

Hypertension and the Kidney

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MILESTONES

Goldblatt H, Lynch J, Hangal RF, Summerville WW: **Studies on experimental hypertension: I. The production of persistent elevation of systolic blood pressure by means of renal ischemia** *Journal of Experimental Medicine* 1934, 59:347-379



Harry Goldblatt

This landmark publication by Harry Goldblatt¹ and his colleagues at the Institute of Pathology at Western Reserve University in Cleveland revolutionized ideas about the pathogenesis of hypertension.

Credit for making the connection between hypertension and renal disease is usually given to Richard Bright, a physician at Guy's Hospital in London even though he worked in the early 1800's, a half century before the existence of hypertension was first recognized.

Bright observed that large, heavy hearts found at autopsy, in the absence of other explanations, often occurred in patients with abnormal kidneys. He exhibited incredible insight by suggesting that a blood chemical of renal origin might be the cause of the enlarged hearts. He speculated that heart enlargement reflected an elevated cardiac workload due to increased peripheral resistance. Although he never measured a blood pressure, in view of what we know today about hypertension and the kidney, Bright was pretty much on target.

Prior to Goldblatt's publication, a large body of experimental work had tested the idea that hypertension had a renal basis. The approaches used had the common outcome of impairing renal excretory function. They included variable degrees of renal ablation; renal vein constriction; and permanent bilateral ligation of the renal artery, renal vein and ureter. These manipulations sometimes resulted in a fleeting elevation of blood pressure, but usually did not.

Goldblatt took the approach of experimentally compromising renal arterial blood flow by placing a clamp on the main renal artery. He got the idea from the observation well-known to pathologists that intrarenal sclerosis of arteries and arterioles were commonly found at autopsy in patients dying with hypertension. Recognizing that no experimental procedure existed for creating the vascular pathology seen in human hypertensive kidneys, he reasoned

that if impaired renal blood flow was the fundamental cause, this could be mimicked by constricting the main renal artery.

Silver clips, especially fabricated for these experiments, were set for varying degrees of constriction and placed on the renal artery of dogs. Goldblatt observed that mild constriction of the main renal artery was sufficient to induce a rise in blood pressure within 24 to 72 hours. In control experiments constriction of the splenic or femoral arteries did not result in elevated blood pressure.

Once hypertension was established, removal of the clip resulted in return of blood pressure to normal levels, a finding suggesting that the ischemic kidney maintained the elevated blood pressure. In some experiments, instead of removing the clip, the clipped kidney was removed. This resulted in a return of blood pressure to normal levels. Subsequently placing a clip on the main renal artery of the remaining kidney resulted in reelevation of blood pressure.

In Goldblatt's early studies, hypertension in most animals lasted from 4 to 6 weeks and then blood pressures returned to normal levels, even though the clamps were still in place. An astute anatomical pathologist, Goldblatt noticed that the return to normal blood pressure was associated with conspicuous development of collateral arterial circulation to the kidney, particularly through the renal capsule. In subsequent experiments he decapsulated the kidney and enclosed it in a membrane to prevent revascularization. When the renal artery of such animals was constricted, hypertension occurred and persisted.

Goldblatt's discovery was soon followed by similar experiments by other investigators using sheep, goats and rats. Interestingly, some argued that Goldblatt's model had little relevance to human hypertension because of the belief, subsequently shown to be erroneous, that renal artery stenosis rarely occurred in humans. It took careful autopsy observation and the development of

sophisticated radiological imaging of arterial vasculature to establish that in 2-5% of cases of human hypertension, patients have a "Goldblatt kidney."

In 70% of these patients renal artery narrowing is due to an atherosclerotic plaque. In the other 30%, typically young females, the narrowing is due to fibromuscular dysplasia of the renal artery. A critical feature of these lesions is that they are correctable. Considering the incidence of hypertension in the general population, hypertension caused by renal artery narrowing is not an uncommon disease.

The experiments of Goldblatt and colleagues further buoyed the idea that the kidney produced a chemical substance that elevates blood pressure. Their findings launched studies by investigators around the world. These led to the purification and characterization of renin; identification of the juxtaglomerular apparatus as its site of synthesis; and biochemical characterization of renin's target effects on the angiotensin system, blood pressure and aldosterone secretion by cells in the adrenal cortex.

Three quarters of a century of physiology and pharmacology research flowed from the Goldblatt discovery, research that led to extraordinary advances. The clock is still ticking. Their classic paper is another example of the tremendous impact that observations made at autopsy have in posing critical questions and guiding the design of laboratory experiments that elucidate disease pathogenesis. The history of medical advances is replete with examples.

It is mind boggling that today's physicians, including many pathologists, seem to have forgotten the incredible power of the autopsy in advancing public health. Tragically, all the evidence I have seen suggests that this memory deficit results from system-wide attitudinal lesions that may not be reversible.

Reference

1. Goldblatt, H, Lynch J, Hangal RF, Summerville, WW: *J Exp Med* 1934, 59:347-379