Tautology vs. Physiology in the Etiology of Hypertension

In 1920 Frederick Allen described the state of hypertension research as follows (1):

The great importance of arterial hypertension or the conditions associated with it, as a widespread and apparently increasing cause of disability and death, is a self-evident incentive to investigation. At the same time it must be recognized that our knowledge of the subject is in a very confused state, as respects its phases of etiology, mechanism and treatment. Just as with diabetes, the literature contains almost every conceivable variety of opinions and suggestions. The first task of an investigator to choose is what seems significant and valuable among this mass of conflicting material, and the second is to build concrete facts with accurate methods in a clinical field which is still largely a morass of tradition and imagination.

One cannot help but wonder whether we are any better off today. Although numerous treatments to lower arterial pressure exist, we are still searching for an accepted rigorous explanation for the etiology of primary hypertension. A brief review of the clinical literature from 100 years ago reveals an active debate on the nature of the relationship between arteriosclerosis and hypertension, and discussions on the role of the splanchnic nerves and circulation. Primary treatments were prescription of diuretics, exercise, and eating in moderation (16). The role of the kidney was debated, and restriction of salt was a suggested but controversial treatment (1).

In the early 21st Century, with the same debates unresolved (5, 9, 10), the field may be described in the same terms used by Allen. In 2013, the Institute of Medicine issued a report questioning accepted recommendations on healthy levels of dietary salt intake (15). Meanwhile, the American Heart Association has not altered their aggressive recommendation limiting salt intake to levels much lower than those recommended by the 2013 Institute of Medicine report (17). Why can’t we get our story straight? Why is there no more clarity on the questions of what causes hypertension and what to do about it than there was 100 years ago? No doubt, our failure can be explained in part by the difficulty of the challenge. Blood pressure is a high-level phenotype effecting and affected by numerous physiological processes (8). My assertion is that progress has been further hampered by substituting tautological thinking for scientific thinking and by a resulting failure to construct rigorous testable hypotheses.

As an example, consider the so-called renocentric view that the kidney plays the dominant role in the long-term control of arterial pressure and that renal dysfunction must underlie primary hypertension (10). This view is encapsulated by the “laws” of blood pressure control enumerated by Guyton and Coleman (6).

1) If the pressure changes, then either or both of the net salt/fluid intake and the renal function curve must have changed.

2) If the equilibrium point on the pressure diagram changes, then the pressure will change to the new equilibrium point.

3) The sole determinants of the long-term pressure are 1) the renal function curve and 2) the salt/fluid intake.

It is profitable to recast these laws in a more abstract form by denoting pressure, \( x \), and the rate of net salt excretion by the kidney, \( y \). Then the renal function curve (which without altering the argument may be observed under any particular arbitrary set of experimental conditions) is by definition \( y(x) \), and the laws of blood pressure control become:

1) If the value of \( y \) changes, then either or both of \( x \) and \( y(x) \) must have changed.

2) If the function \( y(x) \) changes and/or if the value of \( x \) changes, then the value of \( y \) will change accordingly.

3) The sole determinants of the value of a function \( y(x) \) are 1) the function \( y(x) \) and 2) the value of \( x \).

These substitutions reveal these laws of blood pressure control to be a series of statements that are “true merely by virtue of saying the same thing twice” (19). Tautologies like this represent at best a distraction from real scientific investigation and at worst a source of confusion that impedes scientific progress. These “laws” are not testable, predict nothing, and therefore do not represent a valid scientific theory. They are, in a phrase attributed to Wolfgang Pauli, “not even wrong.”

The influence of tautological thinking on cardiovascular research extends beyond this particular example. In the first half of the 20th Century, there was considerable confusion among physiologists regarding the combined role of the heart and the vasculature in determining flows and pressures in the cardiovascular system. Measurements on animals dating back to at least the 19th Century showed that acute lesions to the heart result in increases in the volume of blood stored in the veins and in the central venous pressure, whereas acute increases in flow result in reduced venous pressure (4). By the early part of the 20th Century, it was widely appreciated, based on the works of Frank, Starling, Wiggers, and many others, that in animals “up to the point of decompensation cardiac output is determined by atrial or central venous pressure” (18). Yet observations on human subjects with chronic conditions appeared to both support and contradict this concept. In cases of congestive heart failure in particular, increased venous pressure was interpreted both as a “back pressure” that impedes blood flow and as a compensatory increase in volume maintaining cardiac output in heart failure (18). In a 1945 essay on the topic of venous flow, pressure, and cardiac output, Roberts considers the view of an unattributed author who makes the successive claims that “the output of the heart depends upon the venous inflow” and that “increased efficiency of the heart causes a fall of venous pressure.” Roberts concludes that “The two statements are of course contradictory. Either venous pressure influences the heart or the heart influences venous pressure; they cannot both be true” (14).

Arthur Guyton and colleagues championed one side of this false dichotomy,
arguing that cardiac output is primarily determined by the peripheral circulation and that, under normal conditions, the heart “automatically pumps this incoming blood into the systemic arteries, so that it can flow around the circuit again” (7). This conclusion is supported by a tautological line of reasoning that is more subtle than that applied to renal function curves and blood pressure control. In brief, a mathematical model of a closed compliant circuit (representing the systemic circulation) was analyzed to obtain an equation relating pressure at the outlet of the circuit (venous or right-atrial pressure) to steady-state flow through the circuit (cardiac output). The relationship has the form \( P_v = f(F) \), indicating that venous pressure \( (P_v) \) is some function \( (f) \) of flow \( (F) \). (More specifically, if vascular tone is maintained at a constant level, then an increase in flow causes a drop in venous pressure.) Guyton arranged this relationship in a manner that seems to indicate the assertion that cardiac output is determined by properties of the peripheral circulation: \( F = f^{-1}(P_v) \). The assertion was then interpreted as a demonstration of its validity. In an application of this faulty (tautological) logic, it is claimed that, in heart failure, “the backward force of the rising atrial pressure on the veins of the systemic circulation decreases venous return of the blood to the heart” (7). [Even though this conclusion is directly contradicted by a physically and physiologically correct interpretation of Guyton’s model and his data (3), debates on the point of confusion discussed by Roberts in 1945 continue.] Several chapters in present physiology textbooks and countless articles in the present literature are devoted to re-stating and reinterpreting these tautologies. Equally many articles are devoted to debating the merits and utility of these concepts. It is impossible to estimate how much time has been wasted or to quantify how much progress has been impeded by establishing, promoting, teaching, learning, and defending tautologies like these.

It is therefore suggested to stop. Specifically, it is suggested that we can escape the “morass of tradition and imagination” only by recalling the good old-fashioned scientific method and remembering that “in so far as a scientific statement speaks about reality, it must be falsifiable” (13). Regarding the etiology of primary hypertension, there are (at least) four major lines of thinking regarding the root cause: 1) sympathetic overdrive with causal roots in the nervous system (5); 2) renal dysfunction, causing or caused by alterations in the renin-angiotensin pathway (10); 3) stiffening of arteries; and 4) inflammation in one or more vascular beds (11). The third idea on this list was largely discarded 100 years ago and only recently recast (12). The last item represents the one idea originating in the past century. All of these items are ideas backed up by associations, but they remain nothing more than ideas until they are translated into rigorous hypotheses that make clear, falsifiable predictions.

Two such hypotheses have recently been introduced by Averina et al. (2) and Pettersen et al. (12), representing specific versions of ideas 1 and 3. It is no coincidence that these hypotheses take the form of computational models. (It is difficult for me to imagine a better way of generating unambiguously interpretable predictions of nontrivial hypotheses on the operation of the cardiovascular system.) Regardless of how they are formulated, the key to progress is to formulate testable hypotheses. Either or both of the hypotheses of Averina et al. and Pettersen et al. might be wrong. (Indeed, they are certainly wrong at least in the sense that they are imperfect and incomplete.) Yet, since they are not “not even wrong,” they certainly represent progress.

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References