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HISTORY

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What's old is new again: The anatomical studies of Franklin P. Mall and the fascial-interstitial spaces

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Abstract

Franklin Mall was one of the foremost scientists of the turn of the 19th century, an exemplary mentor as well as researcher, and his revolutionary contributions are still relevant today. Mall's early training in Leipzig with Wilhelm His and Carl Ludwig provided him with an unusual perspective on the integration of anatomy and physiology, and his interest in the links between structure and function guided the work he carried out after joining the faculty of the new Johns Hopkins University School of Medicine. Mall carried out innovative studies on the one hand using dye injection to trace blood and lymphatic supplies to different organs and on the other hand using "putrefaction" to digest tissues and study the organization of the reticular space, demonstrating that it was the underlying source of support for all the organs. These two studies of Mall's, carried out independently, provide the basis for modern studies integrating the understanding of fascia and interstitial spaces.

KEYWORDS
artery, capillary, fascia, His, interstitium, liver, lymphatics, Mall, reticular network, Sabin

1 | INTRODUCTION

Franklin Paine Mall was one of the foremost scientists of his day (Figure 1), described as having "a mind brilliant and original, with a strange enigmatic quality and a complex combination of opposites—wit and wisdom, humor and sadness (Sabin, 1934a)." Noted for his particular contributions to anatomy and embryology, his scientific discoveries revolutionized the teaching of his day and have had a lasting impact on our understanding of the human body and its structure.

While Mall's forward-thinking approaches were notable in his own day, it is remarkable that they are equally relevant to the recent literature. Such is the case for recent studies broadening the understanding of the fascia and interstitium, which have their origins in the work of Mall and which, when viewed through the lens of Mall's findings, provide an understanding of the fascia and interstitium as an integrated structural network enclosing fluid-filled space.

Recent scholarship has approached the fascia and interstitium from two perspectives. On the one hand, clinical practitioners and fascia researchers have come to define fascia as including not only the musculoskeletal fascia but also most (if not all) fibroconnective layers of the body:

> The fascial system consists of the three-dimensional continuum of soft, collagen containing, loose and dense fibrous connective tissues that permeate the body. It incorporates elements such as adipose tissue, adventitiae and neurovascular sheaths, aponeuroses, deep and superficial fasciae, epineurium, joint capsules,

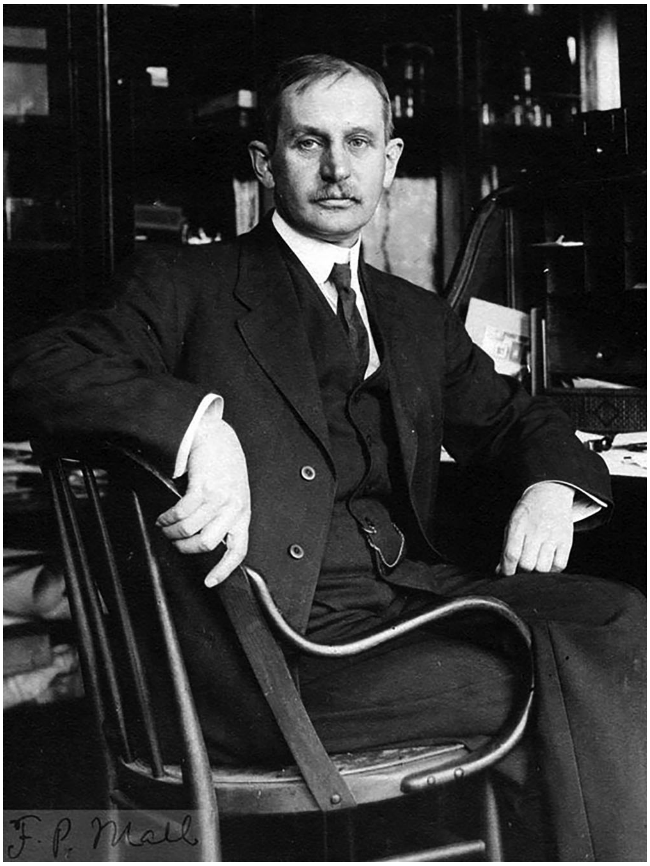

FIGURE 1 Franklin P. Mall, 1911

> ligaments, membranes, meninges, myofascial expansions, periostea, retinacula, septa, tendons, visceral fasciae, and all the intramuscular and intermuscular connective tissues including endo-/peri-/epimysium. The fascial system *surrounds, interweaves between, and interpenetrates* all organs, muscles, bones and nerve fibers, endowing the body with a functional structure, and providing an environment that enables all body systems to operate in an integrated manner. (Stecco et al., 2018)

These "dense fibrous connective tissues that permeate the body" are none other than those that were first well described by Mall. As noted in a "Biographical Memoir of Franklin Paine Mall" by his mentee Florence R. Sabin at the U.S. National Academy of Science in 1934 (Sabin, 1934b) (https://profiles.nlm.nih.gov/spotlight/rr/feature/biographical-overview):

> Mall then discovered that the reticular network of fibers [...] forms the supporting tissues of all the organs, and his work is considered as having established the fact that the reticular framework of organs is independent of cells. Mall showed that reticulum is so labile a framework that it adapts itself to and supports all of the functioning cells of each organ. Thus, when the cells of each organ [...] are removed, the reticular framework so faithfully outlines the patterns of these cells that each organ can be told by the framework alone.

Researchers coming from the perspective of the liver and biliary tree, on the other hand, recently used in vivo microscopy to propose that interstitial spaces throughout the human body are at scales larger than previously recognized, encompassing the fascia to form an interconnected network (Benias et al., 2018).

This work, too, has its origins in the studies of Mall. There are few students of hepatology who have not heard of the eponymous "space of Mall," a microscopic space between stromal elements in portal tracts and found (in cats at least) in the peri-portal region. However, as well known as the space of Mall is, one is hard pressed to find schematic representations, let alone photomicrographs documenting its presence. While it merits an entry in Wikipedia, it is poorly enough understood to receive only one imprecise sentence from late 2022: The periportal space (Latin: spatium periportale), or periportal space of Mall, is a space between the stroma of the portal canal and the outermost hepatocytes in the hepatic lobule and is thought to be one of the sites where lymph originates in the liver. (Burt & MacSween, 2007).

As these two groups—fascia researchers and hepatobiliary researchers—come together to explore the fascial-interstitial network of the whole body, Mall proves to be a singular figure whose early work on the function and physiology of tissues provides the historical context from which contemporary insights can be viewed and woven together.

2 | MALL'S EARLY SCIENTIFIC YEARS: INTEGRATING ANATOMY AND PHYSIOLOGY UNDER THE INFLUENCE OF HIS AND LUDWIG

Mall was born in 1862 in the small and newly-established frontier town of Belle Plaine, Iowa. At age 18, he matriculated at the University of Michigan Medical School, where the curriculum had just been extended to the uniquely long duration of 3 years. After this, in what proved to be a transformational experience that provided a foundation for his most important discoveries, he undertook postgraduate studies in Germany.

Mall spent his first year in Heidelberg, intending to specialize in ophthalmology. However, German universities were in the midst of an intellectual "Golden Age" (Anderson, 1914; Sabin, 1934a), and Mall had the opportunity to move from "the medical high school" at the University of Michigan to the very different environment of European university life, with opportunity for scientific exploration (Sabin, 1934a). As Mall later wrote:

> How different is the study of medicine in Europe from that in America! Their freedom reigns and students

> wander from place to place being controlled only by a fairly rational system of examinations in case they wish to graduate. Weak students fall out, for there is no cram system to drive them onward; able students select great men as teachers and thereby develop themselves and become stronger. (Mall, 1905)

In the fall of 1884, Mall went to Leipzig in search of a research position under Wilhelm His, chairman of anatomy at the University of Leipzig and one of the greatest anatomists of the time (Figure 2). However, His rarely accepted students, and Mall wrote that His turned him down many times before finally accepting him into his laboratory (Mall, 1905). Mall began his work in His's lab studying gill arch development in the chick in an effort to confirm his mentor's hypothesis that the thymus was the product of the ectoderm of the third gill cleft (Mall, 1888a). Instead, Mall's research suggested that the thymus originated in the endoderm of the pharynx. It was a period of debate and the exchange of letters between them—with His's challenges and corrections to Mall's paper and Mall's responses—demonstrates Mall's assertion of independence in his research (Mall, 1888a). This record of these interactions also vividly shows the generosity and lack of insecurity His showed as his student corrected some of his previous findings, a model for confident mentoring and, one may surmise, a foundational experience for the young investigator. To quote Mall writing about his mentor:

> That a great man can increase his productivity enormously without the questionable use of young colleagues is shown by example in the life of His.... All of the details were left to the pupil and it annoyed him to be consulted regarding them. He desired that the pupil should have full freedom to work out his own solution and aided him mainly through severe criticism. (Mall, 1888a).

In October of 1885, on the recommendation of His, Mall applied for entry into the laboratory of Professor Carl F. W. Ludwig, the greatest physiologist of his day and considered by some to be the personification of an ideal professor (Sabin, 1934a) (Figure 3). Ludwig, like His, at first refused to see Mall, in this case because the laboratory was already full. Fortuitously for Mall, however, a an opening arose and it was offered to Mall, who received the letter literally after he had sent off his trunk, intending to leave Leipzig for a position elsewhere (Sabin, 1934a).

In his work with Mall, Ludwig emphasized structure as it related to function, suggesting that Mall study the vasculature of the small intestine and teaching him methods to inject blood vessels and, albeit

FIGURE 2 Wilhelm His, Sr., 1900

FIGURE 3 Carl F. W. Ludwig, date unknown

with greater technical difficulty, lymphatics. Use of these methods later in his career enabled him to produce the stunning lithographic plates found in his article on the stomach (Mall, 1896a, 1896b, 1896c). Notably, in his introduction to the paper, Mall emphasized the critical link between the distribution of blood flow (described in extraordinary detail for all layers of the stomach) and its flow rate and pressure, concepts clearly based on his work with Ludwig.

Per Mall's mentee Florence Sabin, this was still a time before "that artificial separation which certain techniques, such as the kymograph of Ludwig and the microtome of His, were soon to bring between anatomy and physiology." (Sabin, 1934a) Mall's studies with the two great Leipzig professors provided him with an unparalleled and integrated education in both anatomy and physiology, setting the stage for his ground-breaking later work.

3 | MALL'S RETURN TO AMERICA: THE NEW JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

During his time in Leipzig, Mall met William H. Welch (Figure 4), newly appointed Professor of Pathology at Johns Hopkins University in Baltimore and soon to be the first dean of the new Johns Hopkins Hospital and Medical School (Sabin, 1934a). Upon his return to the US in 1886, Mall applied to Welch for an academic position and was appointed a Fellow in Pathology at Johns Hopkins, working as an assistant to Welch until 1889; in the spring of 1893, after a brief period as Adjunct Professor of Anatomy at Clark University, Mall became Professor of Anatomy at the new Johns Hopkins School of Medicine. This was to be key to the remainder of Mall's career and to some of his most important research, as it led to his interactions with William Halstead, who became the first Professor of Surgery at the Johns Hopkins Hospital and who incorporated Mall's research into his development of the Halstead mattress suture, and Florence R. Sabin (Figure 5), a mentee who became one of the great American developmental anatomists.

FIGURE 4 William H. Welch, 1900

This combination of interactions could only have happened at Johns Hopkins. At the time, most of the medical schools in the United States were restricted to men. A significant percentage of the money to establish the new Johns Hopkins medical school, however, was raised by the Women's Medical Fund Committee, formed by four Baltimore women, and donated with the stipulation that the new school accept women. Thanks to these efforts, Sabin was admitted in 1896 in the fourth class of students. Sabin's success in laboratory work brought her to the attention of Mall, and in 1901 she was awarded a fellowship to work with him (Sabin, 1934a). She went on to become one of the foremost anatomists of the modern era, the first woman appointed full Professor at the Johns Hopkins School of Medicine and the first to be elected President of the American Association of Anatomists (Figure 5). In 1925 she became the first (and for 20 years remained the only) woman to be granted membership in the US National Academy of Sciences. She was a leader in studying the developmental origins of lymphatics and, among other structures, connective tissue, contributing significantly to some of Mall's most important findings. Sabin's respect for her mentor Mall was such that she wrote an extraordinary biographical memoir and then a full biography of his career (Sabin, 1934a, 1934b).

4 | THE SPACE OF MALL AND LYMPHATICS

The first of Mall's findings that is particularly relevant to the fascial interstitial network is, as noted above, the recognition of the "space of Mall." The microinjection expertise Mall developed during his time in Ludwig's group led to studies whereby he injected pigmented gels into the vascular supply of cat livers: cinnabar into hepatic arteries and Prussian blue into portal veins. With either tracer, spaces within and around the stroma of the portal tracts filled, and when both were injected simultaneously, mixing was observed. A prominent feature of the liver thus visualized was a "periportal" space, though the spaces described in the paper extend throughout the portal tract stroma (Figure 6).

Mall refers to these spaces as "lymphatics" and wrote that "blue extravasates from the capillaries at the center of the portal unit and invades the connective tissue to reach the beginning of the lymphatics, when of course it is carried rapidly from the liver." (Mall, 1906). Notably, Mall's identification of these as lymphatics differed from his earlier lymphatic studies of the intestines. In the intestines, he had observed the lymphatic filling by their direct injection. In

FIGURE 5 Florence R. Sabin, date unknown

the liver, rather, it was an inference based on the way pigments mixed in the portal tract spaces after more proximal, vascular injections. This work introduced the concept that stromal spaces in the liver are pre-lymphatic.

5 | PUTREFACTION AND RETICULAR NETWORKS

Mall's years at Johns Hopkins and in particular his interactions with William Halsted led to his studies of reticular networks. Halsted was interested in intestinal anastomoses and Mall's work indicated that the fibrous tissues of the submucosa could be used to hold sutures, ultimately leading to the development of the Halstead mattress suture and the publication in 1897 of Halstead's work on intestinal anastomosis (Halsted, 1887; Sabin, 1934a).

This work, which foreshadowed modern-day studies on the fascial interstitium, resulted from Mall's studies (only partly published) of "putrefaction"—whereby he used bacteria fermentation and digestion to "dissect" different tissues, identifying and separating fibrous, reticular, and elastic components. Likely as the result of his studies on the intestinal wall carried out in Ludwig's laboratory, Mall became particularly interested in the reticulum.

When Mall was a student of His, he and his mentor were guided by Bichat's concepts regarding the importance of the connective tissues and focused considerable effort on the "white fibrous coat" (submucosa) of tissues and the "elastic membrane." Increasingly, however, Mall shifted his focus to the "reticulum." His initial knowledge of the structure was likely derived from Billroth (quoted by His in 1861) who identified the multi-polar cells associated with the reticular framework of lymph nodes, and from Ranvier (Ranvier, 1875) and Bizzozero (Bizzozero, 1872) who showed that these cells rested on a network of fibers. In 1861, His himself identified the reticulum by shaking frozen sections of lymph nodes in water until the lymphocytes were gone (His, 1861). This preparation method undoubtedly had an impact on Mall's thinking about reticular tissue, leading to his work that ultimately established the fact that the reticular framework supports the organs of the body in a manner independent of cells.

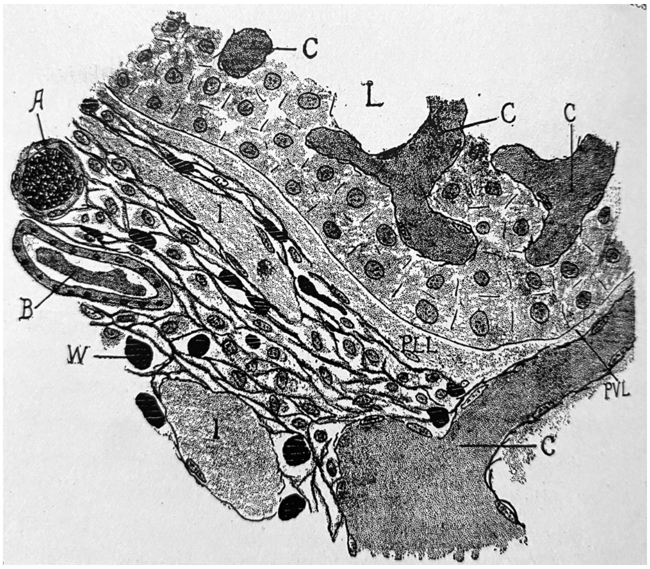

FIGURE 6 Mall's drawing of the portal tract of a cat, showing what would come to be known as the "space of Mall", imaged with Van Gieson stain after injection of the hepatic artery with cinnabar gelatin and the portal vein with Prussian-blue gelatin. This "perilobular space" is labeled "PLL", though other, smaller spaces are evident, as well, between the "bundles of white fibrous tissue" that are labeled "W." Other labels: L, lobule of the liver; D, capillaries; A, artery; I, lymph vessels; PVL, perivascular lymph space; w, bundles of white fibrous tissue. 500X. From Mall (Mall FP. 1906. A study of the structural unit of the liver. American Journal of Anatomy. Volume V, pp. 18–308) (reproduced with permission from the publisher)

This is where the digestive enzymes of bacteria proved useful for Mall:

> Mall discriminated the fibers of the connective tissues by various chemical means; on the one hand, the yellow elastic tissue, and on the other hand, the two closely related types, the white fibrous bundles and the reticular fibers. The yellow elastic tissue, with its protean forms, fibers, fine and coarse, dense networks and membranes, he found to be made up of two different substances, an outer, continuous membrane, not taking any stain, and an inner, discontinuous, stainable material, giving the appearance of fenestrae to the membranes. The elastic tissue he found resistant to acids and alkalies, unless boiled in strong concentration. It, however, could be digested slowly in pepsin, rapidly in pancreatin and papain. In this process, it was the inner stainable material that was attacked by the digestive enzyme. The converse was true of the white fibrous tissue and the reticulum, for they were destroyed by acids and resisted digestion. (Sabin, 1934a).

Application of these enzymes allowed for the decellularization of any tissue or organ to which they were applied while the "reticulated tissues" resisted the actions of the enzymes (Mall, 1888b). In the words of Sabin, Mall thus showed that "the reticular framework so faithfully outlines the patterns of these cells that each organ can be told by the framework alone. When it is realized that this framework also conforms to the pattern of new growths of cells, the significance of this tissue, both in normal structure and in pathological processes can be grasped" (Sabin, 1934a).

Sabin also wrote in 1934: "Mall's beautiful preparations of reticulum are known to all histologists," and quoted from a letter from Ludwig to Mall, written on November 16, 1890: "Day before yesterday on November 14th, I spread your beautiful plates before the astonished sight of the Fellows of our society." (Sabin, 1934a) The work so fascinated Ludwig that he, in turn, took up similar studies in his own laboratory in order to visualize connective tissue fibers.

Mall's plates demonstrated that each organ could be identified from its reticular framework (Figure 7).

As Sabin describes for his preparation of spleen:

> Some of the most beautiful of Mall's preparations were made with the spleen; the method was as follows: the spleen was removed, care being taken not to injure the capsule except for two small cuts at each end, into which small glass cannulae were tied. The entire organ was then submitted to digestion with pancreatin or with putrefactive bacteria. When the splenic cells were digested out, the spleen was attached to the water tap and washed with a slow stream of water until clear of debris. Then the entire reticular framework was immersed in a solution of magenta, and then distended and dried with air. The entire framework of reticulum was then exposed by dissecting off the capsule. (Mall, 1888c)

Such studies had largely fallen out of favor by the middle 20th century. However, similar techniques have been re-visited in the early 21st century as multi-organ stem cell biology and regenerative medicine expanded their scope and ambitions. Decellularization has become a way to obtain matrix scaffolds of organs in which to seed stem and progenitor cell populations to create donor specific, transplantable, and functional organs (reviewed in Kajbafzadeh et al., 2015). While these technologies continue to expand and are moving closer to clinical use, the recently-reported ambitious decellularization of an entire sheep fetus validated Mall's finding—over a century after it was published—of a body-wide reticular framework (Kajbafzadeh et al., 2015). Notably, the authors of that paper do not refer back to Mall's prior findings, presumably unaware of his pioneering work after the passage of a century.

6 | MALL AND THE UNITY AND UBIQUITY OF THE FASCIAL INTERSTITIUM

Through observation of fluid filled spaces with in vivo endoscopic microscopy, the nature of the space of Mall and related spaces has

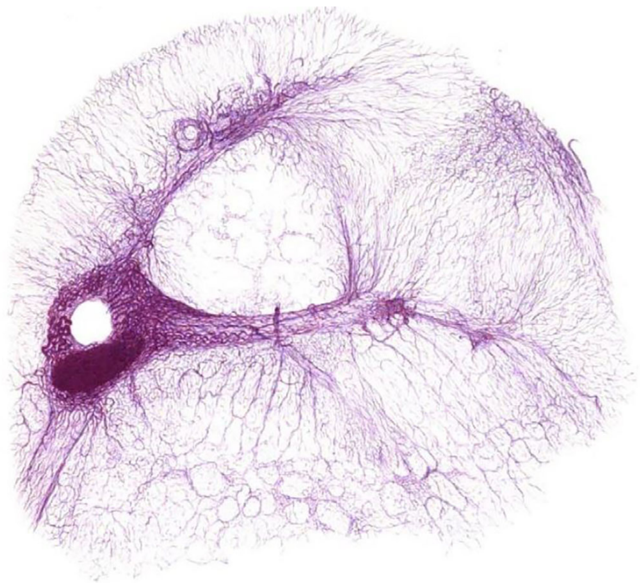

FIGURE 7 Cross section of reticular framework of a dog liver. Plate XVIII shows a transverse section of a liver lobule and the general direction of the fibers. It is shown that the main bundles of the reticulum are parallel with the capillaries. Midway between the apex and the base of the lobule there are, as a rule, three interlobular vessels. The circumference of the lobule between these vessels is filled with slightly ascending capillaries or small veins. As the apex is approached the interlobular vessels branch once or twice, and longitudinal sections of the reticulum at these points give pictures as shown in Plate XVIII. From Plate XVIII of Mall (Mall FP. 1896. Reticulated tissue and its relation to the connective tissue fibrils. The Johns Hopkins Hospital Reports. Volume 1, 171–208. (Reproduced with permission from the publisher)

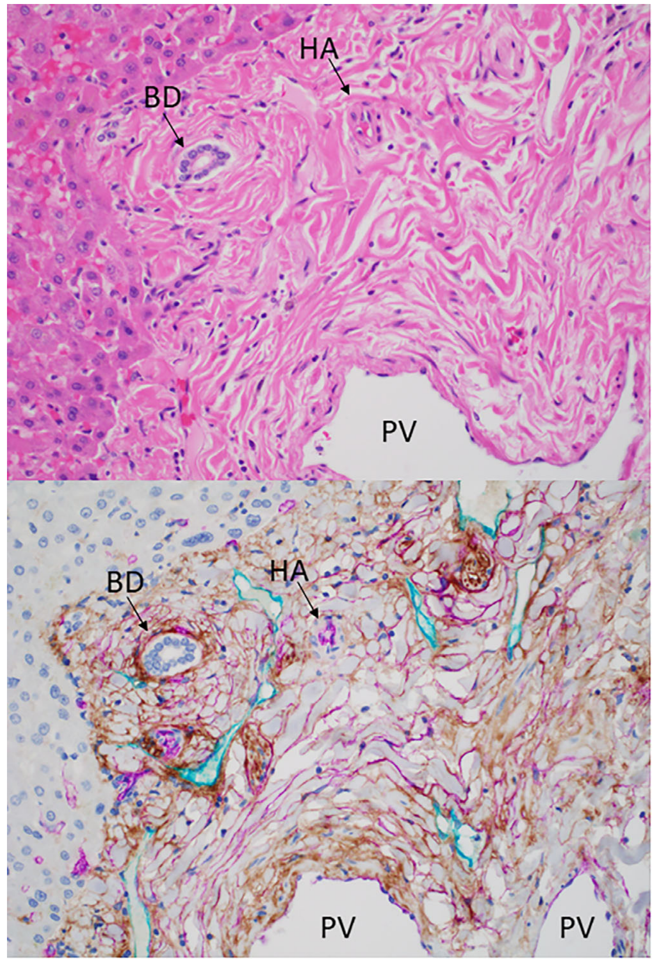

FIGURE 8 Portal tract of a human liver. BD: bile duct; HA: hepatic artery; PV: portal vein (magnification 20×). Top: Hematoxylin and eosin staining shows the thick (pink) collagen bundles that are the stromal meshwork of the portal tracts – what Mall referred to as the liver's inner "reticulum." The white spaces between bundles have otherwise usually been thought of as artifacts of tissue sectioning. The collagen bundles are somewhat finer close around the duct, vein and artery and larger in the areas between. The hepatocytes (left corner) have sinusoidal spaces between them, but no identifiable stroma at this magnification and with this stain. Bottom: Immunostain for CD34 (magenta) shows lining of endothelial cells faintly seen within the hepatic artery and lining the portal vein. Scant "capillarization" of hepatic sinusoids near the portal tract are also seen with this stain. D2-40 immunostain (teal) highlights lymphatic endothelial cells. Brown stain (peroxidase labeled hyaluronic acid, DAB chromogen) shows that the white spaces between collagen bundles (stained faintly blue with hematoxylin counterstain) contain abundant hyaluronic acid. These spaces are the human equivalent to those seen by Mall in his studies of cat liver portal tracts. The collagen bundles stain faintly blue with only a hematoxylin counterstain

also been more fully explored, a century after these structures were first reported (Benias et al., 2018). This investigation of the extrahepatic bile ducts (EHBD) showed that the submucosa of the EHBD, rather than comprising densely compacted connective tissue, is actually a fluid-filled interstitial space supported by a network of collagen bundles, the spaces disappearing with dehydration during tissue sampling and processing into microscope slides. This work further showed that these peribiliary spaces continued up into the liver's portal system and that similar spaces of the stroma around the portal veins and the hepatic arteries make up an interwoven system of such spaces (Benias et al., 2018; Cenaj et al., 2021). These are the human "spaces of Mall," the equivalent of what Mall described in the cat. Subsequent work (Cenaj et al., 2021) shows that these spaces are continuous through fibroconnective tissue networks of the body, essentially the point Mall himself made in viewing the peri-arterial, peri-venous, and peri-biliary stromas to define fully interconnected channels. The demonstration by staining that hyaluronic acid fills all these "empty" spaces confirms that these portal spaces are a unified interstitial network, not virtual or artefactual, but physiologically relevant (Figure 8), filled with macromolecules with unexplored physiological relevance (Khandekar et al., 2020).

7 | SUMMARY

Mall's histological and anatomical insights of over a century ago, as selectively described here, arose on the one hand from his interest in tracing the blood and lymphatic supplies of organs using dye injection techniques, and on the other hand from his digesting cells from tissues and organs to reveal their underlying reticular networks. These were two independent projects for Mall, but taken together today they provide a crucial foundation for current research (Mall, 1888b; 1896a, 1896b, 1896c). Contemporary descriptions of his ideas about the continuity that he called "the reticulated tissues" can be found in a variety of current reviews and textbooks (Schleip & Huijing, 2012; Stecco, 2018; Stecco et al., 2018; van der Wal, 2015). Mall's injections of the hepatic artery and portal vein showed complete filling of the extravascular space, suggesting a complex, inter-anastomosing network, at least in the liver. Recent data demonstrating fluid flow through the submucosa of the extrahepatic bile duct and skin, and showing that similar fluid-filled spaces cross tissue and organ boundaries, are the modern-day extension of Mall's work well (Benias et al., 2018; Cenaj et al., 2021). Thus, Mall's experiments, carried out independently, provide the basis for developing a contemporary and integrated system-wide view of fascia and interstitial tissues.

Beyond the scientific specifics, Mall was an exemplar of the biomedical scientist of his day. Boundaries between disciplines were not as well fixed at the turn of the prior century as they are a century later, and Mall's work benefitted greatly from the integration between anatomy and physiology research at the time. Mall, his mentors His and Ludwig, and his mentee Sabin carried out studies that were more descriptive than quantitative and their missions were not so much hypothesis driven as in the tradition of the "natural philosophers" of the 19th century. Observation and techniques to enhance observation were the lynchpins of the research of Mall's time.

In the 20th century, biomedical sciences became divided into specific domains such as cell biology and molecular biology. These reductive techniques were exceptionally powerful in some ways over the efforts of the prior generations. What might have been called "tissue biology" fell from primacy, often dismissed by funding bodies and editorial commentators as "merely descriptive." Science in the 21st century, however, now reaches to systems biology—recognizing that molecules assemble into cells and that cells assemble into tissues (and tissues into bodies and bodies into ecosystems)—and has fostered mathematical tools for describing and modeling biological systems to more fully reveal that "the whole is more than the sum of its parts."

Today, as during the time of Mall, fresh looks at cell and tissue anatomy at all scales, macro as well as micro, have yielded surprises such as the presence of adult stem cell niches in every tissue (Roberts et al., 2017), the drainage of the brain by lymphatics (Plog & Nedergaard, 2018), the innervation of epithelia (Zanchi et al., 2020), and the demonstration that tissues like mesentery are functional as fully defined organs (Coffey et al., 2021). None of these discoveries would have been possible relying on cell and molecular biology alone, without careful, higher scale anatomical observation.

Mall, Ludwig, His, and Sabin, among many others, detailed extraordinary findings that have become largely lost to contemporary general biomedical knowledge, yet we enrich our own findings if we acknowledge those of our scientific forebears. We also, in some measure, enjoy the possibility of dialogue with those who taught our teachers. Through such work, truly, "what was old is made new again."

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