# Papers and Originals

## Hyperpiesis: High Blood-pressure without Evident Cause: Essential Hypertension*

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Thirty-four years ago when I began to work on the nature of elevated arterial pressure the problem seemed simple. There were a number of maladies in which arterial pressure was raised. Physiological analysis, in which I had been splendidly trained, would reveal what was the basic fault in each. And so I set to work. Now I know the answer in only one of these diseases, phaeochromocytoma. I have learned a great deal about the natural history of the disorders, their differential diagnosis, and the way in which certain symptoms are produced. And on the way Prinzmetal and I (1938) rediscovered renin, buried for forty years since Tigerstedt and Bergman (1898) had described it.

The elusiveness of the basic fault in hypertension made me wonder if indeed there was one. The evidence, that the retinopathy of the malignant phase (Pickering, 1934) and the arteriolar lesion responsible for it (Wilson and Pickering, 1938) were due not simply to elevated arterial pressure but to the degree of hypertension, began to make me think in quantitative terms. This was reinforced by the family studies (Hamilton *et al.*, 1954a, 1954b). The more I thought about this the more it became clear to me that people of my generation were failing to get answers because we were asking nonsensical questions. We were treating a quantity, arterial pressure, as if it were a quality with two alternative attributes, good and bad.

The qualitative approach is still very much a habit of mind of all who have had a medical education. It stems from the emphasis on diagnosis and the vital question, Has the patient a disease or not? And so characteristics associated with "disease" tend to be divided into normal and abnormal, physiological and pathological, good and bad. Medicine in fact can count up to two. Elevated arterial pressure is no exception. Blood-pressure is classed as normal or abnormal, normotension or hypertension. Those with hypertension have the disease, those with normotension have not. Committee after committee deliberates on the dividing-line. W.H.O. makes pronouncements. But the arterial pressure fluctuates, and it tends to rise with age. So the disease is thought to go through a series of stages—prehypertension, intermittent hypertension, labile hypertension, and fixed hypertension—according to whether the pressure seldom reaches, sometimes reaches, sometimes falls below, or never falls below the dividing-line according to the doctor's readings. We now know that there is no dividing-line. To create one is nothing more or less than to create an artifact, and the resulting classification is nothing more than a set of secondary artifacts.

Science progresses by asking questions, by formulating hypotheses that seem to explain the facts and are formulated in such a way as to be refutable by further experiments or evidence. As Jacques Loeb (1924) wrote: "By a scientific theory is meant a rationalistic mathematical theory based on quantitative measurements."

In this lecture I intend to formulate some hypotheses which I hope have these characteristics. It seems elementary that if the hypotheses are concerned with a quantity they should be formulated in quantitative terms. But so rooted is the opposite habit in medicine that attempts to do so in the present instance tend to be greeted by clinicians of my own generation as dangerous nonsense, by other scientists as a glimpse into the obvious. The difference in the quantitative and qualitative approaches is the real basis of the controversy between myself and Platt, who (1964) has recently written: "The subject is made peculiarly difficult . . . because no one can accurately define what is normal and what is abnormal with regard to blood-pressure."

## Clinical Features of Hyperpiesis

### Historical

The condition we are considering here was originally regarded as Bright's disease, which a century ago was probably the commonest cause of a greatly elevated arterial pressure and its consequences. Its identity was recognized pathologically by Gull and Sutton (1872), who termed it "arteriocapillary fibrosis," and clinically by Mahomed (1881), who termed it "chronic Bright's disease without albuminuria." It was separated from Bright's disease by Huchard (1889), who termed it "presclerosis," by von Basch (1893), who termed it "latent arteriosclerosis," and by Allbutt, who eventually gave it its most correct name of classical origin—"hyperpiesis." Allbutt's term was preceded by Frank's (1911) "essentielle hypertonia," a little oddly translated as essential hypertension, by which name it is most commonly known. In 1915 Allbutt wrote: "Thus gradually I became convinced that cases, such as we are considering, must be divided, first, into Bright's Disease . . . secondly, into the class to which soon afterwards I gave the name Hyperpiesis, a malady in which at or towards middle life blood pressures rise excessively, a malady having a course of its own and deserving the name of a disease; and thirdly, into at least one other class of arterial degeneration, one not typically associated with rise of blood pressure, a class in which, indeed, the blood pressure does not exceed, or scarcely exceeds, the rise common to almost all persons in later life; a series of which the course, symptoms and issues are altogether different." Allbutt's classification and his description of the disease stand, though I would prefer Councilman's and Osler's term of "nodular arteriosclerosis" to Allbutt's "decrescent arteriosclerosis," which he gave to the third category.

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## Quantitative Approach

As Allbutt states, this is a disease in which at or toward middle life blood-pressure rises excessively and in which single specific maladies can be excluded. The clinical manifestations are largely to be traced to heart and blood-vessels. If arterial pressure and disease of heart and blood-vessels are related, then three explanations are possible: (*a*) that vascular disease causes elevated arterial pressure, (*b*) that elevated arterial pressure causes vascular disease, (*c*) that both are due to a common cause, "hypertensive disease." The third explanation has not the merit of a scientific theory. It can never be refuted. Unless, therefore, some unequivocal evidence for it turns up (and I sought it for 25 years) it may be omitted from consideration. The second theory is the easiest to refute. If elevated arterial pressure causes cardiovascular disease, then reducing the arterial pressure sufficiently and persistently should arrest or delay the progress and development of the clinical manifestations and prolong life. If reducing arterial pressure does not do this, the hypothesis is wrong.

Thus the reader interested in the nature of the disease should have two questions foremost in his mind: Is there a relation between arterial pressure and any one of its associated features? And does reducing arterial pressure affect it?

It is no part of the quantitative hypothesis that arterial pressure is the only factor concerned in any of these phenomena. If it were, it would be almost unique in biology. For example, when biological assay of insulin and toxic substances was made in terms of the response of an animal it was necessary to choose animals as like as possible to each other in weight, sex, inheritance, and diet, and to use large numbers, so that, for example, the LD50 could be estimated. In a population of patients none of these factors can be controlled. There is a good deal of evidence that rate of rise of arterial pressure is important. For example, in the rabbit section of the buffer nerves raises arterial pressure. If all four are cut at one sitting the animals die of left ventricular failure. If they are cut in two stages this is less likely to happen. Thus it is extemely probable that the dimension, time, is important, but in clinical medicine we have hardly begun to think of it. Finally, in some instances factors are known which, independent of arterial pressure, influence arterial disease—for example, *x* rays in arteriolar fibrinoid necrosis, and the factors reflected by serum cholesterol in coronary artery disease.

It might thus be expected that the size of the arterial-pressure factor might not always be the same. In some it might be very large; in others quite small. The clinical evidence suggests this is so. The following classification may be suggested:

1. Those manifestations in the production of which arterial pressure seems to be a *chief* factor:

(*a*) *The malignant phase:* This can occur in any form of hypertension provided it is severe enough. Rate of rise and other factors probably play a part. It represents the "ceiling" of raised arterial pressure. It is reversible if diagnosed early enough and if the pressure is reduced and kept down.

(*b*) *Left ventricular failure:* Though there are many other causes, this is particularly common in those with very high pressures. In such patients reducing pressure will cut short an attack, and keeping it down will prevent further attacks.

(*c*) *Hypertensive fits,* as in eclampsia: Undoubtedly there are other factors here, since fits are commonest in patients with acute nephritis and pregnancy toxaemia in whom the rise of pressure is recent, and anaemia common; moreover, the pressure may not be so very high. Reducing the pressure brings the patient out of the attack, and keeping the pressure down prevents further attacks.

2. Those in which arterial pressure is a *large* factor:

(*a*) *Aneurysms of the small cerebral arteries,* discovered by Charcot and rediscovered by Ross Russell; probably the chief cause of cerebral haemorrhage and a cause of little strokes and cerebral infarction in patients with elevated pressure. Their rediscovery is so recent that comparatively little is known of their relationships.

(*b*) *Heart failure:* a common event in untreated hypertension. The higher the pressure the more likely that its reduction will cure and prevent heart failure.

3. Arterial pressure is a smaller factor in nodular arteriosclerosis, a disease producing narrowing and ultimately occlusion of large arteries, the chief cause of myocardial infarction and of carotid artery narrowing and occlusion, and thus a cause of cerebral infarction.

These orders of size may require revision in the light of further knowledge. What seems to me of great importance is to recognize that the correlation between height of arterial pressure and its consequences is not always of the same order of size. Those in which arterial pressure plays the largest part are found in the malignant phase, those in which it plays a smaller part are characteristic of the benign phase. Thus the malignant phase has striking uniformity while the benign phase is very variable.

## Arterial Pressure and its Variation

Arterial pressure varies with the artery in which it is recorded, and according to whether the measurement is one of end or side pressure. Functionally arterial pressure is far less important than capillary pressure, which regulates capillary exchange, or venous pressure, which regulates cardiac output. Arterial

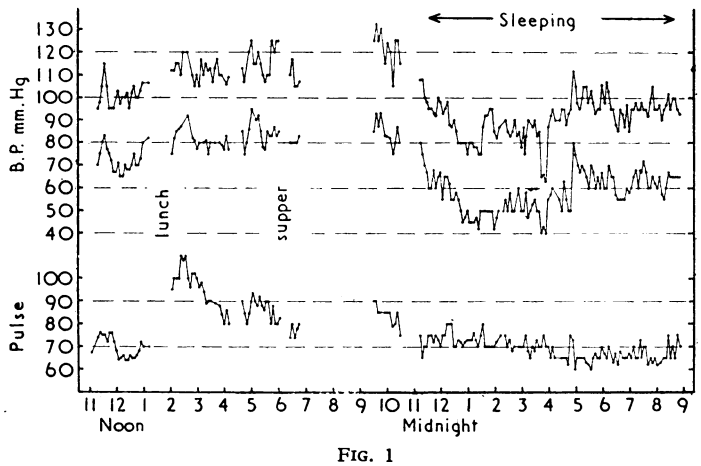



FIG. 1

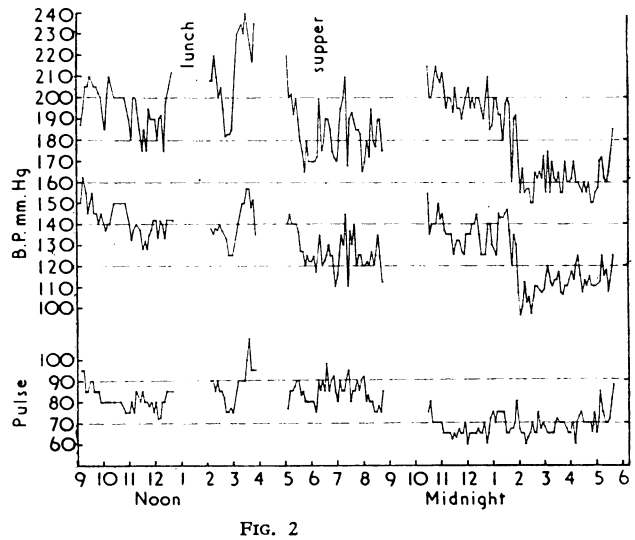



FIG. 2

FIG. 1.—Variation in blood-pressure in a subject with normal blood-pressure throughout 24 hours. (Richardson *et al.*, 1964.) FIG. 2.—Variation in blood-pressure in a hypertensive subject throughout 24 hours. (Richardson *et al.*, 1964.)

pressure is the resultant of a large number of factors—the diameter and length of the various classes of arteries and arterioles, the elasticity of their walls, blood viscosity, and cardiac output—and is influenced by the activity of the brain, the proprioceptive cardiovascular reflexes, the secretions of the various endocrine glands and of the kidneys, the electrolyte composition of the blood, the production and distribution of tissue vasodilator substances, and probably other factors of which we are aware only dimly, or not at all.

## Diurnal Variation

The extent to which arterial pressure varies during the day has hitherto not been appreciated, though in fact the data were obtained by earlier workers (see Pickering, 1955). Recently my colleague F. Stott designed a machine which registers systolic and diastolic pressure from a Gallavardin double cuff on the upper arm, at predetermined intervals—for example, five minutes. Records throughout the 24 hours have shown huge variations—for example, from 135 to 65 mm. Hg systolic in my colleague Dr. David Richardson, Professor of Cardiology in the Medical College of Virginia, who carried out most of the measurements, and from 240 to 150 mm. Hg systolic in a patient with essential hypertension (Figs. 1 and 2). The arterial pressure varies a good deal during waking, when it is influenced particularly by the state of mind of the subject, a well-known component of which is his attitude to his physician. The pressure falls profoundly during sleep, when it is dependent on the depth, rising with E.E.G. and other signs associated with dreams (Richardson *et al.*, 1964). The extent of the variation is shown in Fig. 3. In this small series it will be seen that there is no conspicuous relation between variability and either highest or lowest pressure. The important point is that the variability is common to patients with all grades of pressure and seems neither consistently less nor more in those with high as compared with low pressures.

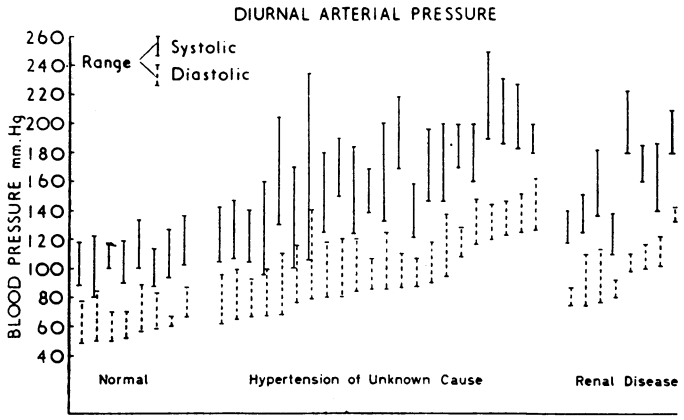



FIG. 3.—Ranges of blood-pressure in eight normals, 22 patients with essential hypertension, and eight subjects with renal disease. Top bar of each range represents average pressure during highest hour of a 24-hour record. The bottom bar represents the average during the lowest hour. (Richardson *et al.*, 1964.)

Honour and Richardson (unpublished) have pursued these investigations using intra-arterial-pressure recording. In sleep the arterial pressure remains steady for long periods, but a K complex in the E.E.G. is followed in a few seconds by a rise in systolic, diastolic, and pulse pressure and of heart rate. During deep sleep the low arterial pressure is not accompanied by increase in heart rate. Evidently, current ideas about the automatic regulations of arterial pressure through the baroreceptors need profound modification. Either the baroreceptors are not functioning during sleep or the number and pattern of impulses the receptors send to the central nervous system are altered, or the response to a given set of afferent impulses is altered. Current theory ascribes the difference between sleep and waking to the activity of the reticular formation. The third explanation is thus most likely.

## Casual and Basal Pressures

It has long been recognized that casual pressures vary and, since Ayman and Goldshine's (1940) demonstration, that the physician is a major determinant. Smirk followed Addis (1922) in the search for a more constant value, akin to the basal metabolic rate. He has produced a series of refinements—early morning, fasting, a sedative, a dark room, familiarity with the physician, soothing talk (see Smirk, 1957). These rather limit usefulness. Dr. Richardson compared basal pressures, by an earlier method of Alam and Smirk (1943), and casual pressures, all taken by himself, with diurnal variability (Fig. 4). It will be seen that casual pressures and basal pressures are both below maximum and far above minimum for 24 hours. Basal pressure, as Smirk now takes it, is more replicable. In fact, an estimation of arterial pressure is like an estimation of blood sugar—it is a value at a point of time of a very changeable character; basal pressure by no means represents the diurnal baseline.

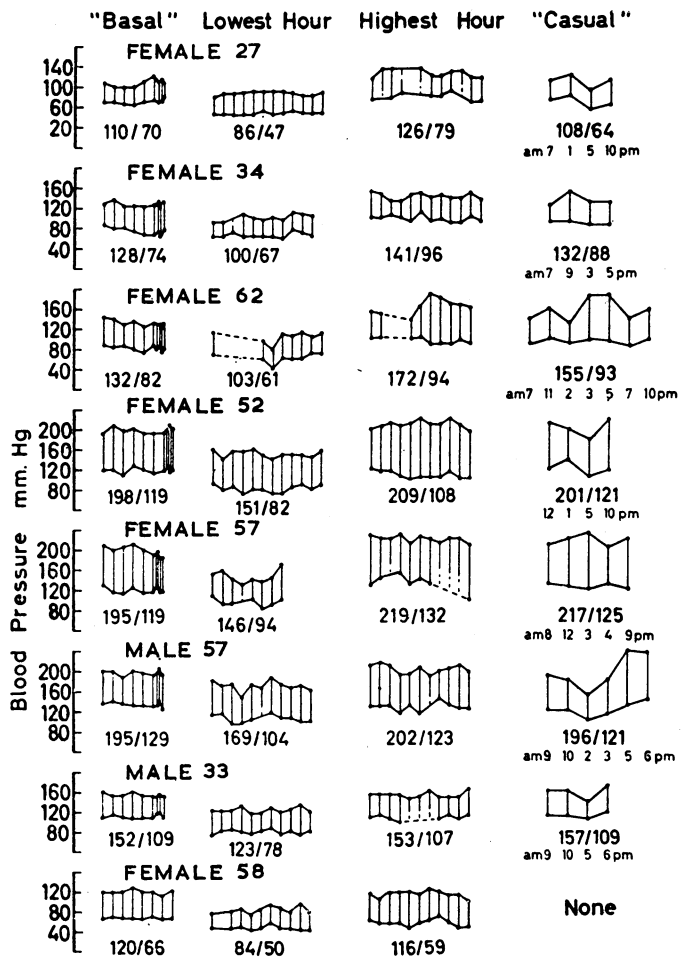



FIG. 4.—Relation of "basal" and "casual" pressures recorded by a physician with automatic records of blood-pressure during highest and lowest hours of same 24-hour period. The numbers below each graph indicate the average pressure during the period represented in the graph. (Richardson *et al.*, 1964.)

## Repeated Observation

Fig. 5 shows the arterial pressure measured at weekly intervals by the same physician in a single patient on a placebo. The pressure falls. This effect is not due to the placebo; it is almost

certainly due to the progressive weakening by repetition of the pressor responses to the circumstances of measurement. This effect is elementary in all long-term studies on individuals.

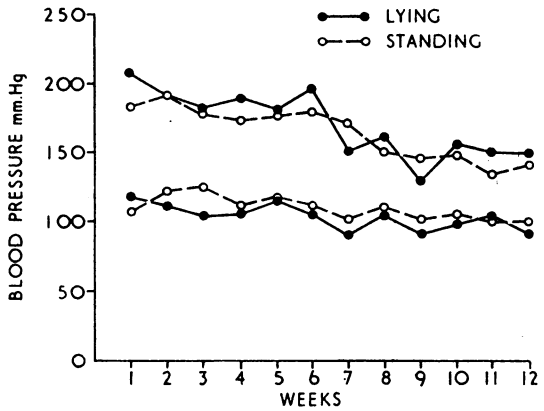



FIG. 5.—Arterial pressure measured at weekly intervals in a clinic patient receiving inert tablets. (Reproduced from Pickering, Cranston, and Pears, 1961, *The Treatment of Hypertension*, Charles C. Thomas, Springfield, Ill.)

## Arterial Pressure in Populations

Fig. 6 shows the mean pressures found by Miall and Oldham (1963) in their measurements of a population sample in South Wales. Evidently arterial pressure tends to rise with age, and, after 40, faster in women than in men. Fig. 7 shows the frequency distribution curves for successive decades in the St. Mary's survey (Hamilton *et al.*, 1954a). Arterial pressure tends to rise with age, but it tends to rise more in some subjects than in others.

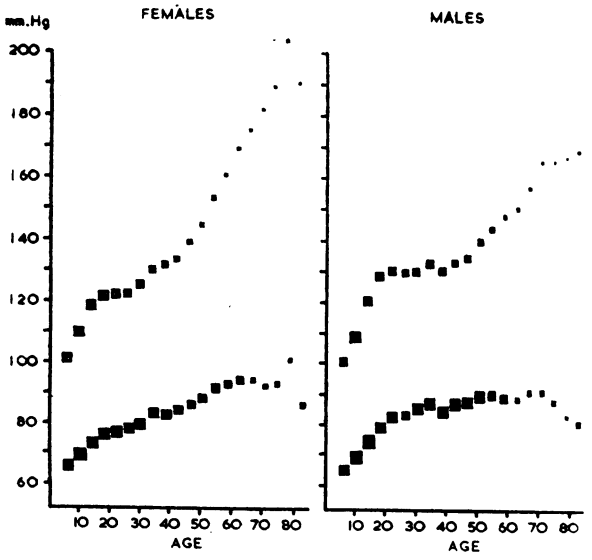



FIG. 6.—Mean systolic and diastolic pressures in the Rhondda Fach and Vale of Glamorgan populations, based on the findings in two surveys. The area of each square is inversely proportional to the standard error of the mean, and so indicates the weight to be attached to each mean. (Miall and Oldham, 1963.)

*Essential Hypertension.*—It has been common practice to regard as abnormal arterial pressures above systolic values of 140 and diastolic values of 90. In the absence of a specific recognizable abnormality, known or suspected to be associated with hypertension, patients with pressures above these values have been labelled "essential hypertension" and thus deemed to have a disease. Miall and Oldham's (1963) curves show that these values are exceeded by the bulk of the population at age 50 in females and age 55 in males. Fig. 7 shows the same and also that the proportion increases in each decade.

*Fallacy of the Dividing-line Between "Normotension" and "Hypertension."*—That in the sixth decade over half the population appears to be "abnormal" should at least raise a doubt in the mind whether we are not, intellectually speaking, being led up the garden path. This doubt is fortified by reflecting that it is an elementary fallacy to suppose that one can adequately describe numbers in terms of kind. That the dividing-line is an artifact is revealed by the following facts: (1) There is no natural dividing-line in the frequency distribution curves (see also Pickering, 1955). (2) The relation between arterial pressure and expectation of life is quantitative.

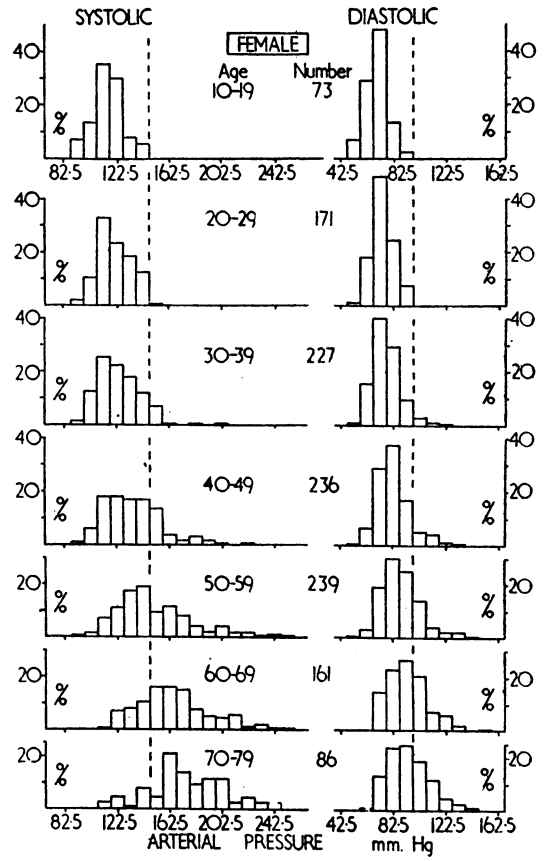



FIG. 7.—Frequency distribution of arterial pressures in females of a population sample, arranged by age in decades (Hamilton *et al.*, 1954).

No discontinuity has ever been displayed (see next section). (3) Table I shows those values ending in 0 which have been chosen as the dividing-line by a series of authors, not chosen as originators but because of the order in which the values appeared in my notes. Had values ending in 5 been included—chosen no doubt by more discriminating minds—the list would have been longer. No evidence has been produced that justifies any of these values.

TABLE I.—*Dividing-lines Between "Normotension" and "Hypertension"*

| | |
|---|---|
| 120/80 | S. C. Robinson and M. Brucer (1939 |
| 130/70 | F. J. Browne until 1947 |
| 140/80 | D. Ayman (1934) |
| 140/90 | G. A. Perera (1948) |
| 150/90 | C. B. Thomas (1952 |
| 160/100 | P. Bechgaard (1946) |
| 180/100 | A. M. Burgess (1948) |
| 180/110 | W. Evans (1956) |

If the dividing-line be accepted as an artifact—and I am delighted to challenge any of your readers to dispute this—then the qualitative approach to the disease loses its decisive battle. The way is open to consider quantity in the only proper way—as quantity.

## Arterial Pressure and Outcome

### Expectation of Life

Life insurance companies have the largest collective stake in relating measurable quantities to subsequent life expectation. They began by accepting medical advice, that there was a normal range of blood-pressure and, on either side of it, hypotension and hypertension. However, data began to accumulate. These revealed that, with the decline in tuberculosis, life expectation was inversely related to arterial pressure at first examination. The relation was quantitative. There was no sudden break. Table II shows figures from the Actuarial Association of America.

TABLE II.—*Mortality Ratios* for Men According to Groups of Systolic and Diastolic (Fifth Phase) Blood-pressure Readings, Without Minor Impairments, All Entry Ages Together (From Actuarial Society of America and Association of Life Insurance Medical Directors* 1941)

| Systolic Reading (mm.) | Diastolic Reading (5th Phase) (mm.) | | | | |
|---|---|---|---|---|---|
| | 64–83% | 84–88% | 89–93% | 94–103% | All % |
| 118–132 | 90† | 91 | 99 | 97 | 92 |
| 133–142 | 99 | 107 | 118 | 134 | 110 |
| 143–152 | 133 | 137 | 141 | 173 | 148 |
| 153–167 | 186 | 178 | 139 | 237 | 210 |
| All | 95 | 100 | 116 | 151 | 106 |

* Actual to expected deaths (expected = 100).
† This included only systolic readings 128 to 132 mm.

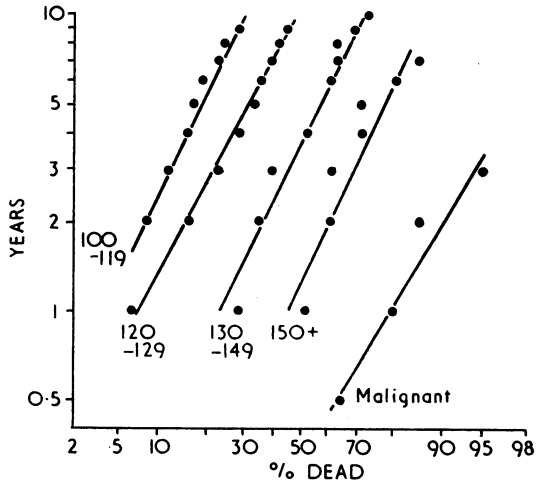
When these figures first came to light they were a surprise. Dublin, Lotka, and Spiegelman (1949) wrote: "It is clear [from the table] that mortality rises steadily and markedly with increasing elevation of both the systolic and diastolic pressure. The significant increase found in mortality with relatively moderate elevation of blood-pressure was contrary to clinical impressions. The classes relating to hypotensives indicate that in general such persons have a low mortality. These findings are in conformity with the clinical impressions and earlier insurance investigations of persons with low blood-pressure. The excessive mortality among the hypertensives is primarily due to the cardiovascular-renal diseases. With increasing departure from average blood-pressure the ratio of actual to expected deaths increased faster for the cardiovascular renal diseases than for all causes. In the group with the highest blood-pressures included in this experience—and these are not considered seriously high by many clinicians—the mortality from cardiovascular-renal disease was nearly 4½ times the average for all standard risks."

This relation between arterial pressure and subsequent mortality from cardiovascular-renal disease is shown in Table III. Cardiovascular-renal disease related to arterial pressure is chiefly represented by the disease being considered here, hyperpiesis or essential hypertension. So that we see, again, the probability that this will develop is quantitatively related to arterial pressure at first examination.

TABLE III.—*Deaths from Cardiovascular-renal Disease. Ratios of Actual Deaths to those Expected from this Cause in the Basic Table. All Entry Ages Together (From the Actuarial Society of America and the Association of Life Insurance Medical Directors,* 1941)

| Systolic Reading (mm.) | Diastolic Reading (Fifth Phase) (mm.) | | |
|---|---|---|---|
| | 54–83% | 84–93% | 94–116% |
| 108–132 | 86 | 101 | 116 |
| 133–142 | 108 | 137 | 171 |
| 143–177 | 175 | 201 | 293 |

Insurance companies have no large body of data for patients with "hypertension." Bechgaard's data from his 1,000 cases of essential hypertension followed for 10 and then for 20 years (Bechgaard, Kopp, and Nielsen, 1956) showed that life expectancy was less in those with the highest pressures, and when analysed by using the norm for age and sex was related to the extent to which it deviated from the norm (Pickering, 1955). Leishman's (1959) data on untreated patients with essential hypertension have enabled survival to be plotted for each decile of arterial pressure. When this is done on a logarithmic scale the survival rates are a series of straight lines (Fig. 8) which move from left to right with the initial level of arterial pressure. Thus in the range hitherto classed as essential hypertension, as in the range of so-called normal pressure, expectation of life is inversely related to arterial pressure. The relationship is quantitative.




| Diast. B.P. | 100 -119 | 120 -129 | 130 -149 | 150+ | Malignant |
|---|---|---|---|---|---|
| Age | 47·0 | 49·5 | 47·2 | 49·8 | 44·3 |
| No. | 87 | 45 | 38 | 21 | 20 |

FIG. 8.—Survival rate in Leishman's untreated patients, arranged according to their diastolic pressures when first seen. The percentage dead is plotted on a probability scale, the time in years on a logarithmic scale. The age for each group is the mean age at which the patients were first seen. (Reproduced from Pickering, Cranston, and Pears, 1961.)

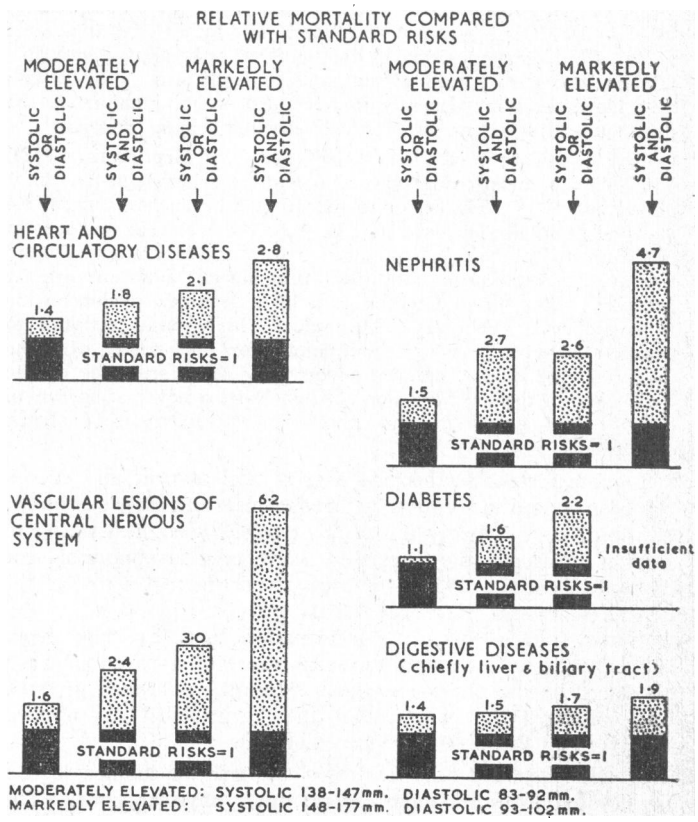



FIG. 9.—Prognosis in elevated blood-pressure. Relative mortality in men, arranged by arterial pressure when first seen, compared with the standard rise. (The experience of 26 companies in 1935–54 compiled by the Metropolitan Life Insurance Company.)

### Outcome in Individual Organs

As we shall see, the commonest causes of death in this disease are from heart disease and vascular disease in the benign phase and from renal failure in the malignant phase. Fig. 9, from the experiences of 26 companies in 1935 to 1954 compiled by the Metropolitan Life Insurance Company, shows the relationship between arterial pressure at first examination and subsequent cause of death. Increasing values of arterial pressure carry increasing liability to a cardiac death, a renal death, and a death from cerebrovascular accident. The rise in mortality with arterial pressure is steepest for vascular lesions of the central nervous system, and least steep for heart and circulatory diseases. Thus, whether we look at the overall picture or at individual organs, there is a quantitative relationship between arterial pressure and its fatal consequences. There is no dividing-line. The concept of normotension and hypertension obscures the truth. This statistical, or probability, relationship between arterial pressure and outcome is a temporal one—that is to say, arterial pressure is recorded first, outcome later. The nature of this relationship is basic to the disease now being considered. We may look, then, at the other end.

## Clinical Picture of Hyperpiesis

### Early Stages

In its early stages essential hypertension is symptomless. The condition is recognized because a high arterial pressure is found at a routine medical examination or in the course of a physical examination for an unrelated complaint. When the condition is recognized because of a symptom related to the arterial pressure, the pressure is usually very high. Here, for example, is a patient in the benign and one in the malignant phase:

*Case 1.*—A woodwork machinist, age 62 (UOH.361877), had never had a day's illness until, in January 1962, his nose started to bleed. His doctor (Dr. Gordon Scott) found his blood-pressure to be 220/110 and began to treat him. His father died at the age of 74, of old age, and his mother at age 80 after breaking her thigh; his one brother was aged 83 and well, and one sister aged 70 had high blood-pressure. Investigation revealed no abnormalities in the urine and no apparent cause for his elevated arterial pressure.

*Case 2.*—(Case 1 of Pickering, Wright, and Heptinstall, 1952.) This man, a meter-reader aged 33, had been symptom-free until November 1945. He began to get frontal headaches and failing vision, first in the left and later in the right eye. He was sent to the Western Ophthalmic Hospital in December 1945, and was found to have "albuminuric retinitis," proteinuria, and an arterial pressure of 240/170. Excision of a hydronephrotic pyelonephritic right kidney in February 1946 reduced his arterial pressure to around 160/110, at which it remained for nine years, when he died suddenly of a cerebral haemorrhage. The arterioles of the kidney and of the suprarenal on the right side, removed at operation, both showed gross fibrinoid necrosis, the lumen being almost obliterated.

I quote these cases because a great deal of time and energy has been wasted in trying to define the onset and early symptoms of the disease. Mostly the search resolves itself into trying to find at what age the arterial pressure became abnormal—for example, Benedict (1956)—ignoring the artifactual nature of the dividing-line and the huge diurnal variations in pressure. An impartial search yields the information that the early stages are iatrogenous—the symptoms are those of a psychoneurosis produced by the physician who has found an elevated pressure and informed the patient that the "grim label" is applied (Ayman and Pratt, 1931; Stewart, 1953).

In the absence of other maladies and with the smaller degrees of elevated pressure, there are no other physical signs. The fundi are normal (it is very easy to find minor degrees of retinal arteriosclerosis, since the signs have a huge observer error). The heart is normal, and the urine is normal. At this stage, and also with greater elevations of pressure, secondary hypertension is excluded by special features.

### Exclusion of Secondary Hypertension

In coarctation of the aorta the femoral pulse is small and the summit delayed. In nephritis there is usually a previous history and the urine characteristically shows protein, red cells, and casts.[1] The collagen diseases have their distinguishing histories and signs. So usually has phaeochromocytoma, and this can generally be eliminated by measuring urinary catecholamines. Polycystic kidneys are often palpable and can be displayed by intravenous urography. Cushing's syndrome is usually evident at first glance, and in any case has a galaxy of signs. Conn's syndrome presents with thirst, polyuria, and episodes of muscular weakness, and the plasma electrolytes show characteristic changes. Renal-artery stenosis usually produces considerable elevation of pressure developing quickly, and is diagnosed by aortography.

By far the most difficult disease to recognize and exclude is chronic pyelonephritis. Some patients present with the characteristic history of recurrent urinary infections. But other patients give none. Characteristic radiological changes have been described (Hodson, 1959). I think the best method of diagnosis is the quantitative excretion of white cells and bacteria before and after the administration of a pyrogen (Pears and Houghton, 1959) or prednisolone. I suspect, however, that, given all these tests, I and others still miss cases of this disease, which in my experience of hospital practice in London and Oxford is now by far the commonest specific lesion associated with hypertension. I put it this way deliberately because I suspect from my own experience (*a*) that pyelonephritis often develops in those who already have elevated pressures, and (*b*) that the onset of pyelonephritis in such patients is the commonest cause for an otherwise unexplained sudden rise of arterial pressure.

Two other points are important. Essential hypertension, as we shall see later, usually represents a more or less gradual rise of pressure with age. Therefore young subjects with gross hypertension nearly always have a form of secondary hypertension (Platt's law). Again, a rapid rise of pressure over a short interval should raise in the physician's mind the possibility of a new development—for example, renal-artery stenosis or pyelonephritis. Here, for example, is a case of pyelonephritis:

*Case 3.*—A woman, aged 46 (UOH.149052), presented on 17 January 1965. A dark spot had appeared suddenly in her right eye three weeks previously. She was symptomless otherwise, apart from occasional episodes of frequency of micturition. The right fundus had a cotton-wool spot at 11 o'clock. There were no other exudates or haemorrhages and no papilloedema. The arterial pressure was 240/145 and the left ventricle was considerably enlarged and forceful. The urine contained a trace of protein, an excess of white cells, and was sterile on culture. The specific gravity was 1021 and the urine contained 2.6% of urea. Blood urea was 30 mg./100 ml. Prednisolone provocation test increased the rate of excretion of white cells from 600,000 to 12,700,000 per hour. The intravenous pyelogram was normal (Dr. F. H. Kemp). There were three previous readings of arterial pressure—in 1957 (incomplete abortion) 110/70, in September 1952 (piles) 130/80, and on 14 February 1962 (irregular periods) 180/120.

### Late Stages

One of Volhard and Fahr's (1914) strokes of genius was to recognize that the disease in its later stages could follow one of two courses—"Gutartige" or "Bosartige," benign or malig-

[1] Though not always. I have under my care a woman of 43 (UOH. 232717) who had acute nephritis at 10, persistent proteinuria, and a cerebral vascular accident at 29, her pressure then being 240/140, for which she was treated with bilateral sympathectomy. She now runs a pressure of around 160/100 and has no proteinuria and no excess of red or white cells in the urine.

nant—and that these two forms presented very different changes in the kidneys, simple bland sclerosis and malignant sclerosis. To explain this arrangement of the clinical facts is the first challenge to the clinical scientist.

## Malignant Phase

In essential hypertension the onset of the malignant phase is usually announced by failing vision due to bilateral neuroretinopathy. At that time urine and renal function may be normal. Soon, however, red cells and protein appear in the urine, renal function begins to decline, attacks of cardiac asthma, hypertensive fits, or "little strokes" occur, and the patient dies within the year, usually of uraemia but sometimes of cerebral haemorrhage, left ventricular failure, or cardiac failure. There is some variation in the precise order. In about half the patients the kidneys are already involved when the patient is first seen, and the presenting symptoms may be haematuria, cardiac asthma, a convulsion and coma, a cerebral haemorrhage, a little stroke, or even uraemia. Nevertheless, three features are usually all present—bilateral neuroretinopathy, gross hypertension, and evidence of renal involvement. The fourth and equally characteristic feature is the rapidity of decline. Few diseases untreated are so swiftly and so certainly fatal. In the two largest unselected series, death rates were 90% and 79% at the end of one year and 99% at the end of five years (Keith, Wagener, and Barker, 1939; Kincaid-Smith, McMichael, and Murphy, 1958). Proof comes from biopsy or post-mortem examination. The medial or inner coats of some small arteries and arterioles in kidneys, gut, adrenals, parathyroid, liver, eye, and brain, in roughly that order, are expanded by material staining like fibrin and thus called fibrinoid. The lumen of the affected arteries is greatly narrowed. It is this lesion that, by expanding wall at the expense of lumen, progressively curtails blood-flow to the kidney, thus causing renal failure and death in uraemia.

The malignant phase is a fairly sharply defined entity. Nevertheless, it has mimics, and the clinically unwary can mistake other diseases. Fibrinoid infiltration of the arterial walls may occur as a result of intense vasoconstriction produced in the kidney by posterior pituitary hormone (Byrom, 1937), by *x*-irradiation (Russell, Wilson, and Tansley, 1949), in the various collagen diseases, and as part of an allergic response. In some of these the experienced can distinguish the arteries of the malignant phase from those of its mimics. For instance, in man and the rabbit the fibrinoid of the malignant phase is associated with only a minor cellular reaction in contrast to polyarteritis nodosa and the allergic response; but in the rat there may be little or no difference. Again, neuroretinopathy resembling that of the malignant phase is found in severe haemorrhage, in bacterial endocarditis, in disseminated lupus, in polyarteritis nodosa, and occasionally in temporal arteritis.

## Neuroretinopathy

Clinically, the *sine qua non* of the malignant phase is bilateral neuroretinopathy, characterized by oedema of the nerve head and often of the retina, large woolly exudates, haemorrhage, and a star figure at the macula. Blurring of one or both disk margins or a large woolly exudate may be the first sign. This neuroretinopathy has to be carefully distinguished from the retinopathy of the benign phase, described and distinguished by Foster Moore in 1917 as arteriosclerotic retinitis, in a masterly paper which no serious student of the disease should fail to read. This form is characterized by small sharply defined white patches, frequently grouped and often unilateral; papilloedema is uncommon and then usually unilateral and transient. Because of their entirely different prognostic and diagnostic importance, the distinction between these two types is of basic importance in this disease. It is the great demerit of the Keith-Wagener classification that it fails to do this, grade III containing both types. I therefore will not have this classification used in my clinic.

Papilloedema in malignant neuroretinopathy closely resembles ophthalmoscopically and histologically that found in cerebral tumour. It is likewise usually associated with raised intracranial pressure (Quincke, 1910; Larsson, 1923; McAlpine, 1932; Shelburne, Blain, and O'Hare, 1932; Pickering, 1934). Though later observers have questioned the inevitability of such association, the correspondence between papilloedema and raised cerebrospinal fluid pressure was higher in the last two series of hypertensive patients than in Ayer's (1929) series of 61 cerebral tumours.

The cotton-wool exudates are collections of oedema fluid in the nerve fibres of the nerve fibre layer, and "cytoid bodies" which seem to be the terminal bulbous swellings of nerve fibres (Ashton and Harry, 1963). Ashton and Harry have shown that exudates compress the capillaries locally and that, as Verwey (1927) and Friedenwald (1935) had earlier found, the arterioles supplying them have lipoid deposits in their walls, and, as they newly report, fibrinoid changes also.

Hodge and Dollery (1964) have taken serial photographs, with and without intravenous fluorescine, of cotton-wool exudates as they appear and regress with treatment in malignant hypertension. The exudates are not due to vascular obstruction, for "in some cases the arterioles feeding into an area of exudation have been demonstrably patent and areas of capillary obliteration were only seen after an exudate formed and not immediately before it did so. Fluorescence studies suggested that increased diffusion of dye from damaged vessels is a characteristic feature of the vascular pathology associated with soft exudates." The distribution of soft exudates close to the disk and to the large vessels "might be predicted if exudates followed arterial damage by high pressure." During effective treatment to reduce arterial pressure, soft exudates clear at a remarkably uniform rate. They leave a normal retina. Hard exudates may appear quite separately during treatment; they tend to have a different distribution and are histologically different. McMichael (1961) described the case of a patient with malignant hypertension in whom neuroretinopathy was restricted to one eye; the other carotid artery was occluded. Finally come Byrom's (1963) beautiful observations on the eye and brain in experimental hypertension in the rat, to be considered in the next section.

Pears and Pickering (1960) showed that neuroretinopathy simulating that of malignant hypertension occurred after severe gastrointestinal bleeding; the exudates often made their first appearance 24 hours or more after exsanguination; they cleared in a few weeks after bleeding stopped and blood was replaced; histologically they resembled the exudates of malignant hypertension (Ashton, Pears, and Pickering, 1961) and adjacent arteries and veins were histologically normal. Ashton and Henkind (1965) have injected minute glass bands into the retinal arteries in animals. Cotton-wool exudates appear after one or two days and subside in two to three weeks. Thus there is clear evidence that cotton-wool exudates can, and do, develop as a result of focal ischaemia, or possibly anoxia.

Taken together, these observations suggest that the exudates represent areas in which protein-rich fluid has leaked out of vessels which have been damaged by some process, and, in the particular instance of malignant hypertension, by either the high pressure or the excessive vascular constriction associated with it. Papilloedema may be due to raised intracranial pressure as a consequence of similar changes in the cerebral circulation. The small white exudates of arteriosclerotic retinopathy are clearly of a different nature and probably of a different origin, perhaps small infarcts.

## Hypertensive Fits

Hypertensive encephalopathy, like other long words, is often used imprecisely, and is therefore a term better avoided by

those who hope to attain clarity of thought. However, what may be the cerebral counterpart of the retinal changes in the malignant phase is well known and often well defined. A patient, usually young, becomes irritable, drowsy, and has some headache, followed by convulsions and coma. It has long been known, since Baker (1859) used veratrum viride to stop eclamptic convulsions, that reducing arterial pressure will stop the attack and, if sustained, prevent recurrences (Jellinek *et al.*, 1964).

Byrom (1954, 1960), whose experimental work has provided so much evidence for the nature of malignant hypertension, has made beautiful experiments on the rat which bring into focus the question of whether pressure or arterial spasm is the basic disturbance. Hypertensive fits occurring in rats with renal-artery constriction were found to be associated with focal cerebral oedema, and this in turn with localized constriction of the cerebral arteries. He also found localized constriction of the intestinal arteries. He supposed that this arterial spasm represented contraction of the arterial wall in response to raised arterial pressure, as postulated by Bayliss (1902), and he supposed that these local contractions, producing foci of tissue anoxia in brain and retina on the one hand and arteriolar necrosis on the other, might represent the functional basis of the malignant phase. Byrom has recently extended these observations to the retina, where similar local arterial constrictions are seen ; they remain constant in position and are not organic since they disappear with general anaesthesia and after relieving the hypertension by removing the clamp. However, these local vascular contractions in the retina are not peculiar to the malignant phase. He writes (Byrom, 1963), " The 'all or nothing' concept of arterial spasm in malignant hypertension must be abandoned in favour of a more or less evenly progressive labile vasoconstriction, irregular perhaps merely because of unevenly distributed muscle fibres, reaching a critical level at which even a small increment is enough to precipitate a local or general vascular crisis which may resolve, recur or persist."

## Fibrinoid Necrosis of Arterioles

This is the crucial lesion, since it determines the destruction of the kidney and thus of the patient. In its fully developed form the whole structure of the artery is destroyed, the lumen being obliterated and the fibrinoid extruding into the perivascular tissue. When the intima is affected it becomes swollen with fibrinoid material which separates the endothelium from the elastica interna, with great stretching and fragmentation of the latter. When the media is involved, muscle nuclei are destroyed and fragmented and the cells largely replaced by fibrinoid material. Plasma cells, eosinophil leucocytes, and occasionally polymorphonuclear leucocytes, may form a granuloma partly replacing adventitia and media. How the two processes, necrosis of media and presence of fibrinoid, are to be brought together in a single process is by no means clear, nor is the identity of fibrinoid, though Lendrum (1961) considers it to be derived from the proteins of the plasma. It may be suggested that muscle necrosis is followed by seepage into the wall of plasma proteins and cells—in fact, that the lesion represents vascular injury and its consequences.

The various hypotheses concerning the causation of fibrinoid necrosis have been reviewed elsewhere (Pickering, 1955). The evidence now strongly suggests that it is in some way a consequence of a very severe hypertension. Thus, Wilson and Pickering (1938) found it only in rabbits with the highest arterial pressures, and with the same distribution as in man except for its absence from the kidney whose renal artery was clamped. Wilson and Byrom (1939) found that severe hypertension could be produced in rats by constricting one renal artery only ; in such rats arteriolar necroses were found in the kidney whose renal artery was intact, but not in the one whose renal artery was clamped. Byrom and Dodson (1948) produced it by suddenly injecting saline into the aorta of rats ; occluding the renal artery by a tape during the injection prevented it. Byrom (1963) has also produced it in rats by intravenous angiotensin in doses sufficient to raise arterial pressure greatly ; the arteries show little change immediately afterwards but show medial necrosis with little fibrinoid 24 hours later.

Byrom and Dodson's results were not replicated by Schaffenburg and Goldblatt (1957) but were by Masson, Corcoran, and Page (1959), who also showed that hydrallazine, an antihypertensive agent, would prevent necrosis or induce its healing. Allison, Blehan, Brown, Robb-Smith, Russell, and I (unpublished) found arteriolar necrosis in small bowel in every rabbit, except one, with an arterial pressure exceeding 135 mm. Hg on two or more occasions ; removing the clamp reduced the pressure. In animals who survived this and repeated gut biopsies, the fibrinoid was largely absorbed in two weeks, virtually completely in four weeks.

Byrom and Dodson's experiments strongly suggest that it is intravascular pressure rather than a vasoconstrictor agent, humoral or nervous, that causes the lesion.

## Nature of the Malignant Phase

I have found nothing in medicine as challenging a problem as the nature of the malignant phase of hypertension. When I was engaged in a detailed study of the mechanisms I was in close and daily contact with my patients. The appearance of a woolly exudate or swelling of a disk in a patient with gross hypertension heralded the end in the not too distant future. There was nothing I, or anyone else, could do to interrupt the inexorable progress of this disease. What was it that killed the patients ? Thus I had what Pasteur called the prepared mind.

The clues came quite unexpectedly from a study of the cerebrospinal-fluid pressure in man and the examination of the tissues of rabbits in which hypertension had been produced by clipping a renal artery. I have told this story before (Pickering, 1942, 1952). These studies on the pathological and clinical *sine qua non* of the malignant phase suggested that it was the intensity of the hypertension that determined the onset and course of the malignant phase, which represented a ceiling, so to speak, to elevated arterial pressure.

This explanation, which these facts suggested to Fishberg (1939) and to me (Pickering, 1942), at once explained the homogeneity of the clinical picture, the higher levels of pressure usual in the malignant phase which Volhard (1931) had first noted and the fact, noted by Derow and Altschule (1935), that the malignant phase can occur in any kind of hypertension provided it is sufficiently severe. I myself have seen it in every kind except Conn's syndrome (in which it is described by Brown *et al.*, 1964) and coarctation of the aorta.

The experimental evidence relating to fibrinoid necrosis of arteries has already been set out. However, the decisive evidence comes from man.

## Evidence from Man

One of the most important tests of a hypothesis is the extent to which predictions from it accord with reality. If the malignant phase is essentially a manifestation of a very severe hypertension, then it should be possible to reverse it by reducing the arterial pressure. The neuroretinopathy should disappear, the arterial and arteriolar lesions should be halted. The course, from being progressively downhill, should become stabilized. Whether or not this happens will also depend on the extent of damage already done to the arteries and arterioles, particularly in the kidneys. This prediction has been fulfilled. Fig. 10 shows survival rates (estimated from life tables) in five series of unselected patients with malignant hypertension treated by chemotherapy. The heavy shaded area encloses the survival

of untreated, unselected series. Light shading indicates the area included by the addition of Schottstaedt and Sokolow's (1953) series of untreated patients with normal renal function. This figure shows clearly the improvement wrought by antihypertensive drugs.

Two of the larger series may be cited. Dustan *et al.* (1958) reported that of 84 patients with malignant hypertension treated with antihypertensive drugs 70% survived one year, 50% three years, 33% five years, and 26% six years. The commonest causes of death were (1) rapidly, or (2) delayed, progressive renal failure, and (3) complications of arteriosclerosis. The first was due to poor control of arterial pressure ; the second was associated with diffuse fibrous intimal hyperplasia of the major renal arteries. The chief complications of arterio-

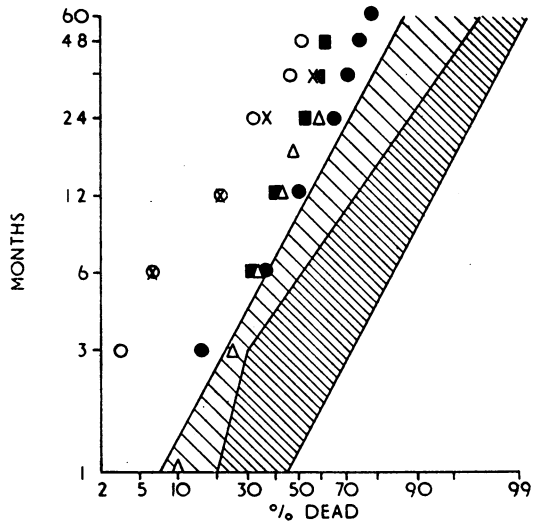



FIG. 10.—Survival rates (estimated from life tables) in five series of unselected patients treated by chemotherapy. The heavy shaded area encloses the survival of untreated, unselected series. Light shading indicates the area included by the addition of Schottstaedt and Sokolow's (1953) series of untreated patients with normal renal function. O= Smirk (1957), 43 patients. ×=Leishman (1959), 15 patients. ■=Newman and Robertson (1959), 53 patients. ●=Harington, Kincaid-Smith, and McMichael (1959), 82 patients. △=Radcliffe Infirmary (1956–9), 33 patients. (Reproduced from Pickering, Cranston, and Pears (1961).)

sclerosis were cerebral haemorrhage, most commonly associated with a poor control of arterial pressure, and myocardial infarction not associated with poor control. Harington *et al.* (1959) estimated that the effect of antihypertensive therapy was to increase the expectation of life in patients presenting with malignant hypertension by six to eight times. The survival period was longer in those with blood ureas under 60 mg./100 ml. ; it was the same in those in whom the malignant phase was superimposed on a renal lesion as in those complicating essential hypertension. Hyalinization and fibrosis were found in renal arteries and arterioles instead of fibrinoid. In four cases there was rapid deterioration in spite of normal or only slightly elevated blood urea. These patients showed conspicuous narrowing of the interlobular arteries with incomplete infarctions of the kidneys.

As has been reviewed elsewhere (Rosenheim, 1954 ; Pickering, 1955), reversal of the malignant to the benign phase is not dependent on the mode of therapy, but only on the reduction of arterial pressure secured. Thus it has been reported with Kempner's rice-fruit diet, sympathectomy and adrenalectomy, adrenalectomy in Cushing's disease, excision of a phaeochromocytoma, excision of a kidney in unilateral renal disease, repair of renal-artery stenosis, as well as with a great variety of hypotensive drugs. Thus, reducing the arterial pressure reverses the malignant phase irrespective of the lesion which causes it and irrespective of the method by which arterial pressure is reduced ; this challenging situation has not been explained by any other hypothesis.

In 1952 Pickering, Wright, and Heptinstall published three cases in which the malignant phase, proved histologically by fibrinoid arteriolar lesions in kidney and adrenal, had been reversed to the benign by measures which reduced arterial pressure ; they had survived six years. The first of these cases has been described already (Case 2). The second case (Case 4 of this paper) was of a girl of 11 with bilateral neuroretinopathy, arterial pressure 240/170, and bilateral pyelonephritis. Bilateral sympathectomy and subtotal adrenalectomy reduced her arterial pressure and abolished the eye changes. Eighteen years later she is still alive and well, with a blood-pressure of 140/104 and a blood urea of 26 mg./100 ml. The pyelonephritis is inactive. The third case (Case 5 of this paper) was of a girl of 13 with bilateral neuroretinopathy, a blood-pressure of 255/180, and bilateral pyelonephritis. After ineffective nephrectomy she had a bilateral subtotal adrenalectomy. The fall of pressure was slight—for example, 220/150—four years after operation, but her retinopathy was resolved. She was subsequently treated with hexamethonium, pentolinium, and reserpine. In August 1964, 18 years after operation, she had just married. Her blood urea was 44, the urine continued to contain protein, and her arterial pressure was 120/80, both sitting and standing.

## Further Evidence

A second piece of evidence from man is the occurrence of fibrinoid necrosis of the pulmonary arteries and arterioles in the severest forms of pulmonary hypertension due, for example, to mitral stenosis or auricular or ventricular septal defect (Parker and Weiss, 1936 ; Heath and Edwards, 1958).

Third, the malignant phase is very rare in coarctation of the aorta, and fibrinoid has not been described in its usual situation. But after repair of coarctation, fibrinoid deposits may occur in the arteries distal to it (Lendrum, 1955 ; Benson and Sealy, 1956 ; Hurt and Hanbury, 1957 ; Reid and Dallachy, 1958). Benson and Sealy's cases are instructive. The first was of a 22-year-old negro with blood-pressure of 240/60 in the brachial and 96/60 in the femoral arteries. Post-operatively the brachial blood-pressure was mostly 190/80 to 200/80 and the pulses in the legs were full and bounding. He died of infarction of the gut nine days post-operatively. "In the walls of the large arteries, including the splenic, renal, mesenteric, gastric and common iliac, were segmental areas of medial necrosis without cellular reaction. . . . In the smaller arteries the necrosis was much more extensive, involving the entire wall and having an intensely eosinophilic reaction." Similar lesions were not found above the obstruction. The second case was of a boy of 4 whose arterial pressure after operation was said to have risen in the legs to 225/180. After 16 days, 24 in. (61 cm.) of gangrenous ileum was removed. "The intestinal arteries and arterioles were essentially similar to those in the first case."

The last piece of evidence strongly suggests that it is the height of pressure which provokes the lesions.

## Other Factors

The objections which have been raised to the idea that the malignant and benign phases express a difference in the severity of the hypertension arise mostly from misunderstanding. Some have supposed that the hypothesis would imply a dividing-line by arterial pressure, those above having the malignant phase, those below not. No such dividing-line would be expected by anyone well acquainted with biological variability and with the behaviour of arterial pressure. Moreover, it has been apparent for many years that factors other than arterial pressure determine the onset of the malignant phase. It occurs at much lower pressures in acute nephritis and pregnancy toxaemia. It

is possible that the anaemia common to these conditions opens the arteries and exposes those more distally ; alternatively, the thickening of the intima and media associated with continued hypertension may protect the arteries distally (Pickering, 1952) ; these are speculations, though the second has experimental support. *X*-irradiation alone may produce arteriolar necrosis (Russell, Wilson, and Tansley, 1949) ; irradiation and hypertension summate (Asscher, Wilson, and Anson, 1961 ; McMichael, 1961). Finally, the variability of arterial pressure during the 24 hours has been noted and the unlikelihood of a single casual reading being fully representative of the whole behaviour. Every series of 15 or more cases which has been investigated since Volhard (1931) has shown that arterial pressure tends to be higher in those with the malignant phase than in those with the benign (Pickering, Cranston, and Pears, 1961). In view of all these considerations, no more could reasonably be expected if the hypothesis were true.

A second difficulty has been the occasional patient in whom hypotensive therapy is instituted and in whom the retinopathy clears without any fall in arterial pressure being measured. In view of what has been said about the variability of arterial pressure, such exceptional cases carry very little weight as against the vast amount of evidence suggesting that, in general, fall of arterial pressure is associated with benefit and lack of control of arterial pressure with failure to affect the course of the disease. It is possible that, were records available throughout the day and night, the pressure would have been observed to fall with therapy, even though an occasional casual pressure had failed to reveal this. Finally, cases have been cited, notably by Perera, in which retinopathy and renal failure progress even though the arterial pressure has fallen or has never been appreciably raised. Unfortunately, such cases fail to carry conviction, since other diseases, such as polyarteritis nodosa and disseminated lupus, were not excluded by the usual tests and post-mortem evidence. As we have already seen, arterial pressures above 140 mm. systolic occur in over half the population in their sixth decade. Neuroretinopathy associated with a mild elevation of arterial pressure is most frequently due to one of the collagen diseases, more rarely to bleeding, bacterial endocarditis, or temporal arteritis. These must be excluded before malignant hypertension is proved.

## Treatment

Controversy is the life-blood of science, and no one welcomes it more than I do so long as the patient's interests are not sacrificed. The corollary of the hypothesis just considered is that malignant hypertension is a medical emergency which demands reduction of arterial pressure—not to-morrow or next week, but now. Unfortunately, the cynics who think that the malignant or accelerated phase is caused by an unknown factor, or the factor responsible for the hypertension, deny this. All of us who have had the satisfaction of seeing this hitherto fatal disease kept under control have had the dissatisfaction of having a patient who received contrary advice, with the return of the malignant phase and ultimate fatal renal involvement. Here is such a case, which incidentally displays the evolution of the malignant phase:

*Case 6.*—This patient was aged 30 when he was found to have an arterial pressure of 170/100 at a routine medical examination. At 33 his gall-bladder was removed ; his elevated arterial pressure fell to 140/90 at rest. At 36 his blood-pressure was 180/110. At 37 he complained of headaches ; blood-pressure 180–150 systolic and 130–100 diastolic. Intravenous pyelogram, blood urea, and urine all normal.

At 39 he was first seen in my clinic for recurrence of headache ; blood pressure 200/120. Urinary white cell excretion was normal. Hypotensive treatment was advised, but ganglion blockers and thiazide diuretics produced symptoms and were stopped by the patient. He attended the American Hospital in Paris at the age of 40: blood-pressure 260/160 ; urine now contained protein, red cells, and casts ; blood urea 65 and 95 ; chlorothiazide produced drug rash. After telephone conversation with my clinic he was put on mecamylamine and sent to Oxford. Before he got to Oxford he had stopped the drug because of side-effects. A month later he was admitted to the Radcliffe Infirmary: blood-pressure 200/135 ; fundi, soft exudates and scattered haemorrhages ; urine contained protein and red cells. He was stabilized on guanethidine and diuretics. He left hospital and came under the care of a French doctor who did not believe in high blood-pressure and stopped treatment.

At 41 he was admitted to the American Hospital in Paris ; blood-pressure 220/140, blood urea 125. Anaemia treated by transfusion ; blood-pressure 270/160, blood urea 240. After telephone conversation with my clinic he was put on guanethidine, with excellent blood-pressure control. Two months later he was seen in Oxford: blood-pressure 260/150 ; fundi, hard exudates only ; blood urea 160 ; urine, red cells and protein.

Two months later he returned to Canada and visited a doctor in New York, who took him off drugs and admitted him for investigation. An aortogram showed no renal-artery stenosis, so a cytoscopy and ureteric catheterization were done for divided renal function studies. No samples were obtained, and for the next 48 hours he passed only a few drops of heavily blood-stained urine. He returned to Oxford, having been off hypotensive drugs for three weeks ; felt tired and sick ; blood-pressure 260/150 ; fundi, papilloedema, soft exudates, and haemorrhages ; blood urea 214. He was stabilized on guanethidine and chlorothiazide, but continued to travel around the Continent. He died in uraemia aged 42. There was no necropsy.

[*The conclusion of this lecture, together with a list of references, will appear next week.*]