

THE RELATION OF BACTERIURIA TO HYPERTENSION

LAWRENCE R. FREEDMAN

It is not easy to determine the natural history of any disease. Even more difficult is the task of determining the natural history of a disease that runs a course over many years, even decades, and that for long intervals may be asymptomatic. These are only some of the reasons so little is known about bacteriuria. To then go on to attempt to relate bacteriuria to high blood pressure compounds complexities. High blood pressure, after all, is little better understood than bacteriuria; it too is relatively asymptomatic, influences the biology of the host for decades and is affected by a wide range of biologic and psychologic forces.

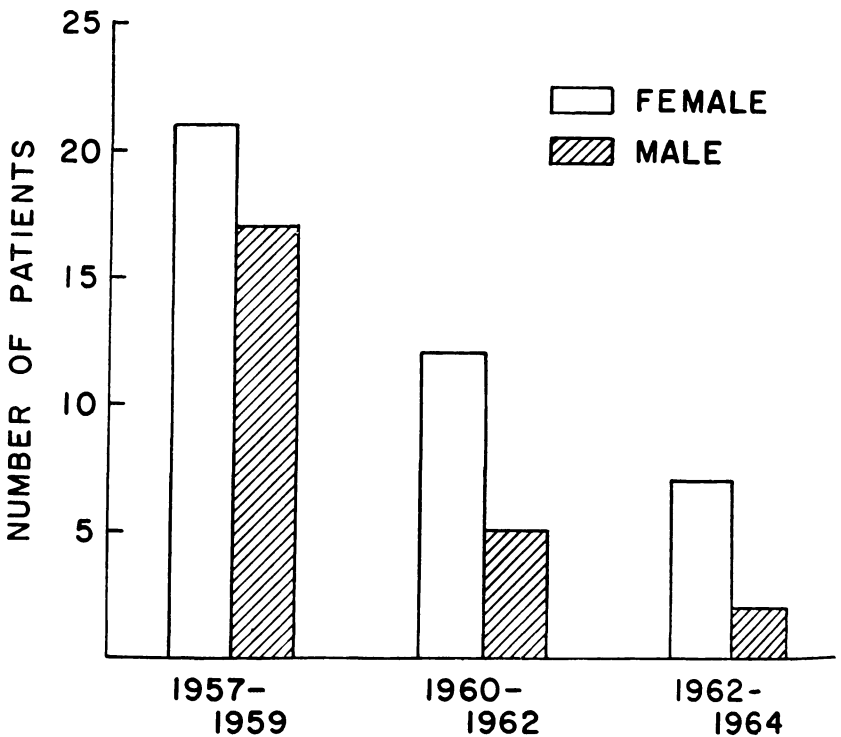
The idea that renal damage resulting from bacterial infection played a significant role in causing elevation of blood pressure dates to the work of Longcope¹ and Weiss and Parker.² The large number of autopsy and retrospective studies that followed had three serious drawbacks.

1. The nonspecificity of the histologic criteria for pyelonephritis was not generally appreciated. This led to the inclusion of many different kinds of renal disease under the heading "chronic pyelonephritis."
2. Bacteriologic studies were uncommon, and when they were used the techniques were qualitative, thus giving many false positive results.
3. It was not realized that the methods of urologic investigation (e.g. retrograde pyelography, bladder catheterization, cystoscopy) were capable of inducing serious urinary infections in patients with any type of underlying renal disease.

An example of the extent to which the frequency of the pathologic diagnosis of nonobstructive chronic pyelonephritis has changed is shown in Figure 1.³ In 1962–1964 the diagnosis was made about one-fourth as often as in 1957–1959. The explanation for this has to do with changing histologic criteria for the diagnosis of chronic pyelonephritis. Thus, the morphologic basis for relating chronic pyelonephritis to high blood pressure is suspect.

The subject received new impetus following the classic epidemiologic investigations of bacteriuria by Miall, Kass, Ling and Stuart⁴ in Jamaica. This study plus our work in Japan⁵ and that of Kunin and McCormack in this country⁶ serve as the background for considering the relation between bacteriuria and hypertension. Table 1 shows data from these three surveys where participation was 80 per cent or more

FIGURE I. DIAGNOSES OF NONOBSTRUCTIVE CHRONIC PYELONEPHRITIS AT AUTOPSY*



* At each interval data from 1,562 consecutive autopsies were tabulated. Males composed 57 per cent and females 43 per cent of autopsies in 1957–1959 and 1962–1964. Reproduced with permission.³

Source: *Annals of Internal Medicine*, 66, 697–710, 1967.

TABLE I. PREVALENCE OF BACTERIURIA IN ADULTS

Age	Jamaican Women		Japanese Women	White Nuns	Japanese Men
	Rural %	Urban %			
18-19			0.8		0
15-24	0.8	1.9		0.4	
20-29			1.0		0
25-34	4.4	1.0		0.3	
30-39			1.8		0
35-44	5.0	1.8		1.2	
40-49			3.1		0
45-54	6.1	4.8		1.6	
50-59			2.8		0.6
55-64	11.8			2.8	
60-69			7.4		1.5
65+				6.1	
70+			10.8		3.6

and where the number of subjects in each age group was at least 100. In these studies a urine culture was considered positive when 10^5 or more bacteria per ml were detected in two or more separate clean voided urine samples.

These data have many fascinating aspects. It is obvious that the rates of bacteriuria increase with age. The explanation for this is not at all obvious. One possibility is that bacteriuria confers survival advantage. Another is that treatment today is much more effective for those acquiring new infections than it was 20 or 30 years ago. Little evidence may be found to support either of these explanations. A possibility that is not easy to discard is that the natural history of urinary infections is more prolonged in older persons. Although disagreement may be expressed on this point, evidence to support this suggestion is not known. Most likely the increasing rates with age indicate increased susceptibility to infection.

It is of interest that this has recently been demonstrated in animals. A strain of *E. coli* is used that is cleared rapidly after inoculation into the bladder and that never produces pyelonephritis after inoculation into the blood stream of $1\frac{1}{2}$ to 2-month-old rats. In rats kept in the laboratory for one year, however, about 25 per cent of animals develop pyelonephritis after hematogenous inoculation of *E. coli* and impairment of bladder clearance is easier to demonstrate (Table 2).⁷

Another fact apparent from the prevalence data (Table 1) is that bacteriuria is a remarkably common finding with considerable vari-

persons with bacteriuria. Furthermore, the differences in blood pressure between women with and without bacteriuria were small, well within the range of increased blood pressure observed with distention of the bladder or voluntary contraction of the sphincters in normal persons.⁸ Nevertheless, the possibility remains that populations with high rates of bacteriuria have an increased frequency of renal scars, which may predispose to higher blood pressure. Alternatively, populations with higher blood pressures may have an increased susceptibility to urinary infections, a view that has support from studies in animals.⁹

We are currently in the position described so accurately by Gertrude Stein: "For a difference to be a difference it should make a difference." Unfortunately, the significance of the relation between bacteriuria and hypertension, which has been demonstrated in epidemiologic surveys, is not yet known.

Quantitative bacteriologic techniques have been in use long enough now to begin to make some long-term observations on the natural history of bacteriuria in individual subjects. The first patient to be described was 16 years old when she was first seen and had a family history of diabetes mellitus and hypertension (Figure 2). She had slight systolic blood pressure elevation early in life followed by nine years of normal blood pressure ($< 145/95$ mm Hg) and most recently definite hypertension ($> 145/95$ mm Hg). She has had two definite episodes of toxemia of pregnancy and five clinically typical, bacteriologically proven episodes of acute pyelonephritis. Her blood urea nitrogen and two intravenous pyelograms have remained normal.

This patient might well be taken to demonstrate the role of urinary infection in the elevation of blood pressure. However, the situation is obviously complex; blood pressure was abnormal early in life and toxemia of pregnancy is believed by some to predispose to hypertension later in life. In addition, the family history suggests the operation of genetic factors.

The next patient was 18 years old when first seen and has also developed definite hypertension (Figure 3). She also had two episodes of toxemia of pregnancy and, in addition, is known to have ingested large quantities of phenacetin-containing analgesic mixtures for many years. She has had three episodes of pyelonephritis over a period of one year, but has had sterile urine (save for a single equivocal culture) for the next eight years. Her blood urea nitrogen and intravenous pyelograms has also remained normal.

In this instance one is more reluctant to implicate urinary infection

FIGURE 2. FEMALE, AGE 16 AT FIRST VISIT. FAMILY HISTORY INCLUDED DIABETES MELLITUS AND HYPERTENSION

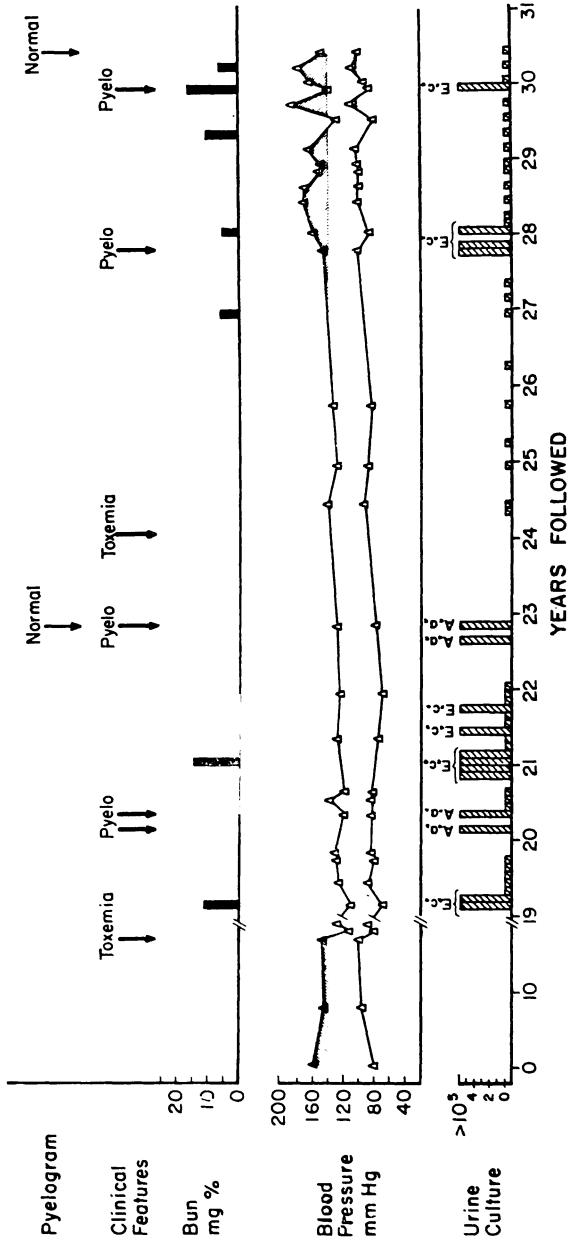
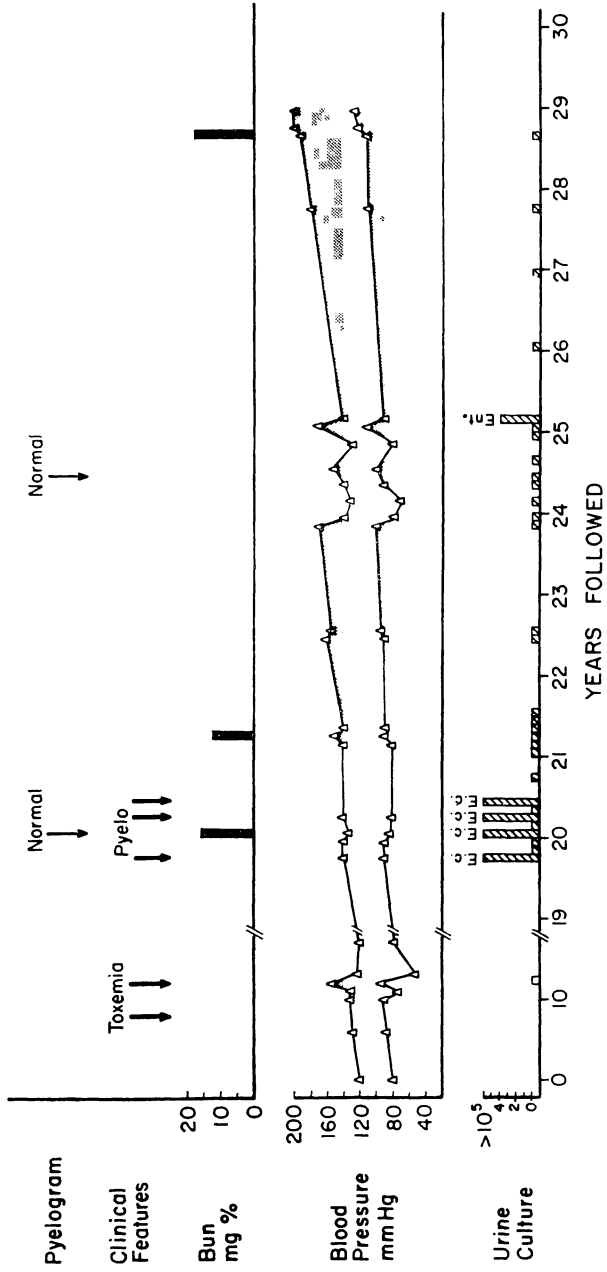


FIGURE 3. FEMALE, AGE 18 AT FIRST VISIT. SHE HAD A HISTORY OF EXCESSIVE INGESTION OF ANALGESIC MIXTURES CONTAINING PHENACETIN



as a cause of her hypertension because excessive analgesic ingestion and toxemia of pregnancy by themselves might well explain the blood pressure change.

The third patient presents perhaps the most typical clinical experience (Figure 4). This patient was 21 years old when first seen and has had six episodes of typical acute pyelonephritis and virtually continuously positive urine cultures for the ten years she has been followed. Blood pressure, blood urea nitrogen and intravenous pyelograms have remained normal throughout this period.

It is no easy matter to sort out the various factors that may have an influence on blood pressure, but it is already clear that the mere presence of bacteriuria or episodes of acute pyelonephritis is not enough to assign to these processes a causal role in the development of hypertension.

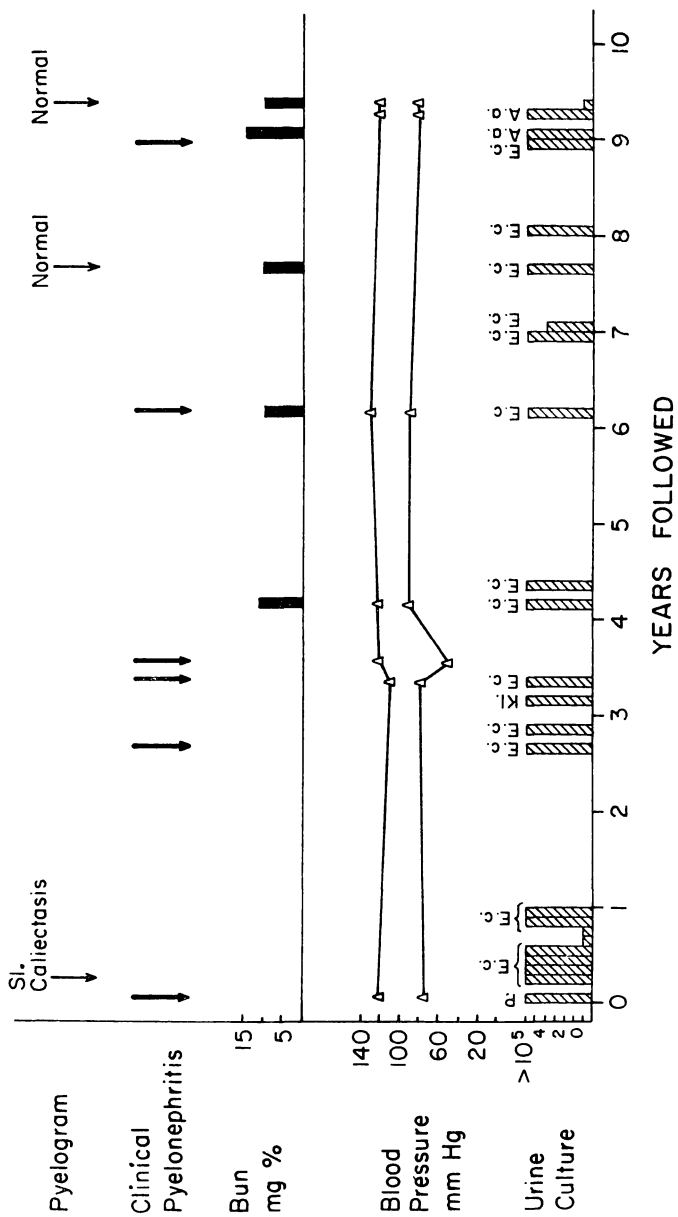
Vincent Andriole and I have recently reviewed the data from 250 women with urinary infections who have been followed in a special outpatient clinic at the Yale-New Haven Hospital for long periods of time (half the group for five or more years, 34 per cent of the group for eight or more years). Dividing the patients into normotensive (blood pressure $< 130/85$ mm Hg), \pm hypertension (130–145/85–95 mm Hg) or definite hypertension ($> 145/95$ mm Hg), 42 per cent remained normotensive throughout the period of follow-up, 27 per cent reached levels of \pm hypertension and 31 per cent had definite hypertension. Approximately 75 per cent of the group were less than 40 years of age when they were first seen.

Diabetes mellitus or a history of toxemia of pregnancy were found in 12 per cent of the normotensives, 44 per cent of those with \pm hypertension and 73 per cent of those with definite hypertension. Of the 77 patients with definite hypertension only nine did not have diabetes mellitus, a history of toxemia of pregnancy, excessive analgesic intake or some other type of kidney disease. Of these patients, eight had family histories of hypertension, diabetes or kidney disease.

At the time the subjects were first seen 126 were normotensive. During the follow-up period eight of these developed definite hypertension. Of these eight patients seven had diabetes mellitus, excessive analgesic intake or other types of kidney disease. The remaining patient had a history of toxemia of pregnancy and a family history of diabetes.

The same experience held for patients with abnormal intravenous pyelograms or elevated blood urea nitrogen.

FIGURE 4. FEMALE, AGE 21 AT FIRST VISIT. REPRODUCED WITH PERMISSION⁹



Source: Strauss, M. B. and Welt, L. G., DISEASES OF THE KIDNEY, second edition, Boston, Little, Brown and Co., in press.

In conclusion, remarkably little evidence is available to describe a role for urinary infection in the production of hypertension or renal disease in the absence of other conditions known to predispose toward or to be able by themselves to produce renal or vascular disease.

It must be emphasized, however, that the period during which the natural history of urinary infections has been studied is still short and the number of patients followed still relatively small to be content with what is known. If the natural history of elevated blood pressure (essential hypertension) were being studied few firm conclusions would have been reached at this stage.

More important, perhaps, is the realization that in the absence of underlying disease of the urinary tract, bacterial infection does not represent an immediate threat to life. Therefore, therapeutic measures that carry significant risks or that are of questionable benefit have very little place in management of these patients.

REFERENCES

- ¹ Longcope, W. T., Chronic Bilateral Pyelonephritis: Its Origin and its Association with Hypertension, *Annals of Internal Medicine*, 11, 149-163, 1937.
- ² Weiss, S. and Parker, F., Jr., Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, *Medicine*, 18, 221-315, 1939.
- ³ Freedman, L. R., Chronic Pyelonephritis at Autopsy, *Annals of Internal Medicine*, 66, 697-710, 1967.
- ⁴ Miall, W. E., Kass, E. H., Ling, J. and Stuart, K. L., Factors Influencing Arterial Pressure in the General Population in Jamaica, *British Medical Journal*, 2, 497-506, 1962.
- ⁵ Freedman, L. R., *et al.*, The Epidemiology of Urinary Tract Infections in Hiroshima, *Yale Journal of Biology and Medicine*, 37, 262-282, 1965.
- ⁶ Kunin, C. M. and McCormack, R. C., Bacteriuria and Blood Pressure among Nuns and Working Women, *New England Journal of Medicine*, 278, 635-642, 1968.
- ⁷ Freedman, L. R., Experimental Pyelonephritis XV. Increased Susceptibility to *E. coli* Infection in Old Rats, *Yale Journal of Biology and Medicine*, in press.
- ⁸ Szasz, J. J. G. and Whyte, H. M., Effect of Distention of the Bladder and of Contraction of Sphincters on Blood Pressure, *British Medical Journal*, 2, 208-210, 1967.
- ⁹ Freedman, L. R., Urinary Tract Infection, Pyelonephritis and other Forms of Chronic Interstitial Nephritis. in Strauss, M. B. and Welt, L. G. (Editors), *DISEASES OF THE KIDNEY*, second edition, Boston, Little, Brown and Co., in press.

ACKNOWLEDGMENTS

This study was supported by U.S. Public Health Service Career Development Award No. 6K3-HD-22,587, National Institute of Child Health and Human Development, and by Research Grant No. 4767, Institute of Allergy and Infectious Diseases.