Sir Thomas Lewis redivivus: from pebbles in a quiet pond to autonomic storms

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History without heroes would make dull reading indeed. In today's egalitarian world there is a regrettable shortage of heroes, making each of us appreciate all the more those genuine ones from earlier times. It is now just over 60 years since Sir Thomas Lewis chaired the first meeting of the British Cardiac Club, which was later to become the British Cardiac Society. Today, nearly four decades after his death, Lewis still inspires everyone in what may be called civilised medicine, for he led the way in bringing scientific principles and methods into the mainstream of clinical practice.

All his life Lewis continued to see patients but never strayed far from his love for research, seeking experimental verification (or disproof) for hypotheses derived from clinical observations. This attractive combination of clinical skills and scientific inquiry is becoming vanishingly rare and, some say, in imminent danger of extinction. The "impossibility" of being expert at the bedside as well as the bench is lamely excused on the basis of the complexity of modern science, but I suspect that a more valid explanation may be too few Lewises today. There has never been an abundance of men with such dedication, intelligence, energy, and clarity of perception, but it is largely by the aura of their kind that others are lured into the way.

Lewis was fond of aqueous metaphors, often speaking or writing of rushing streams and waterfalls, no doubt as a legacy from his youth in the beautiful land of Wales. He was also gifted in the choice of striking and unforgettable phrases to illustrate his scientific points, as indicated by his comparison of atrial excitation with the ripple formed when one tosses a pebble into a quiet pond.¹ But to describe palpitation and hypertension so often associated with anginal pain it is difficult to think of a term more suitable than his "autonomic storm."

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Of course, if Lewis was judged only from his publications it would be a flawed verdict and a grave injustice. In his time he stimulated and inspired several generations of young physicians to appreciate the beauty of clinical science. As much as any man then or since he showed how the scientific method must support the reasoned, compassionate, and intelligent care of patients. But surely one of his most becoming attributes was the durability of his friendship, which was carefully and selectively bestowed. Decades after they first met and collaborated in research the late Frank N Wilson of Ann Arbor could still evoke nostalgic memories of their watching birds together in Michigan.

Sir George Pickering, one of Lewis's last students and the first to deliver this eponymous lecture, often came to Birmingham (Alabama) to visit his old friend Tinsley Harrison. It was my privilege to act as his academic host on several of those occasions, during one of which he spied on my shelf a treasured early copy of *The Mechanism and Graphic Registration of the Heart Beat*. This led him to reminisce that his own copy was a wedding present from his mentor, with whom he was then working. Pickering further recalled for me how profoundly Sir James McKenzie had influenced the young Lewis, for example in the classic studies of atrial fibrillation, and I was reminded how the same McKenzie was also the stimulus to Sir Arthur Keith when he and Martin Flack discovered the sinus node. Ultimately, Pickering was to write a touching and memorable tribute to Lewis when he died.² Although many must have known it when *The Mechanism and Graphic Registration* was a newer book, few today realise what a gold mine of references it contains. The 1003 citations not only serve as a generous acknowledgement of the contributions of others, they provide an invaluable overview of the origins for the scientific basis of cardiology.

On this occasion I want to consider certain familiar contributions of Lewis which have particular meaning for me because of my own work. Beyond that element of personal bias, I believe that those particular contributions also epitomise what he did so well and will serve to illustrate its contemporary relevance. Obser-

Fig. 1 Photomicrographs of two different normal human sinus nodes. Periarterial distribution of the sinus node is marked with four arrows in (a). All of the tissue shown in (b) is sinus node. SVC, superior vena cava; CT, crista terminalis. van Gieson elastic stain; all magnifications are indicated with reference bars.

ventions from my own laboratory will be used to depict how Lewis's work relates to current concepts. As an outline for my remarks I have divided Lewis's works into three groups. The first group deals with the sinus node, atrial arrhythmias, and atrial conduction and represents what may be seen as his electrophysiological period. The second group includes clinical dysautonomic states, from the time when he became interested in the functional relation of the brain and the heart. The third group concerns the microcirculation, a logical outgrowth of the work on neural control of the cardiovascular system. Although these three arbitrary groupings do not exactly fit the calendar of his life, they come close to representing the early,

middle, and later periods. Some overlap is obvious when one notes that the wartime studies of soldier's heart and neurocirculatory asthenia³ were followed more than a decade later by commentaries on Nothnagel's syndrome⁴ and angina pectoris.⁵

Sinus node, atrial rhythms, and atrial conduction

Since all electrical activity of the heart normally originates in the sinus node, it seems particularly fitting that Lewis's earliest major work dealt with that structure and its functional importance.⁶ There was a special timeliness for the paper, appearing as it did only a few years after the remarkably lucid and comprehen-

Fig. 2 Electron photomicrograph of a child's sinus node prepared with fixative about three hours post mortem. The unavoidable artefacts of glycogen depletion and similar changes do not obscure the well preserved intercellular junctions and myofibrils. Sufficient detail is retained to demonstrate the distinct features of P cells (p) in the sinus node of human hearts. c, collagen.

sive report by Keith and Flack describing their discovery.⁷ Although the deductive logic by which Keith and Flack interpreted the functional significance of the sinus node was to prove correct, the experimental studies by Lewis and his colleagues gave valuable support. Some who disdain the subject of anatomy would say that the understanding of sinus rhythm was assured *only* when its physiological behaviour was defined, but this is as unfair as it is wrong. Lewis knew just what to study precisely because of the careful anatomical description by Keith and Flack. There is ample credit to be shared by both anatomists and physiologists.

In those days and even up until the middle of the century the histological composition of the sinus node was described as specialised "fibres." Once electron microscopy was available the discrete cellular structure of the myocardium became clear, and the idea of a fibre-filled syncytium was no longer tenable. It is now known that the sinus node⁸ is normally organised within a dense collagen framework surrounding a conspicuously large central artery (Fig. 1), leading Söderström aptly to describe the node as resembling an enormous adventitia of its artery.⁹ This periarterial disposition may serve a stabilising autoregulatory purpose.¹⁰ Within the collagen frame there are many capillaries and nerves and at least two special types of myocytes distinctly different from working myocardium and from Purkinje cells.¹¹

Because both kinds of nodal myocytes are abundant in the sinus node but are so different from each other it is wrong to call either of them *the* nodal cell and probably unwise to call both of them that. The first type of cell is small, round or ovoid, has very few specialised intercellular junctions, and contains only sparse amounts of glycogen and hardly any organised sarcoplasmic reticulum. There is a paucity of myofibrils, which in turn contain few myofilaments and are randomly oriented within the cell. The small mitochondria vary in size and configuration, are conspicuously simple in structure with few cristae (Fig. 2), and are also randomly distributed within the cytoplasm. Owing to the small number of organelles and the minimum amount of glycogen these cells are pale and primitive in appearance. Based upon correlative electrophysiological studies¹² it seems likely that they are the true site of origin of the pacemaking sinus impulse (Fig. 3). Because of these several attributes of structure and function we have suggested that these small round nodal myocytes be called P cells.¹¹

In addition to P cells the sinus node contains many elongated slender myocytes with longitudinally oriented myofibrils and more complex intercellular junctions. We have designated these as transitional cells¹¹ for two reasons: they are morphologically intermediate in internal complexity between working

Fig. 3 Drawing to show relation of typical transmembrane action potentials to anatomical sites where they were recorded in and around a canine sinus node which had been studied *in vitro* and preserved by selective perfusion through the sinus node artery. Details of the study are published elsewhere.¹² Spontaneous depolarisation from a cell in the mid-sinus node is shown in A, from the margin of the sinus node in B, from ordinary atrial myocardium in E and F, and from internodal pathways in C (middle pathway) and D (posterior pathway).

myocytes and P cells and they almost certainly function to distribute the sinus impulse from P cells into the atrium. P cells connect only with other P cells or transitional cells, whereas transitional cells connect with the atrial myocardium. In contrast to P cells, which typically occur in small grape like clusters predominantly in the central part of the sinus node, transitional cells throughout the node form the slender interweaving fibres characterising the light microscopic appearance recognised by Keith and Flack. There are still other fine structural features of the sinus node such as the disposition of glycocalyx about clusters of P cells but not between them individually,¹³ which contribute to understanding its special function.

Once the sinus impulse is formed it must then be distributed to the atria and delivered to the atrioventricular node¹⁴ and thence through the His bundle via its branches to the ventricular myocardium. The history of our knowledge of the conduction system of the heart and how its components integrate so well is a fascinating chapter in medicine.¹⁵ Very early after the sinus node and atrioventricular node were recognised, there began a debate on the nature of the anatomical routes by which internodal conduction occurred. Two different pathways were proposed by Wenckebach¹⁶ and Thorel,¹⁷ and later an interatrial route was described by Bachmann.¹⁸ Several authorities of the time challenged these findings, notably Mönckeberg,¹⁹ but the coup de grace was given by Lewis *et al.*²⁰

Much of the debate about internodal pathways then and now²¹⁻²³ is based on a distracting insistence, firstly, that if such pathways exist they must be shielded or isolated and, secondly, that they should be comprised exclusively of "specialised" cells (although no one has yet said exactly what is meant by that). Both of these unfortunate misconceptions stem from an arbitrary wish to make internodal pathways of the atria resemble or be identical to the left and right bundle branches of the ventricles, which is in some respects a shibboleth or straw man. Furthermore, the paradoxical truth is that the cellular organisation and composition of the bundle branches themselves are not those of a single cell type, and the right branch is remarkably different in its histological organisation and cellular composition from the left branch.²⁴

In the human heart¹⁴ as well as that of the dog,²⁵ rabbit,²⁶ horse,²⁷ and cow²⁸ there are three distinct pathways for internodal conduction (Fig. 4). None of these is shielded or isolated, and none of them is composed exclusively of "specialised" cells, although each of them does contain many cells with special ultrastructural features (Figs. 5 and 6).²⁹⁻³¹ As now described by many different observers,³²⁻⁴⁷ those three pathways do form familiar muscular bundles^{48,49} such as the crista terminalis, Bachmann's

Fig. 4 Drawing showing the course of the three normal internodal pathways (A, anterior; M, middle; P, posterior) and their relation to sinus node (SN), sulcus terminalis (ST), Bachmann's bundle (BB), eustachian ridge (ER), AV node (AVN), coronary sinus (CS), and superior vena cava (SVC).

bundle (the anterior interatrial myocardial band), the torus Loweri, and the eustachian ridge. Rapid conduction within them^{37-39,41,50-57} may indeed be in part due to longitudinal orientation of their component fibres as recently emphasised.⁵⁸ The predominantly linear orientation of fibres is clearly visible even on gross inspection, especially in Bachmann's bundle and in the crista terminalis. But there are likely additional important explanations. Furthermore, it is both incorrect and misleading to say that all the anatomical features of "specialisation" are like Purkinje cells or bundle branches or even that we know very much about what such features must be. For example, few would quarrel with a concept of the sinus node as being specialised tissue, but it contains no Purkinje cells and looks nothing like either bundle branch.

Both experimental and clinical evidence, the combination so dear to Lewis himself, offer strong support for preferential conduction via the internodal pathways. As recently reconfirmed,⁵⁹ poisoning with potassium will arrest atrial mechanical activity but does not stop the sinus impulse from forming nor prevent its conduction to the atrioventricular node.⁶⁰ Supernormal conduction occurs in Bachmann's bundle.^{51,56} Certain cells in the internodal pathways have a distinctive transmembrane action potential,⁶¹ and we have found such cells predominantly within the internodal pathways (Fig. 3), the same areas in which cells with special appearance are located. Cells in the internodal pathways contain an unusual form of myosin.⁶² The property of automaticity found in certain cells in the internodal pathways is the probable basis for so called subsidiary atrial rhythms.⁶³ In the human heart studied during and after cardiac surgery there have been repeated reports of preferential atrial conduction in the internodal pathways.⁶⁴⁻⁶⁶ Thus the bulk of anatomical, experimental, and clinical evidence supports the concept of preferential atrial conduction through one or more of the three internodal pathways.

Although Lewis held that the sinus impulse spread like fluid poured on a flat surface²⁰ or, as some have interpreted, like waves from a pebble tossed into a quiet pond, one of his own important contributions is difficult to explain that way. Harper and Pitt⁶⁷ have recently argued that Lewis may have been the first to describe an unusual example of interatrial block,⁶⁸ an interpretation with which Hollman agreed.⁶⁹ Interatrial block could theoretically be due to arrest of an entire atrium or destruction of many separate connexions, but it is much simpler to conceive of it as being due to interruption of a preferential route. Bachmann's own original experiments dealt with how interatrial conduction could be delayed or prolonged by ligating the anterior interatrial myocardial band,¹⁸

Fig. 5 Light micrographs prepared from sections embedded in epon and stained with toluidine blue illustrating the heterogeneous cellular population of the anterior internodal pathway in Bachmann's bundle of a canine heart. The dark lines in (a) appear to ensheath several Purkinje cells cut in longitudinal section, but this isolation did not persist in other areas. Random orientation of various cells is seen in (b).

Fig. 6 Electron micrograph of the posterior internodal pathway of a dog showing a remarkable variety of myocardial cells. Different profiles of several P cells are marked P and transitional cells T. A unique cell having amoeboid configuration is marked A and is seen intertwined between several P cells. A small nerve is marked N and a capillary Cap. The distinct difference between P cells and transitional cells is well shown.

Fig. 7 Diagrams showing the likely routes of circus movement about the superior and inferior venae cavae, utilising the three different internodal pathways in one direction or its opposite, as a possible anatomical substrate for atrial flutter.^{72 73} See Fig. 4 for additional orientation.

and clinicopathological studies have demonstrated lesions there in patients dying with delayed interatrial conduction expressed as P mitrale in the electrocardiogram.^{70 71} Thus preferential internodal pathways are presently the most plausible explanation for both interatrial block and sinoventricular conduction.

Utilisation of preferential conduction within the internodal pathways has provided a new understanding of atrial flutter.^{72 73} Actually, Lewis's own explanation of circus movement in the atria followed a course around the great veins^{74 75} and fits admirably with the architecture of the internodal pathways (Figs. 4 and 7). The fact that these pathways are

punctuated by "natural" obstacles such as the fossa ovalis or the two venae cavae simply contributes to an orientation of the routes by which preferential conduction occurs.

For perhaps the most practical of reasons, cardiovascular surgeons have come especially to appreciate the importance of the internodal pathways if the problem of atrial arrhythmias after the repair of large defects in the interatrial septum or of transposition of the great vessels is to be minimised.^{32 35 36 76-82} Furthermore, preservation of the sinus node and the internodal pathways is crucial to the electrical stability of a transplanted heart,⁸³ particularly since most escape rhythms are intrinsically unstable⁸⁴ and especially in the denervated state,⁸⁵ which is unavoidable after transplantation.

To return to Lewis's penchant for aqueous metaphors, the spread of atrial excitation may not be best described as resembling the flow of liquid poured on a flat surface nor like the waves caused by a pebble tossed into a quiet pond. Rather, it is like the Gulf Stream in the Atlantic Ocean, not shielded or isolated in a pipe but, nevertheless, a consistent flow within a larger mass of water. Reasons for this preferential distribution of flow, whether in relation to ocean currents or atrial excitation, are only partially understood at present, and improvement of our knowledge about that should be high on the agenda for future electrophysiologists.

Dysautonomia and the heart

SOLDIER'S HEART AND MITRAL VALVE PROLAPSE "Nervous" symptoms among young soldiers may be fully understandable and appropriate in some circumstances, but they may also occur inappropriately and can be disabling. Difficulty in explaining the palpitation, breathlessness, dizziness, chest pain, paraesthesia, weakness, and occasional syncope has long vexed serious investigators. Da Costa was an early student of this problem,⁸⁶ but its persisting magnitude and seriousness prompted the British army to assign its study to Lewis during the first world war.

A dysautonomic basis could be intuitively suspected for most and perhaps all of these distressing symptoms, and in fact they are closely mimicked by the condition known as diencephalic epilepsy.⁸⁷ It is thought that the spells of diencephalic epilepsy represent focal discharge from the vasoregulatory centres in the diencephalon, a concept which is supported by the gratifying clinical response to treatment with either diphenylhydantoin or phenobarbital. Proof of such focal neural discharge is difficult to obtain since cortical activity of the brain remains normal; however, special encephalographic leads (for example, within the nose) show promise for this purpose.

Fig. 8 Effect of four months' treatment with phenobarbital in modifying the abnormal autonomic responses of a young man with mitral valve prolapse and "neurocirculatory asthenia" during a Valsalva manoeuvre (a) and in response to tilt (b). With only brief periods of quiet standing he became faint and severely hypotensive before treatment but had no such symptoms after treatment. Concomitant with this clinical improvement, the overshoot abnormalities were completely corrected and both the strain and the standing abnormalities were modulated favourably. Boxed blood pressures are after treatment and others are before. *, resting heart rate from which the changes during testing are plotted; (●), control values ($n = 15$); (▲) values before treatment; (△) values during treatment with 15 mg phenobarbital four times daily.

With the remarkable recent clinical interest in mitral valve prolapse, no doubt in large measure attributable to the steady availability—some might say overuse—of echocardiograms, there is growing appreciation that certain of these patients have troublesome symptoms that also represent a form of dysautonomia.^{88–91} With simple autonomic tests such as a modified Valsalva manoeuvre and a tilt response, Coghlan and colleagues have demonstrated an assortment of dysautonomic responses in such patients, including abnormal hypotension and inappropriate slowing or acceleration of the heart rate.⁸⁸ Furthermore, selective pharmacological therapy not only improves or abolishes the symptoms but also objectively modifies the abnormal response to autonomic tests (Fig. 8).

Given the very large number of individuals with prolapsing mitral valves, it is well that the great majority have no dysautonomic symptoms. Even in those who do, there is no good evidence that the valve problem and the symptoms are causally related and some evidence⁹² that their coexistence is only happenstance. If either the valve problem or the dysautonomia causes the other, how it happens remains to be explained, although there are some conjectural possibilities. There may be an intriguing analogy in the long QT syndrome, where congenital deafness was a dramatic associated finding in the original description⁹³ but in truth may have little or nothing to do with the abnormal repolarisation, cardiac electrical instability, and sudden death.^{94 95}

In those individuals with dysautonomia, its aetiology and pathogenesis likewise remain elusive. An otherwise minor bout of encephalitis and subsequent Guillain-Barré syndrome, or some other form of autonomic neuropathy, are both plausible hypotheses but presently no more than that. The recent demonstration that cardioneuropathy,⁹⁶ probably viral,⁹⁷ may be associated with sudden unexpected death adds another dimension to the problem. There are, of course, a multitude of other causes for cardioneuropathy.⁹⁸ Individuals with cardioneuropathy and sudden death, who presumably had a lethal electrical instability of the heart, include those with the long QT syndrome.⁹⁵ The latter condition sometimes responds well to treatment with phenobarbital,⁹⁹ and the mechanism of this benefit could be centrally mediated—for example, by quieting a desynchronising focal discharge from the midbrain. Even though the exact pathogenesis remains poorly understood in most cases, there are clinical markers for some examples of autonomic neuropathy such as that found in patients with diabetes mellitus (Fig. 9).

For conditions as seemingly dissimilar as soldier's heart and the mitral valve prolapse syndrome it now seems likely that dysautonomia is the common fun-

damental fault. Furthermore, an untold but possibly large number of "neurotic" patients may be similarly afflicted. It would be sweet irony if many of these uncomfortable and unhappy people, who sometimes respond to treatment with phenobarbital, got much better for a surprising reason—not because of mild sedation per se but because of the fortuitous correction of a serious dysautonomia.

Given that a central fault (diencephalic epilepsy) can produce dysautonomic symptoms, and that individuals recently recovered from certain viral illnesses sometimes develop such symptoms,¹⁰⁰ both chronic and acute viral infections must be ranked high among suspected causes of "idiopathic" dysautonomia. The site of such infection could be central (brain) or peripheral (heart) or both. But whatever the exact basis for dysautonomia may eventually prove to be, and one would expect that there will be several different causes, dysautonomia is already one attractive and plausible explanation for soldier's heart.¹⁰¹

AUTONOMIC STORMS

When Lewis made the observation that very high blood pressure sometimes appeared during angina pectoris⁵ there was the immediate question of whether the pain itself caused the hypertension. Levine and Ernstene soon answered that by showing that blood pressure rose before pain began.¹⁰² Although new hypertension appearing during angina pectoris or very early in acute myocardial infarction has been repeatedly confirmed as a clinical observation over the past few decades, how or why it happened was poorly understood.

Then in 1965 Horwitz and Sjoerdsma reported their findings from four patients referred to them for investigation because of severe paroxysmal hypertension suspected to be due to pheochromocytoma.¹⁰³ What they discovered was not pheochromocytoma but that every bout of paroxysmal hypertension occurred just before anginal pain, an elegant confirmation of Lewis's original observation. In a prescient speculation, Horwitz and Sjoerdsma further suggested that a chemoreceptor within the heart might be the origin of the hypertension.

Actually, Comroe had demonstrated a hypertensive chemoreflex in 1939,¹⁰⁴ which he attributed to activation of "aortic bodies" even though his own work showed that their blood supply very often came from the coronary arteries. In 1971 Eckstein and his colleagues¹⁰⁵ contributed two important further observations: firstly, that there was a chemosensitive site with blood supply from the proximal left coronary circulation of the canine heart and, secondly, that hypertension occurred after stimulation with 5-hydroxytryptamine (serotonin), a naturally occurring substance carried in the circulating blood of most

Fig. 9 Histological appearance of both microvascular (curved arrow in (a)) and neural abnormalities in sections from the heart of a young woman who died with juvenile diabetes mellitus. Boxed area in (a) shows nerve at higher magnification in (b) (three open arrows). An adjacent degenerating nerve is indicated with an open arrow in (a). Goldner trichrome stain.

Fig. 10 Electron micrograph showing a coronary chemoreceptor of a dog. Fenestrations (f) in a capillary (Cap) are marked with arrows. Nf, nerve fibres; SC, sustentacular cells; CC, chief cells. The ultrastructure is not distinguishable from that of carotid body even though the response to serotonin is remarkably different.

mammals, including man, which is almost entirely bound to platelets.¹⁰⁶

Stimulated by these intriguing observations, my colleagues and I embarked on a series of studies of what we have come to call a cardiogenic hypertensive chemoreflex.¹⁰⁷ Serotonin administered into the distal coronary circulation of the dog produces the Bezold-Jarisch depressor reflex but when administered into the proximal left coronary circulation of the same animal the same amount of serotonin causes a mirror image response, the most remarkable feature of which is a virtual doubling of aortic pressure within 4–8 s.

In parallel studies we found not only a chemoreceptor with blood supply from the proximal left coronary circulation of the dog but a histologically and anatomically similar structure in the human heart. Several years earlier Anton Becker, in a study conducted for an entirely different purpose, had also described such structures (which he called intertruncal glomera) lying between the origin of the aorta and pulmonary artery in several species including man, and published an exceptionally clear illustration of their blood supply from the main left coronary artery.¹⁰⁸ At the fine structural level¹⁰⁹ this chemoreceptor is presently

Fig. 11 Cardiac hypertensive chemoreflex and associated respiratory changes (see pneumogram) in an awake dog before and after the administration of atropine. The vagally mediated cardiac slowing is abolished and the hypertensive response accordingly magnified, but breathing changes are similar with or without vagal blockade.

indistinguishable from the carotid body (Fig. 10). In the dog, however, serotonin causes no appreciable response when administered into the carotid artery.^{107 110} Just what accounts for this anatomical similarity and physiological difference remains to be determined, one possibility being that methods so far used have simply not been adequate to display some fine structural or histochemical difference that actually does exist.

There are other physiological characteristics of the cardiogenic hypertensive chemoreflex. The afferent neural pathway is via thoracic vagal branches,¹¹¹ thus differentiating it from other cardiogenic pressor reflexes which have their afferent course via spinal sympathetic nerves.¹¹² Cyproheptadine blocks the reflex at the receptor site but methysergide does not.¹¹³ During the cardiogenic hypertensive chemoreflex there are simultaneous sympathetic and parasympathetic efferent events, and both are quite powerful. Although the sympathetic events usually predominate, the pronounced hypertension may be delayed several seconds by a transient vagally mediated bradycardia or heart block (Figs. 11 and 12).^{107 114 115} This vagal component is variable between dogs and even from one time to another in the same dog, but it can be eliminated in both the awake and the anaesthetized state by the administration of atropine (Fig. 11), thus converting the efferent response to one exclusively of hypertension and tachycardia.¹¹⁵ In the awake dog a brief period of hyperpnoea is evident (Fig. 11) (which is again a mirror image of the Bezold-Jarisch hypopnoeic effect),

but this has no appreciable influence on the hypertension.¹¹⁵ In some dogs there is transient atrial fibrillation (Fig. 12) during this brief but powerful vagal influence, and this may be attributed at least in part to the important effect which the vagus nerve has on atrial repolarisation.¹¹⁶

Hypertension during the cardiogenic chemoreflex is due to the simultaneous occurrence of arterial vasoconstriction plus a powerful positive inotropic action on both ventricles.¹¹⁷ A negative inotropic effect ordinarily predominates within the atria but is readily converted to a purely positive response after the administration of atropine. Although blood flow sharply decreases in the femoral and mesenteric circulations, little effect occurs in the pulmonary circulation, and there is a conspicuous absence of any coronary effect at all.¹¹⁸

As a result of these several different studies, we have teleologically reasoned that the cardiogenic hypertensive chemoreflex may serve a valuable protective purpose. If aggregating platelets in the proximal left coronary circulation are the natural source of serotonin to engage the reflex an abrupt hypertension could disrupt any further organisation of a potentially lethal coronary thrombus. The "stutter" effect seen if there are a few initial vagal pauses may usefully compound the propulsive force of the intermittent powerful contractions (Figs. 11 and 12). In addition to the hypertension newly found during angina pectoris or very early in acute myocardial infarction, the cardiogenic chemoreflex may also participate in the new hypertension seen after coronary bypass grafting.¹¹⁹

Fig. 12 Bipolar electrograms recorded from right atrium (RA) near the sinus node, from a catheter tip in the non-coronary sinus of aorta (HBE), and from the epicardium of both right (RV) and left (LV) ventricles. If response by the sinus node is selectively eliminated by direct perfusion of a very small amount of atropine (10 μ g), then during the cardiogenic hypertensive chemoreflex there is no sinus slowing, but three other vagal effects remain: transient heart block (atrioventricular node did not get atropine), progressive P-Tp segment elevation (asterisk), and transient atrial fibrillation (AF). Both of the latter two effects represent response from parts of the atria not perfused by the sinus node artery and therefore not receiving any atropine.

and possibly aortic valve replacement,¹²⁰ which appears to be neurally mediated.^{121 122} Much further study is needed of the exact nature of the phenomenon in man, but today 50 years later we may finally have an explanation for Lewis's accurate clinical observation of "autonomic storms."

Small arteries of the heart

Lewis could have been drawn to studies of the microcirculation as a logical consequence of his work with

neurocirculatory asthenia (soldier's heart) and the obvious importance of small vessels in the control of the vascular system by the nervous system. I am not aware that he was much interested in the small arteries of the heart, but knowledge of their structure and function fits naturally with his much broader orientation.

It is unfortunate that during decades of growing interest in normal and abnormal structure of coronary arteries the focus has been so predominantly on the large branches. Several factors may help to explain

Fig. 13 Photomicrographs of sections from a patient who died of scleroderma heart disease showing marked narrowing of many small coronary branches¹²⁸: (a) shows left ventricular myocardium and (b) the atrioventricular node artery. Goldner trichrome stain.

Fig. 14 Histological appearance of cardiomyopathy associated with Friedreich's ataxia¹²⁵ showing widespread narrowing of small coronary arteries with a variety of histological processes. An unusual feature typical of Friedreich's cardiomyopathy seen here at two magnifications (a and b) is the intramural deposit of an amorphous periodic acid Schiff positive material. Both (a) and (b) are from sections prepared with the periodic acid Schiff stain.

this bias. Firstly, the sudden occlusion of large coronary arteries certainly has immediate major consequences which are easy to see and understand. Secondly, there are only a few large coronary branches, and their assessment is not difficult. Thirdly, the myriad of small (1 mm or less in diameter) coronary arteries makes them more difficult to assess; quantification of the extent of small coronary disease, if the entire heart is to be examined, would be a formidable undertaking. Fourthly, most morbid anatomists are unfamiliar with the location and functional role of certain easily found small arteries such as those supplying the sinus node, atrioventricular node, or coronary chemoreceptor.

Through other reasons for a personal interest in these special small coronary arteries supplying the conduction system and the coronary chemoreceptor, I have for over 20 years taken careful note of their condition during clinicopathological correlative studies.¹²³ From that orientation one cannot only come to recognise the variety of histological abnormalities (Figs. 13 and 14) that are found, and have the rich opportunity for meaningful functional interpretation because of the specific structures supplied, but also gain an appreciation of the extent and severity of similar abnormalities within other small coronary arteries such as those in the ventricular myocardium. Furthermore, individual variations can be compared because the same special small arteries are examined in each heart. This is not the approach which purists of quantification would choose or at times even condone, but it does offer several practical advantages. A major one is reasonable simplicity and another is common sense interpretation.

If a patient dies suddenly and unexpectedly, or with a known arrhythmia or heart block, and distinct abnormalities are found in the blood supply to the conduction system, it would seem unwise to ignore those rather than to accept a probable causal relation. Then if similar abnormalities are also found in many small ventricular arteries combined with widespread focal myocardial fibrosis, there is strong circumstantial evidence that the small coronary disease was functionally significant in an even broader context.

For some diseases, such as congenital homocystinuria,¹²⁴ Friedreich's ataxia with cardiomyopathy,¹²⁵ and diabetes mellitus,¹²³ the narrowing and obliteration of small coronary arteries can be remarkably widespread. The same may be said for amyloidosis of the heart¹²⁶ and for collagen diseases such as polyarteritis nodosa,¹²⁷ scleroderma,¹²⁸ and lupus erythematosus.¹²⁹ Some but not all cases of asymmetric hypertrophy of the heart show widespread small coronary disease.¹³⁰ For most of these examples there is no special predilection for arteries supplying the conduction system to my knowledge,

but in some cases of focal fibromuscular dysplasia there may be such a predilection.^{131 132} One of the most intriguing recent discoveries has been the finding of Whipple bacilli (Fig. 15) within the tunica media of small and large coronary arteries and the possibility that these bacteria may be a previously unsuspected cause of chronic degenerative coronary disease.^{133 134}

In addition to structural abnormalities of small coronary arteries there are problems due to their spasm, which is now suspected as a cause of certain forms of cardiomyopathy.¹³⁵ It has furthermore been suggested that scleroderma heart disease may in part represent a "Raynaud's phenomenon" of the heart,¹³⁶ a suggestion which undoubtedly would have pleased Lewis in the light of his own contributions on the subject.¹³⁷ Actually, in 1938 Lewis published a beautiful study demonstrating that in patients dying of scleroderma those with warm hands had normal digital arteries but those with cold hands (Raynaud's phenomenon) had appreciably narrowed digital arteries,¹³⁸ the morphological appearance of which is remarkably similar to that of those in the heart (Fig. 13).

It is presently uncertain how often and under what conditions the spasm of small coronary arteries may be neurally mediated. For example, coronary resistance and coronary flow are not at all affected during one powerful hypertensive chemoreflex,¹¹⁸ the coronary circulation being conspicuously spared. In fact, the mechanism of coronary spasm (large or small arteries) cannot be exclusively neurogenic since it has been shown to occur even in the transplanted heart.¹³⁹ If coronary spasm is to be attributed to non-neural local vasoconstrictive substances platelets become the major suspect. Small coronary arteries not only fill with platelets in thrombotic thrombocytopenic purpura,¹⁴⁰ disseminated intravascular coagulation,¹⁴¹ congenital homocystinuria,¹²⁴ and pheochromocytoma¹⁴² but are also the terminal site for embolic silting when platelets become disaggregated spontaneously or therapeutically from upstream sites within large coronary branches. We have much yet to learn about the mechanism of coronary spasm, including whether it occurs in the same way in different patients or even in the same patient at different times.

When the small coronary arteries are the targets of any progressive narrowing disease a vicious cycle of mutually compounding complications is set in motion (Fig. 16). Each of these complications is intermittently worsened by transient episodes of spasm or temporary obstruction by platelets. Because of these multiple harmful interactions, it is hardly surprising that so many examples of "cardiomyopathy" exhibit a clinical course of inexorably worsening congestive

Fig. 15 Photomicrographs showing the presence of periodic acid Schiff positive Whipple bacilli within the tunica media of a coronary branch in the left ventricle. Area boxed in (a) is seen at higher magnification in (b), where individual bacilli can be recognised. There is some overlying intimal proliferative response, but the bacilli are predominantly within the tunica media. Periodic acid Schiff stain.

Fig. 16 Schematic diagram showing the sequence of functional consequences which occur during progressive narrowing of small coronary arteries. As more and more arteries are narrowed, even lesser lesions become more clinically significant, and the downhill course is consequently accelerated. SN, sinus node; AVN-B, atrioventricular node and His bundle.

failure accompanied by arrhythmias, conduction disturbances, and sudden death.¹⁴³

To close this discussion of blood supply to the heart I note with regret that none of us yet knows the exact way in which the pain associated with myocardial ischaemia is produced.¹⁴⁴ It may be reasonably assumed that some noxious substance or abnormal event stimulates nociceptive nerve fibres in the heart, but what the substance or event may be remains to be discovered. It would help greatly in understanding the alleviation of pain by successful coronary artery bypass grafting, for example, if we knew more about what caused angina pectoris. Lewis had personal reasons for his own research into the mechanisms of pain,¹⁴⁵ himself suffering from angina pectoris for many years and surviving two myocardial infarctions before dying of the third.² While it is doubtful if today there are better minds to think about the question, we do have the advantage of new concepts and knowledge about coronary physiology and myocardial metabolism and new methods for their study. The fundamental cause of angina pectoris is one of the most challenging opportunities for needed new discoveries through clinical investigation.

Epilogue

Lewis began his work just after the start of this century and we are now near its end. No one can know what cardiology will be like in the future, but we can already see the lasting value of Lewis's research. Even more, we can be grateful for his teaching us the value of careful scientific experimentation to examine and either confirm or discard clinical hypotheses. That approach, which is the heart of clinical science, will always stand strong in the science of the heart.

There are fascinating lessons to learn by reviewing

Lewis's career. For example, did he leave the field of electrocardiography too soon? His widely quoted prediction about its limited future could be said to have been poorly considered. But there is a different and infinitely more important lesson which should be a caveat for any clinical investigator. Today, when so many young physicians become enamoured with dazzling technological tools, Lewis stands as an example of the creative scientist who understood how to use technology but not become its slave. What he went on to study was probably more important at the time that anything Lewis could have done with the electrocardiograph then, although of course a decade or two later things changed a great deal in the world of clinical and basic electrocardiography.

Where Lewis excelled and remains an inspiration is in the beauty of ideas, the essence of creativity in any discipline. He was not bound by convention, but he was not reckless with innovation. His research dealt with fundamental biological principles but never strayed far from clinical medicine. To do these things well one must assuredly begin with an original thought, but their successful completion always requires patience, hard work, honesty, and poise with confidence. The best physicians now and in the future can do no better than to emulate Sir Thomas Lewis, but in truth we all know that there will never be many like him.

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