simple type of respiration. Such a condition in its earliest inception is represented by the circulatory apparatus of *Amphioxus*. With the elevation to more advanced vertebrate organization this mixed lymphatico-hæmal type of circulation no longer suffices for the growing respiratory requirements, and, in response to the resulting functional demand, a separation of the original single circulatory system into two divisions begins to develop. One of these divisions continues on the hereditary lines as the rudiment of the future lymphatic system in the narrower sense, with cell free plasma, while the other, arising primarily in response to the ever increasing demand of the tissues for oxygen, differentiates as the anlage of a hæmal circulation with the hæmoglobin cell as its distinctive biochemical and morphological character.

In this process the bloodvascular system has gradually and continuously assumed more and more complex relations to the organism and has taken on successively higher and higher biochemical activities in addition to the original function of serving in the respiratory exchange, until it has morphologically and physiologically become the predominant vascular structure. The separation from the lymphatic channels has in consequence become more and more pronounced, until it has progressed in mammals to the point where, as the final outcome of the process, two distinct sets of vessels are established side by side. The component channels of one set, further specialized as arteries,

veins, blood capillaries and heart, are closely associated and mutually interdependent, and give structural expression to the importance attained in the course of phylogenetic evolution by the hæmal vascular system. The second set, that of the lymphatic channels, is in its main extent independent of the first, simpler and more primitive in its organization, and more restricted in function, closely interlocked with the venous division of the blood-vascular system which it in certain functional respects supplements.

This division must of course have occurred gradually, and rather by multiplication of channels than by septal division of a single preëxisting system into two components. Naturally this process should offer in the phylogenetic series many stages in which the division is still incomplete, and hence the gradual solution of peripheral organic continuity between hæmal and lymphatic vascular organization, in proceeding from the lower to the higher types, is, even with our present scanty knowledge, quite evident in the vertebrate series. No recent contributions to comparative vascular anatomy have done more to clear this question and to advance our correct perspective than the investigations of Favaro¹ on vascular organization in fishes.

The Italian anatomist has described a very close and intimate relationship in teleosts between lymphatic and venous organization. In several forms the same vessels appear to function at certain periods as lymphatic channels, while at others they are physiologically venous in character. Hand in hand with this interchangeable functional relationship goes a marked complexity of the lymphatic and venous "hearts."

The investigations of Allen² have led to similar results.

In ascending the zoölogical scale we encounter, together with the increasing independence of hæmal and lymphatic vascular

¹ Favaro, Guiseppe, 1905: Il cuore ed i seni caudali dei Teleostei Ahi R, 1. Veneto di sc. lett. et arti, 1905-06, tome 65- Part II. Append. alla Dispensa, bet. 1906. Venejin 1906. Anat. Anz. Bd. 27, p. 879-880. Archivio di Fisiologia, Bd. 2, Fasc. 5.

² Allen, W. F.: Distribution of the Subcutaneous Vessels in the Head Region of the Ganoids, Polydon and Lepisosteus. Washington Acad. Sc. Proc., vol. ix, pp. 79-188, 1907. Distribution of the Subcutaneous Vessels in the Tail Region of Lepisosteus. Am. Jour. Anatomy, vol. viii, pp. 50-89, 1908.

organization, a progressive and phylogenetically most significant reduction in the number, complexity and histiological differentiation of the lymph hearts. Favaro's demonstration of the primitive relationship between the teleostean lymphatic and venous system now completes the chain between the conditions presented by *Amphioxus* and those encountered next above the fishes in the urodele amphibians. This ascent is marked by a more definite separation of venous and lymphatic pathways, although the still large number (14-20) of the urodele veno-lymphatic hearts recalls the former more intimate association of the two systems.

A reduction of the lymph hearts to two pairs, an anterior and a posterior, is next encountered in the anure amphibians. In the reptiles only a single (posterior) pair of these organs is carried into the adult organization. The anterior lymph heart appears, however, during the ontogenesis in a rudimentary form, as determined by recent examinations of the 7.5 mm. and 9 mm. embryo of *Scleroporus undulatus*.

In birds the posterior lymph heart is retained throughout life in some forms. In others, as shown by Sala,³ it develops in the embryo, but disappears soon after the assumption of free life. While the subject is still under investigation, there is reason to believe that the presence of a rudimentary anterior lymph heart in birds during the ontogenesis can be demonstrated, and that this structure effects the final lymphatico-venous connection.

In mammals, finally, a reduced single pair of anterior organs, the jugular lymph sacs, alone persists, as far as we at present know, as the sole remnants of the extensive antecedent series of lymphatico-venous connections and serves as the bond between the otherwise completely separated venous and lymphatic systems.

Thus the more prominent and highly specialized the hæmal vascular system appears as compared with the lymphatic, the higher in general is the animal organization possessing this type. Conversely, in descending the zoölogical series, the individuality and independence of the two systems diminishes steadily until they finally merge into the single common archæal anlage.

³ Sala, L.: Sullo sviluppo dei cuori linfatici e dei dotti toracici nell'embrione di pollo. Roma, 1900.

As previously stated⁴ the lymph hearts represent in this evolutionary process, on the one hand, the line along which the gradually acquired organic separation of the blood-vascular and lymphatic systems proceeds, while on the other hand, they play in the various phases of this process of segmentation the important rôle of links between the lymphatic and the hæmal channels, which, in ascending the scale, are becoming progressively and increasingly more independent of each other.

For obvious physiological and mechanical reasons this original connection can never be entirely interrupted, but we see in the relative organization of the lymphatic and venous systems in the mammalia, in comparison with the conditions formed in lower vertebrates, the highest degrees of this phylogenetically acquired independence.

I have in a previous publication⁵ pointed out the fact that the possibility exists in the plan of mammalian lymphatic organization for the establishment of lymphatico-venous connections at other points in the adult than those afforded by the typical connections of the anterior lymph heart or jugular lymph sac with the veins at the common jugular and jugulo-subclavian angles. Such connections, if they exist in certain forms, must be interpreted with our present knowledge of mammalian lymphatic organization, as retentions of other primitive lymph heart bonds between the lymphatic and venous system which, in the greater number of mammalia, are not developed and carried into the typical adult plan, but which may, while atypical for the general class, appear in certain specialized forms.

It is quite conceivable that development on these lines would lead to results which would serve the mammalian physiological demands equally well, if not better, than the prevalent type of mammalian lymphatic organization. It is possible that the reported instances of the termination of the thoracic duct in one of the azygos veins or its tributaries in the adult human subject can be interpreted as variations depending for their genesis on the

⁴ Huntington: The Genetic Interpretation of the Development of the Mammalian Lymphatic System. *Anatomical Record*, vol. ii, nos. 1 and 2, 1908, pp. 1-44.

⁵ Loc. cit., p. 30.

atypical development and retention of a lymphatico-venous heart formation at points other than the ones normally concerned in the production of the jugular lymph sac. The reported cases are, however, not sufficiently authentic to accept them at their apparent face value, and the available evidence is too scanty to warrant the assumption that these variations, if they exist, are of a progressive character tending toward the eventual reduction of the thoracic duct and the substitution for the same of a more direct connection of the abdominal lymphatic channels with the venous system.

The more our knowledge of comparative vascular anatomy grows, the clearer the perception becomes, that in spite of the apparent structural and functional differences between venous and lymphatic organization, the two systems are but parts of an originally single and united whole, and hence must be primarily of equal and identical origin. The genetic unity of all vascular structure is a proposition which is constantly becoming more self-evident. Even if it were not for the direct observations to the contrary, this fact alone negatives the assumption of the derivation of the systemic lymphatics from the veins as secondary products of their endothelial proliferation. The line of reasoning above outlined, if carried to its logical conclusion, stamps the entire complicated hæmal vascular apparatus of the higher vertebrate types as the genetic descendant of a pre-existing simple lymphatic vascular system. In other words, in place of considering our modern lymphatics as derivatives from the veins, I believe that in a correct valuation of the relative position of veins and lymphatics, we are obliged to regard the lymphatic system as the primary organization, from which gradually in the phylogenesis the bloodvascular system has been derived. In spite of the predominance of hæmal over lymphatic structure in the higher forms, the latter should be recognized as the phylogenetically older primary structure.

The separation between the two has in the evolutionary sense become more and more pronounced, until it has progressed in the mammal to the point where, even in the ontogenesis, the anlagen of both are laid down independently. But their common genetic

basis is to be found in the vascular strands of the early mesoderm. It is however not at all improbable that the mammalian lymphatic system, as we at present know it, in the relatively few forms that have been carefully studied, is still in the evolutionary sense undergoing progressive changes which in their broader significance trend toward further reduction and simplification of the lymphatic, as compared with the hæmal vascular organization. In view of the predominant association of the mammalian lymphatic channels with intestinal alimentation and the metabolic processes of digestion, such further evolutionary modification of lymphatic organization from the type now prevalent in mammalia, would in all probability be in the direction of still greater development of this physiological character. This might find structural expression in the higher development of the intestinal lymphatic complex and a coincident reduction of the general lymphatic channels at present associated with them. The mammalian lymphatic system would under these conditions correspond mainly to the hepatic-portal venous channels and would convey the products of digestion directly to the systemic venous current.

The organic principle of the above described phylogenetic separation of a hæmal from a preëxisting single primitive lymphatic circulation repeats itself within the far narrower circle of the former in the phylogenetic division which leads, through the Dipnoean and Perennibranchiate lines, to the replacement of the primitive single branchial type of respiration and circulation by the double cycle of the air breathing forms. This change in environment, with its resulting enlarged scope of vertebrate life, has led step by step to more highly organized structural types within the framework of the primitive hæmal vascular system, through which stages the single-hearted, cold-blooded branchial form has advanced to the double-hearted, warm-blooded pulmonary type.

In its physiological significance this general evolutionary process again means primarily vastly greater and more rapid tissue metabolism or combustion in the broad sense. The structural response to this functional demand is strikingly given in the

phylogenetic (and ontogenetic) development of the intra-cardiac and intra-aortic septa. We encounter here on a large and unmistakable scale, and associated with an evident biochemical function, the division of part of the originally simple and uniform hæmal vascular system of cardiac chambers and truncus arteriosus into two bilateral and equivalent elements. This change is effected primarily not by addition from *without* (except the neomorphism of the pulmonary vein) of something *new* but by a change and rearrangement of parts already existing *within* the framework of the primary bloodvascular system. If, therefore, as McClure and I have definitely proved,⁶ the mammalian jugular lymph sac, or cervical lymph heart, is secondarily separated from the mammalian embryonic pre- and postcardinal veins, this process of division of originally single hæmal channels into completely separate elements is not genetically a *new* process, confined to the lymphatico-venous terminal, but follows on a smaller scale and much more obscurely, genetic lines already laid down in the division of the primitive single heart tube into its completely distinct dextral and sinistral components.

The question here involved is of great and far reaching importance in establishing the correct relative position and value of the hæmal and lymphatic vascular systems.

If the metabolic demand for increased and more rapid supply of oxygen is capable of calling into existence, within the already organized confines of the hæmal division of a simple vertebrate circulation, the structural changes leading to the divided heart and the lung in place of the antecedent branchial type of circulation and respiration, then the same force is evidently sufficient to derive, in far earlier phylogenetic stages, from the primitive general non-cellular circulatory system, a separate set of channels conveying plasma with free hæmoglobin cells as the circulating medium, and developed primarily in the service of the oxygen-carbon dioxide exchange of the tissues.

In this way there comes to be established the phylogenetic

⁶ Huntington and McClure: The Anatomy and Development of the Jugular Lymph Sacs in the Domestic Cat. *Anatomical Record*, vol. ii, nos. 1-2, 1908, pp. 1-18.

anlage of a secondary bloodvascular system, derived from the primitive general vascular apparatus circulating non-cellular plasma. With the appearance of the hæmal system the distinction between it and the persistent portion of the primitive vascular organization as a lymphatic system develops.

Thus the primitive simple hæmal system, subsequently destined to undergo under the stimulus of phylogenetic advance, a complete secondary division, was in its own turn originally segmented from a simpler antecedent circulation of lymphatic type for the purpose of satisfying the earliest demand of the tissues for oxygen by becoming the carrier of hæmoglobin cells, while the persistent elements of the earlier system are retained as lymphatic vessels serving a new physiological purpose under changed conditions of metabolism.

As stated above the series of lymph hearts would in this genesis of the bloodvascular system represent points where the original continuity of lymphatic and hæmal elements is retained, in a specialized and modified form for definite physiological purposes. The number and distinctive character of these lymph hearts would then naturally diminish in proceeding serially from the lowest to the highest types, coincident with the serially developed greater and greater independence of the hæmal and lymphatic divisions of a general vascular system.

This change implies an enormous degree of adaptability and structural response to functional demands. Many examples of this extreme plasticity of vascular organization are encountered throughout the entire formative period of the mammalian embryo, in which the bloodvascular system is the predominant agency of nutrition as well as respiration. This character appears not only in the crystallization of definite assymetrical arterial and venous pathways from an antecedent symetrical bilateral type, but also in many of the more intricate relations of the bloodvascular channels to the temporary and the future permanent metabolic demands of the tissues. Thus, for instance, in the placentalia the vitelline veins appear in the rôle of the earliest embryonic nutritive and respiratory channels. They subsequently, in the placental period, yield this part to the secondarily involved um-

bilicals. Their own primary significance is lost and remains in abeyance throughout the whole of the placental epoch, to suddenly reassert itself when the hepatic portal channels, as the direct descendants of the afferent vitelline veins, assume with, the establishment of intestinal alimentation at birth, the important share in the nutritive processes of the body which they are henceforth to maintain throughout the life of the individual. The anlagen of these vessels were, so to speak, side-tracked for the very considerable umbilical or placental period of embryonic and foetal existence. But they continued to develop during this entire period of functional displacement and obscurity, and became associated with the growing alimentary canal, in anticipation of the moment when, with the first establishment of post-foetal conditions, they resumed their original significance and entered into their now definite and permanent function as nutrient afferent hepatic vessels.

In the same way the entire extensive series of structural changes within the three divisions of the bloodvascular system, leading finally to the establishment of the pulmonary circulation, is developed in anticipation of the sudden assumption of pulmonary respiration at birth.

This law of anticipatory ontogenesis is of very wide application and expresses especially the cardinal character of extreme adaptability, both to present requirements and future needs of the organism, in all developing vascular structure.

It is quite possible, that the lymphatic vessels, which we must recognize in the broad phylogenetic ground plan of vascular organization, as the primary and earliest channels, appear in the complicated and highly specialized mammalian vascular system of predominantly hæmal type, in a subordinate and secondary position, owing to genetic influences of this general character.

They are formed, during the embryonic period, just as the portal and pulmonary channels are formed, but like these, they develop in anticipation of assuming their functional activity only with the altered environment and changed nutritive conditions of the post-foetal period.

In this sense they appear as secondary structures, allied to the

all important hæmal embryonic channels, just as the placental vitelline veins, within narrower phylogenetic limits, appear subordinate to the new bloodvascular conditions dependent upon the acquisition of the umbilical vein as the main embryonic nutritive and respiratory vessel, in the phylogenetic ascent from the vitelline to the placental phase of embryonic development.

This brings us to the question of the comparison between the ontogenesis of the mammalian systemic lymphatics and the lymphatic organization of the lower vertebrates. Briefly stated, our observation as to the development of the mammalian lymphatic vessels, can be summed up as follows:

1. The first anlagen of the bloodvascular channels and of the systemic lymphatic vessels in the mammalian embryo are identical. These common anlagen are formed by independent intercellular mesodermal tissue spaces, which, in enlarging, become lined, in obedience to the mechanical pressure effects of the clear fluid contents of the spaces, with endothelium.

2. The spaces become confluent to form larger and continuous channels. The bloodvascular system differentiates genetically from the lymphatic system by the secondary inclusion of the specialized mesodermal hæmoglobin cell of the blood islands in the clear non-cellular stream of the plasma circulating during the primary stage in the hæmal system of channels in response to the cardiac pulsations.

The systemic lymphatic channels continue on the other hand, to convey a clear fluid containing no, or only a few, cellular elements.

3. This histogenetic identity, and the fact that subsequently the only criterion defining respectively the early embryonic bloodvascular and lymphatic channels is the red blood cell content of the former, precludes definite differentiation of the two sets of vessels prior to the period at which the hæmal channels acquire their distinctive free cellular elements.

4. Hence we must accept three chronological possibilities in regard to the ontogenetic period at which these anlagen begin to appear.:

- a.* The bloodvascular and lymphatic channels develop simul-

taneously as capillary anlagen side by side, and subsequently differentiate from each other as above detailed.

b. The lymphatic anlagen are the first to develop. Subsequently a portion of the common system, or a second generation of equivalent channels, differentiates as the hæmal component of the vascular system, in contradistinction to the persisting primary lymphatic system.

c. The bloodvascular system is ontogenetically the first to develop in the mammalian embryo. The lymphatic anlagen appear secondarily as an equivalent system of mesodermal spaces, which subsequently unite. The resulting channel system does not acquire the free circulating blood cells characteristic of the hæmal division, but finally gains access to the blood vascular system by union with the jugular lymph sacs, derived from the veins, and is thus enabled to enter as an integral component into the triple constitution of the general circulatory apparatus.

From the phylogenetic standpoint the second of the above enumerated possibilities is the one which is most consistent with the hæmo-lymphatic organization as seen in its general evolution in the vertebrate series. At the same time the last of the three possibilities appears from the evidence at hand to represent most accurately the conditions encountered in mammalian embryos. The separation between bloodvascular and systemic lymphatic organizations has here not only progressed to a degree in which even the ontogenetic anlagen of the two channel systems are laid down independently of each other, but has further resulted in placing their first appearance into different embryonic periods.

From the phylogenetic standpoint this must be regarded as the result of factors operative in the specialization of the highest vertebrate types, and not as the original common condition. The mammalian ontogenetic relationship between the hæmal and lymphatic anlagen appears as an expression of the tremendous development which in the evolution of the higher zoölogical types, the bloodvascular system has gained over the primary lymphatic circulation. This paramount influence of hæmal over lymphatic vascular development has even reversed the relative ontogenetic period in which the first distinct anlagen of

each system appear. The bloodvascular organization has gained the complete ascendancy, the lymphatic has been relegated to a secondary position, with highly curtailed and specialized function. Moreover, as above stated, the actual assumption of this function has been in the mammalian ontogenesis postponed to the end of the placental epoch, and the assumption of individual nutrition with the establishment of the definite postnatal conditions.

Compared with the position of the lymphatic circulation in the ancestral series, one is almost tempted to characterize its development in the placental embryo as the reversional appearance of a system, formerly of much greater extent and importance, but now to a large extent replaced by more modern zoölogical acquisitions, and retained only in a modified and reduced form with greatly restricted functional application.

At any rate, there is no radical inconsistency in the observed facts, either of the phylogenetic or ontogenetic history of vertebrate lymphatic vessels.

In respect to their genesis in the mammalian embryo, it makes but little difference as to exact embryonic period in which they make their first appearance as definite lymphatic anlagen.

Their development may be synchronous with that of the earliest hæmal channels, or precede these, or finally, as seems to be actually the case, they may first appear distinctly after the main embryonic bloodvascular lines have been laid down.

Their ultimate secondary union with each other, and then with the venous system through the intervention of the complicated jugular lymph sacs, and the entire character of the completed adult lymphatic-system as a "shadow-picture" of the venous organization, suggests strongly that the mammalian lymphatic vessels have phylogenetically acquired this secondary position relative to the dominant hæmal vascular system.

This subordination of lymphatic to bloodvascular structures manifests itself not only in the morphological relations existing ontogenetically and in the adult between the two systems, but the same influence has operated to retard the embryonic appearance of the first definite lymphatic anlagen to a period in which the

blood-vascular organization has already assumed clear cut and definite character.

We thus reach the end-link in the long chain of successive differentiations which lead through the vertebrate series to the final stage in which the greatest attainable degree of independence between lymphatic and hæmal vascular structure has been reached, and in which the primitive relative value to the organism of the two systems has been reversed, in obedience to the law which has stamped the bloodvascular system as the main organic line of evolutionary progress.