Three Centuries of Lymphatic History – an Outline*

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Some ten years ago, during the Christmas holidays, Mrs. *Mayerson* and I were invited to a cocktail party. The party was in full swing when we arrived. As we entered the room, one of my intimate friends looked up and exclaimed to the assembled guests: "Look who's here – the lymphomaniac." The label has stuck and it is in this vein that I now say to you as a lymphomaniac to fellow lymphomaniacs, many thanks for giving me the chance to "ventilate". I am properly sensible of the privilege of being with you and reviewing some of the developments regarding the lymphatic system as they have occurred over the last three centuries. Lymphomania is obviously infectious and contagious and knows no national boundaries for otherwise it would be diffcult to explain the magnificent attendance at this Congress.

Where should we start our historical survey? Who first saw a lymphatic and recognized its function? This is always a difficult question to answer. There are many references in ancient *Hebrew* and *Greek* literature of swelling of the foot and other parts of the body, of elephantiasis and lymphedema, Erasistraties of Chios in Mesopotamia described "arteries containing milk", a fairly accurate description of the mesenteric lymphatics or lacteals, in the third century B.C. Herophilos of Chalcedon, also writing during the same period, made interesting and reasonably accurate descriptions of lymphatics. These were forgotten and it actually took 18 centuries for the study of anatomy and physiology to become sophisticated enough to enable observers to describe and relate their findings and attempt to explain them.

The first "modern" account of lymphatics is that of *Gaspar Aselli* better known by his latinized name, *Asellius.* He was born in Cremona, Italy in 1581, studied in Padua and, later, became professor of anatomy and surgery in Milan, where he also served as Surgeon-in-Chief of the Royal Army. In 1622, he discovered the lacteals. The account of the discovery as translated by Sir *Michael Foster* (1) deserves to be recited.

"On the 23rd of July of that year (1622) I had taken a dog in good condition and well fed, for a vivisection at the request of some of my friends, who very much wished to see the recurrent nerves. When I finished this demonstration of the nerves, it seemed good to watch the movements of the diaphragm in the same dog, at the same operation. While I was attempting this, and for that purpose had opened the abdomen and was pulling down with my hand the intestines and stomach gathered together in a mass, I suddenly beheld a great number of cords as it were, exceedingly thin and beautifully white, scattered over the whole of the mesentery and the intestine, and starting from almost innumerable beginnings. At first I did not delay, thinking them to be nerves.

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But presently I saw I was mistaken in this since I noticed that the nerves belonging to the intestine were distinct from these cords, and wholly unlike them, and, besides, were distributed quite separately from them. Wherefore struck by the novelty of the thing, I stood for some time silent while there came to my mind the various disputes, rich in personal quarrels no less than in words, taking place among anatomists concerning the mesaraic veins and their function. And by chance it happened that a few days before I had looked into a little book by *Johannes Costaeus* written about this very matter. When I gathered my wits together for the sake of the experiment, having laid hold of a very sharp scalpel, I pricked one of the cords and indeed one of the largest of them. I had hardly touched it, when I saw a white liquid like milk or cream forthwith gush out. Seeing this, I could hardly restrain my delight, and turning to those who were standing by, to *Alexander Tadinus*, and more particularly to Senator *Septoluis*, who was both a member of the great College of the order of Physicians and while I am writing this, the Medical officer of Health, 'Eureka' I exclaimed with Archimedes, and at the same time invited them to the interesting spectacle of such an unusual phenomenon. And they indeed were very much struck with the novelty of the thing."

That *Asellius* should have exclaimed 'Eureka' seems to me to be most inappropriate for he really wasn't looking for lymphatic vessels. Rather this was a fine example of what we now term "Serendipity". Be that as it may, *Asellius* operated on another dog on the next day and, to his disapointment, no vessels were visible. He correctly concluded that the absence was related to time of feeding and again tried the experiment, this time on a dog recently fed, with his same friends watching, and now white vessels were again visible.

Asellius' discovery was unquestionably exciting. It was also disconcerting, for the facts needed to be explained and fitted into current *Galenic* concepts. *Asellius* concluded that chyle was absorbed by the vessels and then transported to the liver. Chyle was "white" blood which the liver transformed into red blood.

Asellius' findings were published posthumously through the generosity of *Nicholas Peiresc* in 1627 (2). As *Fulton* (3) points out, the plates accompanying this tract are the first colored anatomical illustrations of importance in the history of bookmaking. It may be of interest that the same *Nicholas Peiresc*, who was the Principal Court Judge of Aix-en-Provence, confirmed *Asellius'* findings in man. He had a condemned criminal fed before execution and on autopsy some 90 minutes later found lacteals filled with chyle.

Recall that *William Harvey* had announced his discovery of the circulation on April 17, 1616 – a week before Shakespeare's death – at his Lumlean Lecture to the College of Physicians in London but his experiments were not published until 1628. *Asellius* could not have been aware of *Harvey's* concepts, but *Harvey*, on the other hand probably knew of *Asellius'* work published the previous year and certainly knew of it later. But *Harvey*, in spite of his brilliance and deep insight, could not divorce himself completely from *Galen* and, to his dying days, maintained that lymphatics were merely veins which carried white blood to the liver.

Asellius' discovery, of itself, was perhaps not of prime importance for it remained an isolated bit of knowledge until 1651, when *Jean Pecquet*, a French physician who practiced first in Dieppe and later in Paris, published his "Experimenta nova anatomica" and made known experiments he had performed as a medical student in

Montpellier (4). He had opened the thoracic cavity of a dog and removed the heart and noticed a large quantity of thin whitish fluid escape from the stump of the superior vena cava. At first, he supposed that an abcess had been opened; but he noted that, upon compressing the abdomen, the flow of fluid increased. Further experiments enabled *Pecquet* to accurately describe the cisterna chyli and its continuation as the thoracic duct. He showed that *Asellius'* lacteals pour their contents into the receptacle and that the thoracic duct pours its contents into the venous system at the junction of the jugular and subclavian veins. In the following year, 1651, *Johannes van Horne,* Professor of Anatomy in Leyden, independently made the same discovery in man as he was performing an autopsy.

As *Foster* (1) has pointed out "By this discovery of the thoracic duct and its entrance into the veins, a wholly new aspect was given to *Asellius'* original observation. The mere existence of special vessels such as the lacteals in the mesentery was quite consistent with, indeed supported the old view of the circulation. *Pecquet's* observations were wholly inconsistent with them; but between *Asellius* and *Pecquet, Harvey's* book had appeared; and it may be taken as a proof of how profoundly *Harveys'* arguments had in so short a time influenced men's minds, that *Pecquet's* observations, which if put forward thirty years before would have been rejected as impossible, were now accepted without misgivings. Indeed they afforded no little support to the new theory of circulation."

Further support was supplied at the same time by *Olaus Rudbeck.* This was a remarkable man. He went to the University of Upsala in 1648 where he studied medicine and botany. As a medical student he worked on the lymphatic system, the details of which I shall discuss shortly. After finishing his medical course, he went to Leyden and later returned to Upsala to teach not only medicine but chemistry, astronomy, mathematics, architecture and music. In 1661 at the age of 31 he was made Rector of the University but found time to contribute extensively to the field of Botany as well as to write a historical monograph in which he attempted to prove the antiquity of Swedish culture (5).

Rudbeck's interest in the lymphatic system was stimulated in 1650 by his observation of a whey-like fluid present near the supra-clavicular notch in a calf that was being butchered. He then began a series of experiments which eventually involved the use of almost 400 animals (cats, dogs, calves, sheep, goats and wolves). In these experiments, he discovered the lymphatic plexus of the colon and rectum and he traced these structures to the cisterna chyli and showed that the vessels described by *Asellius,* originating in the spleen, liver and bowel wall also empty their contents into the cysterna chyli. Influenced by *Harvey,* he traced the course and flow in lymphatics all over the body by ligating the lymphatic vessels and watching them distend below and collapse above the ligatures. His chief contribution, like that of *Harvey's* is that he really showed the lymphatic system as being a second "circulation", that flow of lymph was away from tissues and that lymph eventually returened to the blood stream via the thoracic duct Incidentally, he emphasized that the liver was in no way involved in the formation of blood. It was *Rudbeck,* too, who gave one of the most succinct descriptions of the difficulties in working with the lymphatics, difficulties only too well known to many of us. He wrote, in 1653, as follows:

"Of the many structures difficult to find in anatomical dissections, these vessels, I must confess, are by no means the least. For usually they will not tolerate the finest blunt probe, a sharp knife, a suction tube, or any other instrument whatever. And even though abundantly present, they are often obscured by fat, or are overlooked if not at the moment filled with fluid, when seen they may disappear if not ligated. Thus in elusiveness they rival the lacteals and must be handled with utmost care."

I shall not go into detail about the controversy that developed at this time as to whether *Rudbeck* should receive the credit for having "discovered" the lymphatic system or whether *Thomas Bartholinus* deserves priority. *Bartholinus* was professor of anatomy in Copenhagen. Influenced by the work of *Pecquet,* he made numerous observations on the anatomy of the thoracic duct and lacteals. He eventually came to the same conclusions as did *Rudbeck,* denying the function of the liver in blood formation. The controversy was an example of lymphomania at its worst, with accusations of plagiarism and considerable other invective. In retrospect, both investigators contributed considerably to our knowledge of the lymphatic system and should share the honors and our respect.

We now move about a century for distinct progress in the field – to the work of *William Hunter* and his pupils. During this century, the injection corrosion technique was developed by *de Groat, Swammerdam* and *Ruysch* and applied to the study of the lymphatic system as a supplement to the dissection technique. *Antin Nuch,* surgeon in the Hague, used mercury in this way, a method widely adopted by other investigators. In 1745, *Lieberkühn* brought the use of the microscope to the study of the origin of lymphatics in intestinal villi. As *Gans* points out (6), *Lieberkühn's* description of their origin in the bowel wall can be found unaltered in some of our contemporary anatomy textbooks.

I agree with *John Fulton* (3) that the foundation of modern knowledge concerning the function of the lymphatics was laid by the *Hunters, John* and *William,* their collaborator, *William Hewson* and *William Hunter's* pupil, *William C. Crinkshank.* In 1784, *William Hunter* (7) wrote "I think I have proved, that the lymphatic vessels are the absorbing vessels, all over the body; that they are the same as the lacteals; and that these altogether, with the thoracic duct, constitute one great and general system, dispersed through the whole body for absorption; and this system *only* does absorb, and not the veins; that it serves to take up, and convey, whatever is to make, or to be mixed with the blood, from the skin, from the internal cavities or surfaces whatever. This discovery gains credit daily, both at home and abroad, to such a degree that I believe we may now say, that it is almost universally adopted; and if we mistake not, in a proper time, it will be allowed to be the greatest discovery, both in physiology and pathology, that Anatomy has suggested, since the discovery of the circulation". This is certainly reasonably close to our present concept of the function of the lymphatics.

In spite of *Hunter's* claim, however, his concepts were far from "almost universally adopted". Indeed, *Magendie* in his textbook on Human Physiology written in the early part of the nineteenth century (8) spends considerable space in describing experiments by him and others in which results were diametrically different from those of *Hunter.* To quote "Thus the principal experiment of a distinguished author, who is said to have seen other fluids than chyle absorbed by the lymphatic vessels appears to be, if not an illusion, at least so imperfect that no important inference can be drawn from it. The other experiments of *John Hunter* being less conclusive than this, I have passed them over in silence. They have been unsuccessfully repeated by *Flandrin,* nor have I myself been more fortunate in attempting them".

The arguments and discussion continued until after the middle of the century when *Carl Ludwig,* the great teacher and physiologist, and his pupils showed that it was possible to cannulate subcutaneous lymphatics and thus collect lymph form sources other than the thoracic duct. Furthermore, the course of the lymphatics could be traced by use of Berlin blue, a substance much less toxic than the tracers previously used. It was now possible to relate events in blood capillaries to lymph formation and lymph composition and *Ludwig* brought forth evidence which he interpreted as showing that it was formed by a process of filtration. Lymph flow was determined by differences of pressure and composition between the blood in the capillaries and the tissue fluid which accounted for exudation from the capillaries. Secondly, chemical differences between blood and tissue fluid set up osmotic interchanges through the capillary wall (9).

But here again, there were difficulties. Increased capillary pressure as a result of venous obstruction increased lymph flow but there was only an insignificant change when hyperemia was produced or when there were significant increases in systemic blood pressure. And thus there began another controversy between investigators who followed *Ludwig's* mechanistic approach and investigators who followed *Heidenhain* in the belief that "vital" forces were additionally involved, i.e., that there were specific substances, lymphologues, which acted specifically to increase transudation from capillaries just as diuretics increase secretion of urine by the kidney. *Heidenhain* maintained that the water in lymph came from the cells and fibers of the tissues rather than from the blood stream (10). Even my old chief and mentor, *Lafayette B. Mendel,* got into the controversy during his sojourn in *Heidenhain's* laboratory in Breslau (11). He supported *Heidenhain* because he found a higher concentration of NaI in thoracic duct lymph than in the blood. *Heidenhain* and his pupils had also found a higher concentration of sugar and NaCl in lymph than in the blood.

The controversy was finally put to rest by the brilliant, painstaking work of *Starling* during the latter part of the last and early part of this century. Step by step he examined the work of the "vitalistic" school and by careful experiments pointed out the flaws in reasoning of *Heidenhain* and his group. His results are summarized in his *Herter* lectures given in New York in 1908 and published in the historic monograph entitled "The Fluids of the Body" (11). I should remind you that *Starling* went to work with *Heidenhain* in Breslau in 1892 and while there, went along with *Heidenhain's* explanations and concepts. It was only after his return to England and much repetition and refinement of the Breslau experiments that he came to doubt the interpretation of his results. In 1896, he discovered the missing factor in support of *Ludwig's* filtration hypothesis – the colloid osmotic pressure of the plasma proteins. It had been previously supposed that the osmotic pressure of proteins, being so insignificant compared to that of salts, must be of no account in physiological processes. *Starling* showed the reverse to be true since the capillary is impermeable to proteins. He set to work to measure the osmotic pressures of the proteins in serum and found them to be, though small, of the order of magnitude of the capillary pressure. The problem was solved. The hydrostatic pressure and the osmotic pressure supplied the balance of forces necessary to explain the experimental observations.

Time does not permit a detailed account of how *Starling*, blow by blow, demolished his opponent's arguments. But it is difficult to resist some of his quips such as "I would point out at the onset that we are not justified in assuming an unknown cause so long as phenomena can be explained by a cause which is familiar to us". And further "To call in vital activity as a sort of irresponsible deity to explain irregularities in our experimental results is an unscientific and I might say cowardly device".

Starling began his fourth *Herter* Lecture as follows: "Under the term internal media of the body we include three distinct fluids, all of which may be regarded as derived from the original coelonic fluid. These are:

1. The circulating *blood*, contained in a closed system of tubes and everywhere separated from the tissues by a layer of endothelium.
2. The *lymph*, also contained in a closed system of endothelial tubes connected at one or more points with the blood vascular system.
3. The *tissue fluid*, filling all the spaces of the body and in immediate contact with the tissue cells.

This last-named is the real internal medium of the body, into which the cells discharge their waste products, and from which they derive their sustenance as well as their necessary oxygen."

In boldly asserting that the lymphatic system was a closed system of tubes, he denied the concept of *von Reklinghausen* that the lymphatics opened into the tissue spaces and firmly aligned himself with another stalwart, *Florence Sabin* who, in 1911 (13) wrote "Lymphatics are modified veins. They are vessels lined by an endothelium which is derived from the veins. They invade the body as do blood vessels and grow into certain constant areas; their invasion of the body is, however, not complete for there are certain structures which never receive them. The lymphatic capillaries have the same relation to tissue spaces as have blood capillaries. None of the cavities of the mesoderm, such as the peritoneal cavity, the various bursae and serous capillaries, forms any part of the lymphatic system. The lymphatic endothelium once formed is specific. Like blood vessels the lymphatics are for the most part closed vessels".

Rusznyak, Földi and *Szabo* in their monograph on *Lymphatics and Lymph Circulation* (14) have reviewed the controversies regarding the origin of lymphatics and their embryological development. They aptly conclude:

"It was the appearance of *Sabin's* work that released the long debate of American anatomists about the evolution of lymphatics, a debate which gave rise to nearly a hundred publications without leading the problem essentially nearer to a solution and without succeeding in inducing any of the opposing parties to revise their attitude." This is but another example of the peculiarities of lymphomaniacs.

We have now arrived to the time of the first World War and its aftermath when science marched forth as never before. Work on the lymphatic system was no exception. The introduction of polyethylene tubing facilitated cannulation of lymphatics. New dyes and advances in radiological techniques made visualization more feasible in experimental animals and patients. The introduction of isotopes made possible more definitive studies on exchange between capillaries and lymphatics. The electron microscope gave us a better idea of intimate structure. It would be presumptuous of me to attempt to even summarize the progress in the last several decades. Many of you have contributed to this progress. But I would be remiss if I did not conclude with some mention of *Cecil K. Drinker,* for it was he who aroused my interest (and I suspect that of many others) in the lymphatic system. As a young instructor, I had the assignment of developing a laboratory course in physiology for medical students. Having read *Drinker's* publications latter summarized by him and *Fields* in the monograph on *Lymphatics, Lymph and Tissue Fluid* published in 1933 (15), I decided it would be good to devise a laboratory experiment on lymph. The first step was to learn to cannulate the thoracic duct in the dog. This was a frustrating experience but I finally arrived at the point when I could cannulate it 4 out of 5 times and so for some 30 years, I, like *Asellius* and *Rudbeck,* demonstrated with enthusiasm the effect of various experimental procedures on lymph flow to my friends, students – in fact to anyone who would stop and listen. In retrospect, however, I perhaps missed something in not having as illustrious auditors as did *Asellius* and *Rudbeck* – I did not ask my Congressmen and Senators to watch me demonstrate.

Drinker, as you recall, maintained that the principal function of the lymphatic system was to return to the blood stream protein which had leaked from blood capillaries. His evidence was presumptive and derived chiefly from differences in protein concentration in lymph and serum. In the early forties, with the advent of isotopes, I was able to label the serum proteins with radioactive iodine and show directly that lymph protein originated chiefly from the blood stream (16). It was my privilege and good fortune to discuss this data with Dr. *Drinker* shortly before his death and to witness his pleasure in this confirmation of his concepts.

I have given you episodes in the history of the lymphatic system this afternoon from the point-of-view of a physiologist. There is much more of interest to tell about the subject. Hopefully, programs of future Congresses will reserve time for the immunologist, the clinician and other specialists to continue the recitation of the exciting development of concepts regarding the function of the lymphatic system in health and disease.

Again, my thanks to you for the honor and privilege of being here. Lymphology has come of age. Much important history is being made by all of you. Good luck and may your lymphomania persist and intensify to the benefit of all mankind.

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Blastogenic Responses of Lymphocytes from Patients with Untreated and Treated Lymphomas [1, 2]

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Introduction

Small lymphocytes play a central role in mammalian immune responses (1). These cells proliferate in lymphoid tissues, a proportion are long lived (2) and recirculate from lymphoid tissues through lymphatic channels to peripheral blood, and back through the lymphoid tissues (3). These cells participate in delayed hypersensitivity, homograft and graft versus host responses and may be the effector cells of these reactions (1). They are the immunological memory cells and both specific immunological reactions and tolerance can be transferred with them from one animal to another (1).

An effective method for study of human peripheral blood lymphocytes is to culture them with mitogenic agents such as the red kidney bean extract phytohemagglutinin (PHA) (4). This substance induces the majority of peripheral blood lymphocytes from normal subjects to enlarge into easily recognizable lymphoblastoid cells. This response has been used as a measure of the functional normality of lymphocytes although it does not necessarily reflect their ability to respond immunologically (5).

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