Papers and Originals

Renin and Acute Renal Failure: Studies in Man

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Summary: Plasma renin concentration was increased, usually appreciably, in 22 out of 25 patients with acute renal failure, the average value being 226 units/litre (mean for normal subjects 8·2 units/l.). The highest renin values were found in the first 10 days of the disease; lower and sometimes normal values were found subsequently. Unequivocal acute tubular necrosis was present in only two of the eight cases examined post mortem.

These findings are compatible with Goormaghtigh's proposal that an excess of renin and angiotensin may act within the kidney to produce acute renal failure.

Introduction

The cause of oliguria in acute renal failure is not agreed. Reduction of renal blood flow or glomerular filtration and obstruction or necrosis of the renal tubule have each been considered the primary event (Trueta *et al.*, 1947; Bull *et al.*, 1950; Oliver *et al.*, 1951; Sevitt, 1959; Merrill, 1960; Brun and Munck, 1964; Biber *et al.*, 1968). Goormaghtigh (1942, 1945, 1947) proposed a role for renin and angiotensin in which an increased concentration of angiotensin formed in the region of the glomerulus in such states as the crush syndrome and eclampsia might reduce renal blood flow and glomerular filtration, thereby precipitating renal failure. There is much to support this idea (Sevitt, 1959; Kovalevskii, 1963; Schnermann *et al.*, 1966; Ruiz-Guiñazú *et al.*, 1967; Hollenberg *et al.*, 1968; Kokot and Kuska, 1969).

The objects of this communication are to present studies of plasma renin concentration in patients with acute renal failure and to discuss this and similar evidence in animals (Brown *et al.*, 1970a) which suggests that renin and angiotensin might be important in producing the disease.

Terminology, Methods, and Patients

There is much evidence to suggest that acute tubular necrosis is not an invariable pathological accompaniment of the clinical syndrome of acute renal failure: acute renal failure may occur without light microscopical evidence of acute tubular necrosis and vice versa (Brun and Munck, 1957; Sevitt, 1959; Finckh *et al.*, 1962). In all patients the diagnosis of acute tubular necrosis was based on one or more of three signs of tubular cell death—karyolysis, karyorrhexis, and pyknosis. Depending on the stage of the disease, these abnormalities were associated with a decrease in the height of tubular cells, an apparent increase in the diameter of the tubular lumen, basophilia of the cytoplasm, and mitotic activity. Oedema and subacute inflammatory changes were sometimes seen in the space surrounding the renal tubule. Post-mortem change, which can to some extent simulate and obscure the changes of acute tubular necrosis, was carefully considered and excluded so far as was possible in each case.

Studies in Man

The method of Brown *et al.* (1964a) was used to estimate the plasma renin concentration on 47 occasions in 25 patients with acute renal failure. In each patient the diagnosis was based on a fall in daily urine volume to 500 ml. or less, an increase in blood urea to 130 mg./100 ml. or more (see Table), and a decrease in urine/plasma-urea ratio to 10 or less. Possible causes of acute renal failure varied widely, and in most patients more than one potential cause was present (see Table). We have excluded from this analysis patients known to have underlying chronic renal failure or renal papillary necrosis. Before the first plasma sample was taken for determination of plasma renin concentration, eight patients had been given diuretics, 10 had been given mannitol, and 16 had had either peritoneal dialysis or haemodialysis against fluid with a sodium concentration which varied between 134 and 144 mEq/1. (see Table). Dietary sodium intake before the development of acute renal failure was unknown. During treatment sodium intake (oral and intravenous) varied between 50 and 150 mEq daily, depending on urinary sodium excretion. Sixteen patients died. This relatively high mortality (64%) may reflect the large number of patients with severe underlying disease or injury (see Table), since in most cases death did not result from renal failure (see also Cameron *et al.*, 1967). Four clinical stages are sometimes described in acute renal failure: an onset phase, oliguria or anuria, diuresis, and, in some, recovery (de Wardener 1963; Heptinstall, 1966). We have no measurements of renin in the onset phase and only one after recovery in a patient (Case 18) whose blood urea had by then decreased to 19 mg./100ml.

Results

Plasma renin concentration was abnormally high on at least one occasion in 22 of the 25 patients with acute renal failure (Table and Fig. 1), the mean value for the group (226

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Data in 25 Patients with Acute Renal Failure. Timing of Plasma Renin Samples in Relation to Onset of Disease is Shown in Fig. 1

Case No.	Sex	Age	Aetiological Factors of Possible Importance	Plasma Renin Concentration (units/l.)	Max. Blood urea (mg./100ml.)	Dialysed	Mannitol Given	Diuretics	Outcome
1	M	34	Carbon tetrachloride ingestion	97, 59, 21, 25	330	+	-	-	Survived
2	F	72	Pneumonia, dehydration, hypotension	446	300	+	-	+	Died
3	M	63	Gall-stone surgery, hypotension	116, 86, 56	258	+	+	-	Died
4	F	54	Perforated D.U. Peritonitis, hypotension, surgery	348	254	+	+	-	Died
5	M	62	Perforated D.U. Peritonitis, subphrenic abscess	59, 78	420	+	+	-	Died
6	M	46	Jaundice, gall-stone surgery, dehydration	202	142	-	-	-	Died
7	F	29	Pregnancy, haemolysis, hypotension	15	330	-	+	-	Survived
8	F	29	Abortion, *C. Welchii* infection, haemolysis	11·5, 11·0, 10·0	400	-	+	-	Survived
9	F	6	Urinary infection, haemolysis	180	414	+	-	-	Died
10	M	72	Intestinal obstruction, dehydration, hypotension, surgery	291, 280, 58	184	-	-	+	Died
11	F	56	Peritonitis, septicaemia, hypotension	555	399	+	-	+	Died
12	M	57	D.U. haemorrhage, hypotension	69	288	+	+	-	Died
13	M	64	Perforation, peritonitis	75	429	-	-	-	Survived
14	F	70	Resp. infection, heart failure, diuretics	253	190	-	-	+	Survived
15	M	37	Trauma (road traffic accident), haemorrhage, hypotension, surgery	37, 79, 54, 12·6	372	-	+	-	Survived
16	M	51	Allergic response to intravenous pyelography, hypotension	53, 15·5	212	+	-	-	Survived
17	M	14	Trauma, haemorrhage, dehydration, peritonitis, surgery	3,200, 1,900	267	-	+	-	Died
18	M	45	Gastrointestinal infection, dehydration	229, 36, 12, 6	567	+	-	+	Survived
19	M	56	Intestinal obstruction, volvulus, hypotension, surgery	33	340	+	-	+	Died
20	F	45	Overdose of Diconal, hypotension	16, 12	405	+	-	-	Survived
21	F	31	Pregnancy, subacute bacterial endocarditis, dehydration, hypotension	180	402	+	-	+	Died
22	M	61	Obstructive jaundice, surgery, hypotension	46	588	+	+	-	Died
23	M		Myocardial infarct, hypotension	410	354	+	-	-	Died
24	M	35	Trauma (road traffic accident), haemorrhage	192, 146, 226, 228	130	-	-	-	Died
25	M	77	Intestinal obstruction, dehydration, surgery	39	274	+	+	+	Died

units/1.) being grossly raised above the means of 8·2 units/1. for normal subjects (t = 2·82, P<0·005). The increase of plasma renin concentration was most pronounced at an early stage of the disease (correlation between log plasma renin concentration and time in days, r = —0·54, P<0·001), and serial measurements of renin showed a decrease in 9 out of 11 patients (Fig. 1). The lowest value in this series, 6 units/l., was from

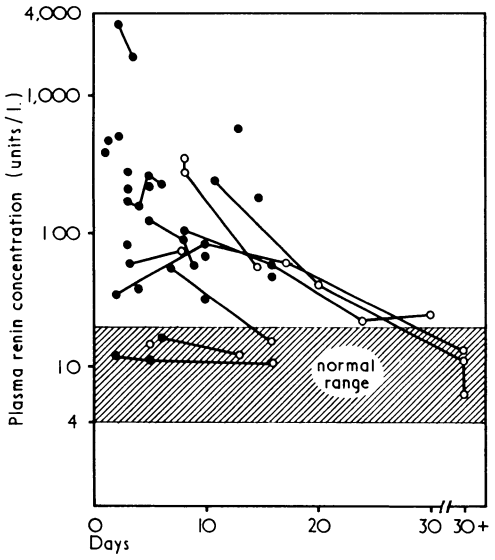

FIG. 1.—47 estimations of plasma renin concentration in 25 patients with acute renal failure. Horizontal axis refers to duration of disease. The empty circles indicate values at a time when daily urine volume was greater than 1 litre, and solid circles values when urine volume was less than this. Lines join estimates from the same patient.

the only patient (Case 18) in whom renin was measured during the recovery phase (see Methods). Earlier values in this patient were greatly increased (see Table). Normal renin levels were otherwise found during the first week of the disease in two patients (cases 7 and 8) whose acute renal failure was associated with pregnancy and in another (Case 20) with hypotension following an overdose of Diconal (dipipanone hydrochloride and cyclizine). There were no significant differences in the mean plasma renin values of patients treated with mannitol, diuretics, haemodialysis, or peritoneal dialysis as compared with patients not treated in these ways (t tests with P>0·05 in each instance). Plasma renin concentration was not significantly related to the concentration of sodium, potassium, or urea in the same sample of plasma (P>0·05). Plasma renin concentration was related inversely, however, both to systolic (r = —0·30, P<0·01) and to diastolic (r = —0·42; P<0·001) arterial pressure. The average plasma renin level was higher in patients who died (401 units/1.) than in those who survived the episode of acute renal failure (mean 52 units/1., t = 2·37, P<0·05).

Of the eight fatal cases examined post mortem, only two showed unequivocal acute tubular necrosis (see Terminology). In the kidneys of one of these (Case 6) there was extensive karyolysis, reduction of tubular epithelial height, casts, and interstitial oedema, and in the other (Case 19) there was pyknosis and karyorrhexis together with mitotic activity, reduction of tubular epithelial height, cytoplasmic basophilia, casts, and interstitial oedema with subacute inflammatory changes. Of the remaining patients, two (Cases 2 and 10) had none of these abnormalities. Case 17 had interstitial oedema only, Case 12 had casts only, and Cases 3 and 4 had reduction of tubular epithelial height with casts. Kidney weight varied between 110 and 200 g. (average 151 g.).

Discussion

Results described here and in a paper shortly to be published by Schröder (1970) show that plasma renin concentration is often but not always increased in patients with acute renal failure. The increase seems most pronounced during the early phase of the disease. Plasma renin activity (Tu, 1965; Kokot and Kuska, 1969) and angiotensin blood levels (Massani *et al.*, 1966) are also increased in these circumstances, and similar changes have been observed in experimental animals with acute renal failure produced by glycerol (Brown *et al.*, 1970a). This association of raised renin or angiotensin with acute renal failure could be explained in several ways. Firstly, renin might be increased as a result of acute renal failure either by excessive renin release or by reduction in its rate of clearance from blood. Secondly, renin release and acute renal failure might be provoked independently of each other by some stimulus. Thirdly, renin might produce acute renal failure.

That acute renal failure might at least contribute to the increase of renin by reducing its clearance from blood is

suggested by the increased survival of injected renin in blood following bilateral nephrectomy (Houssay *et al.*, 1942). This is unlikely to be the whole explanation, however, as the increase of renin is unrelated in magnitude and timing to the impairment of renal function. Furthermore, the increase of plasma renin concentration coincides with a decrease in the renin content of kidney tissue (Brown *et al.*, 1970a), and this suggests a discharge of renin from the kidney into blood, though it does not exclude simultaneous impairment of clearance and renin synthesis without change in renin release.

There is also some basis for the second explanation: that renin and acute renal failure are provoked independently of one another by a third factor. Haemorrhage, surgery, or depletion of sodium and water might act in this way. Each is well known as a cause of acute renal failure and each can increase renin without necessarily producing acute renal failure (see discussion on renin release). Haemorrhage, surgery, or depletion of sodium and water were incriminated as causative factors in 14 patients, and it is possible that in these the increase of renin was a consequence of the stimulus to acute renal failure. A similar problem of interpretation arises from the increased levels of plasma renin concentration sometimes found in patients susceptible to acute renal failure. Plasma renin concentration would then be abnormally raised before the disease develops.

These difficulties of interpretation led to a study of plasma renin concentration in animals before and during the development of acute renal failure. The work is reported in detail elsewhere (Brown *et al.*, 1970a) and an outline of the main findings is as follows. Rabbits were injected with an amount of glycerol sufficient to produce haemolysis and acute renal failure. Samples of blood were taken for estimation of urea and plasma renin concentration before glycerol and again shortly before they were killed, 6, 24, or 72 hours after the injection. Plasma renin concentration increased sixfold to a maximum at 24 hours; lower values were found after 72 hours. Blood urea increased to an average of 268 mg./100 ml. after three days. Acute tubular necrosis was present in all kidneys removed at three days. By contrast, acute tubular necrosis and acute renal failure did not develop and plasma renin concentration did not change appreciably in control animals injected with saline.

This study again demonstrated high plasma renin levels in acute renal failure and, in addition, showed that the increase occurred during the development of acute renal failure and that it was independent of haemorrhage (but not of haemolysis), surgery, and depletion of sodium and water. These observations do not resolve the important question of whether the increase of renin is a cause or a consequence of acute renal failure. Studies of susceptibility to acute renal failure and of changes of glomerular filtration and renal blood flow during the development of acute renal failure are more helpful in this respect.

Renin and Susceptibility to Acute Renal Failure

Susceptibility to acute renal failure is often associated with an increased concentration of renin in plasma or kidney tissue. Susceptible states in which renin is known to be increased (see Brown *et al.*, 1966a) include pregnancy, depletion of sodium or plasma volume, Addison's disease, cirrhosis with ascites, and terminal cardiac failure (Black and Williams, 1962; Shear *et al.*, 1965; Thiel *et al.*, 1967; Papper and Vaamonde, 1968; Kinsey Smith *et al.*, 1968; Domenet and Evans, 1969). Conversely, sodium loading reduces plasma renin concentration (Brown *et al.*, 1963, 1964b) and protects against acute renal failure (Teschan and Lawson, 1966; Wilson *et al.*, 1967; Henry *et al.*, 1968). Moreover, denervation of the kidney reduces its renin content (Ueda *et al.*, 1967), and there is evidence that it may also protect the kidney against acute renal failure (Powers *et al.*, 1957). This circumstantial evidence is suggestive of a causal role for renin in acute renal failure. Oken (personal communication)* and Henry *et al.* (1968) drew a similar conclusion from the protective effect of sodium loading.

Renal Blood Flow and Glomerular Filtration Rate

It is now well recognized that renal blood flow is reduced to 30-50% of normal in acute renal failure (Walker *et al.*, 1963; Brun and Munck, 1964; Hollenberg *et al.*, 1968). Trueta *et al.* (1947) had suggested that in acute renal failure the circulation of the renal cortex is diminished or even arrested, while medullary blood flow is maintained. That such a diversion of flow from the peripheral cortex occurs has been confirmed by subsequent work (Daniel *et al.*, 1952; Kovalevskii, 1963; Brun and Munck, 1964; Gömöri *et al.*, 1964; Carriere *et al.*, 1966; Truniger *et al.*, 1966; Hollenberg *et al.*, 1968), though doubt still surrounds Trueta's further proposal that a vascular shunt opens in the renal medulla during acute renal failure. Kovalevskii (1963) and Hollenberg *et al.* (1968) suggested that renin may be responsible for diversion of blood flow from the peripheral cortex during haemorrhage and acute renal failure. Their proposal is compatible with the graded distribution of renin in the renal cortex (Cook *et al.*, 1957; Cook and Pickering, 1959; Brown *et al.*, 1965) and, if diversion of blood is important in pathogenesis of acute renal failure, with the notion that renin is causally related to the disease.

Glomerular filtration, as measured by both clearance and micropuncture techniques, is also greatly reduced at an early stage in many forms of acute renal failure (Bull *et al.*, 1950; Sevitt, 1959; Nickel *et al.*, 1963; Bálint *et al.*, 1964; Flanigan and Oken, 1965; Jaenike, 1967). Direct observation of the surface of the kidney at this time shows collapse of peritubular capillaries and reduction in the flow of proximal tubular fluid (Oken *et al.*, 1966; Ruiz-Guiñazu *et al.*, 1967). Sevitt (1959) and Finckh (1962) suggested that vasoconstriction and reduction of glomerular filtration rate are the primary events leading to acute renal failure. Finckh further suggested that the afferent glomerular arteriole was the site of vasoconstriction, while Sevitt considered renin as its possible cause. Renin, located in the wall of the afferent glomerular arteriole (Cook, 1968; Faarup, 1968), is well placed to produce these effects. For renin to act in this way, however, the enzyme(s) responsible for the conversion of angiotensin I to the vasoactive angiotensin II must also be present in the kidney. Though there is some evidence that this may be so (Sundsfjord, 1969; Thurau, 1969) the point is by no means established (Ng and Vane, 1968).

Renin may therefore cause acute renal failure by reducing the glomerular filtration rate and renal blood flow. The alternative interpretation, that renin is simply released as a result of acute renal failure, implies that during its release into the circulation of the superficial cortex renin does not produce the vasoconstriction and reduction of glomerular filtration rate which are known to occur in this site, and which are thought to be of primary importance in acute renal failure.

Renin and Pathological Lesions

An important point against a primary role of tubular necrosis in acute renal failure is that acute tubular necrosis may not be present in a proportion of patients with acute renal failure (Brun and Munck, 1957; Sevitt, 1959; Finckh *et al.*, 1962). In our own series of eight patients studied at necropsy, two had undoubted acute tubular necrosis and two had histologically normal kidneys. Intermediate changes were found

*Since this paper was completed, Dr. Oken's findings have been published in the *Proceedings of the Society for Experimental Biology and Medicine*, 1969, **131**, 610.

in the remainder. It is possible that the changes of acute tubular necrosis had been present in all patients at an earlier stage.

Histological abnormalities reported in acute renal failure include acute tubular necrosis and, less commonly, cortical necrosis (Oliver *et al.*, 1951; Sheehan and Moore, 1952). The anatomical relation between these lesions and the distribution of renin within the kidney is of interest. More renin can be extracted from superficial than from juxtamedullary glomeruli. Renin has not been detected either in the renal medulla or in the thin aglomerular rim of cortex (the cortex corticis) lying beneath the capsule of the kidney (Cook *et al.*, 1957; Cook and Pickering, 1959; Brown *et al.*, 1965). The distribution of necrotic lesions in acute renal failure, particularly those of cortical necrosis, follows a similar pattern. Generally, the most pronounced lesions are to be found in the superficial renin-rich part of the cortex; the juxtamedullary zone is usually less severely affected and the medulla and cortex corticis are often spared (Oliver *et al.*, 1951; Sheehan and Moore, 1952; Lauler and Schreiner, 1958).

Sometimes, following cortical necrosis, the viable cortex nd medulla become separated from the dead renin-bearing glomerular zone by bands of calcification (Lloyd-Thomas *et al.*, 1962). Thus the parts of the kidney most liable to damage in acute renal failure are those containing the most renin. This association is more compatible with a role for renin in producing tubular damage than with the converse proposition. It should be noted, however, that the closest relation between renin and histological changes is to be found in renal cortical necrosis, and there is little information on plasma renin concentration in this condition. Secondly, the survival of the cortex corticis may be a consequence of its relatively independent blood supply from capsular vessels.

Renin Release

The event which precipitates acute renal failure in man and animals is often one which increases renin. Thus haemorrhage, surgery, diuretics, bacterial toxins, nervous stimulation, and occlusion of the renal artery can increase the concentration or activity of renin in blood (Vander, 1965; Brown *et al.*, 1966a, 1966b; McKenzie *et al.*, 1967; Vaughn *et al.*, 1967; Hosie *et al.*, 1970). Also, when sufficiently intense, each of these stimuli is capable of producing acute renal failure or acute tubular necrosis (Scarff and Keele, 1943; Phillips *et al.*, 1946; Trueta *et al.*, 1947; Clute and Fitzgerald, 1948; Schroeder, 1949; Daniel *et al.*, 1952; Bull *et al.*, 1955; Merrill, 1960; Shear *et al.*, 1965). One interpretation of this association is that renin release may be an incidental consequence of the stimulus producing acute renal failure rather than of direct pathogenic importance, and, as we have discussed, this accords well with the observation that most of these stimuli usually provoke renin release without acute renal failure. On the other hand, such an explanation does not account—other than as a coincidence—for the fact that most of the known stimuli to renin release are also capable, when sufficiently intense, of producing acute renal failure.

It seems more likely to us that the act of producing acute renal failure is in some way the pathological extreme of a physiological stimulus to renin release. If this is so, it raises the question of whether the manifestations of acute renal failure are also the pathological extreme of the physiological action of renin within the kidney. That such a physiological effect might occur has long been suspected (Pickering and Prinzmetal, 1940). By analogy with acute renal failure, the main features of this physiological effect should be: reduction of blood flow and filtration to a greater extent in the superficial than the deep cortex, together with reduction of urine flow and urinary sodium excretion. Pomeranz *et al.* (1968) and Horster and Thurau (1968) proposed that some of these changes occur in physiological circumstances as a result of an intrarenal action of renin, and we have considered elsewhere (Brown *et al.*, 1970b) the possibility that the same mechanism may be deranged in cardiac failure.

Varied Pathogenesis of Acute Renal Failure

Oliver *et al.* (1951) suggested that acute renal failure may be of two main types: "toxic," as produced by mercuric chloride or uranium salts, and "circulatory" (haemorrhage, haemolysis, etc). Histological lesions certainly differ in the two groups (see Oliver *et al.*, 1951; Biber *et al.*, 1968; Kempczinski and Caulfield, 1968), and the reduction of the glomerular filtration rate may well be less in "toxic" acute renal failure (Bank *et al.*, 1967; Biber *et al.*, 1968). Such evidence as we have considered on the relation of renin and acute renal failure applies only to cases of the "circulatory" type; we have little evidence on which to incriminate or to exclude renin as a cause of "toxic" acute renal failure.

Hypothetical Mechanisms

The idea that renin might produce acute renal failure is not new. Goormaghtigh (1942, 1945, 1947) suggested that the anuria or oliguria of the crush syndrome and eclampsia might result from constriction of glomerular vessels caused by renin liberated from the juxtaglomerular apparatus. He also considered the possibility that renin might remain fixed within the juxtaglomerular apparatus, and that an excess of angiotensin might then be produced by increased access of substrate to the enzyme (Goormaghtigh, 1942, 1944). Elsewhere, he proposed that the glomerular circulation and renin release were normally controlled by changes in the composition of tubular fluid at the near-by macula densa (Goormaghtigh, 1937, 1944) and that abnormal tubular fluid might act via the macula densa to reduce glomerular filtration in the crush syndrome (Goormaghtigh, 1947). These ideas foreshadow each of the hypotheses discussed below.

Our own view of the process (Fig. 2) is based directly on Goormaghtigh's proposal that pathologically large amounts of

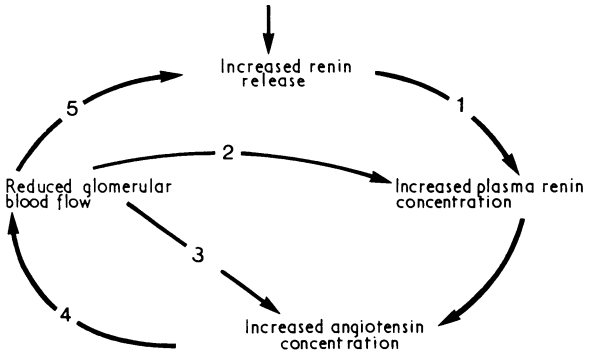

FIG. 2.—Schematic representation of three ways in which increased concentration of angiotensin might be produced in the glomerular region. This would reduce glomerular blood flow (effect 4) and thereby produce a further increase in angiotensin (effects 2 and 3).

angiotensin are formed in the glomerular region in acute renal failure. This may result from increased renin concentration caused either by increased renin release (effect 1, Fig. 2) or by reduced glomerular blood flow with constant renin release (effect 2, Fig 2). Slowing of glomerular blood flow would also enable more angiotensin to be produced within the kidney by a given concentration of renin provided the reaction was not

normally completed during the circulation of blood through the kidney (effect 3, Fig. 2). A critical point would be reached when angiotensin reduced renal blood flow (effect 4, Fig. 2) and a situation would then have developed in which an increase of angiotensin produced a further increase of angiotensin (effects 2 and 3, Fig. 2). Once initiated the system would tend to be self-perpetuating, and removal of the provocation would not then necessarily arrest the sequence of changes. We suggest that the consequences of the increase of angiotensin are constriction of afferent glomerular arterioles, and/or glomerular capillaries with reduction of glomerular filtration rate and peritubular blood flow, oliguria, and, in some instances, tubular or cortical necrosis (see also Sevitt, 1959; Finckh, 1962).

The macula densa has long been considered a possible sensory element in the renin release mechanism (Goormaghtigh, 1937, 1944; Hess and Gross, 1959; Fisher, 1961; Brown *et al.*, 1964b; Thurau, 1964; Eigler, 1967). After haemorrhage or renal artery occlusion the sodium concentration of tubular fluid in the region of the macula densa increases, and the near-by glomerulus collapses. The authors of this experiment (Schnermann *et al.*, 1966) concluded that renin and angiotensin were the cause of glomerular collapse and that increased macula densa sodium, resulting from impaired reabsorption in the proximal part of the tubule, was the stimulus to renin release. Britton (1968a, 1968b) combined some of these features with Goormaghtigh's concept of renin as an intracellular enzyme, and Henry *et al.* (1968) considered a model of acute renal failure similar to Schnermann's, with an additional positive feedback link by which angiotensin reduces renal blood flow and thereby increases macula densa sodium further. These varied suggestions are in no way incompatible with one another, and in Fig. 3 we illustrate a

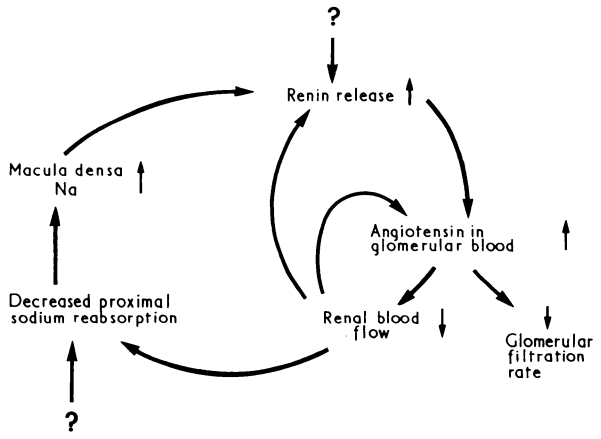

FIG. 3.—Composite hypothesis including the mechanisms represented in Fig. 2, and the proposal of Henry *et al.* (1968). The angiotensin concentration of glomerular blood reaches a critical point when it reduces renal blood flow. By one or more of three mechanisms this produces a further increase of angiotensin with a further decrease in blood flow.

composite hypothesis derived from the main features of each.

Much evidence relating renin and acute renal failure is based on studies of renin in peripheral blood. If the mechanism of acute renal failure outlined in Fig. 2 is correct, however, the renin concentration of peripheral blood may underestimate that of blood within the kidney. Thus, if renal blood flow is reduced and renin release remains constant (effect of Fig. 2) the concentration of renin in renal blood will increase without change in peripheral plasma renin concentration.

A second series of animal experiments was therefore undertaken to determine the extent to which renal venous plasma renin concentration increases at a time when renal blood flow is greatly reduced (Brown *et al.*, 1970a). Plasma renin concentration was measured in the arterial and renal venous plasma of anaesthetized rabbits before and at the end of a four-hour period of renal artery occlusion. This led, after a further 24 hours, to histological changes of acute tubular necrosis in the affected kidney. During occlusion reanl venous plasma renin concentration increased twelvefold, while arterial plasma renin concentration did not change appreciably. The experiment showed that gross reduction of renal blood flow could lead to a large increase in the renin content of blood within the kidney in the absence of a change in peripheral blood.

Vasoconstrictor Substances

The hypothesis outlined in Fig. 2 suggests that injection of any vasoconstrictor substance (including renin) may lead to acute renal failure by reducing blood flow in the renal cortex (by effects 2 or 3 of Fig. 2). There is some evidence for this: acute renal failure, acute tubular necrosis, or cortical necrosis can be produced in certain circumstances—such as pregnancy or after treatment with steroids—by adrenaline (Penner and Bernheim, 1940), 5-hydroxytryptamine (Waugh and Pearl, 1960), pitressin (Byrom, 1937), oxytocin (Byrom and Pratt, 1959), and methoxamine (Herbertson and Kellaway, 1960). Injection of renin also produces angiographic evidence of ischaemia, most pronounced in the superficial cortex (Daniel *et al.*, 1954), and it may also produce tubular necrosis with vascular lesions (Masson *et al.*, 1952). On the other hand, injections of angiotensin II do not usually produce acute tubular necrosis (Byrom, 1964). This negative result does not, however, exclude a primary role for renin, as angiotensin II, in contrast to noradrenaline, is rapidly inactivated during a single passage of the renal circulation (Akinkugbe *et al.*, 1966, Ng and Vane, 1968). In any case, systemic injections of angiotensin are an inadequate test of an intrarenal role of renin and angiotensin, as the site in which the injected material exerts its greatest effect may well be different from that of angiotensin formed within the kidney.

There is also evidence that injection of angiotensin normally inhibits renin release (Vander and Geelhoed, 1965) and reduces plasma renin activity (De Champlain *et al.*, 1966; Klaus and Heizmann, 1967) and this would tend to interrupt the feedback mechanism (at stage of Fig. 2). In cases of cirrhosis and Addison's disease with increased plasma renin activity, however, injection of angiotensin may increase plasma renin activity further (Klaus and Heizmann, 1967). If renin plays a part in the pathogenesis of acute renal failure, this unusual response could be related to the increased susceptibility of patients with cirrhosis and Addison's disease to acute renal failure, as an increase of endogenous renin in these susceptible states would tend to produce a further increase of renin.

Interpretation of Relation between Renin and Acute Renal Failure.

As has been discussed, the rise of plasma renin concentration in acute renal failure could have three main explanations: increased renin could be a cause, an independent variable, or a consequence of acute renal failure. At first sight the most plausible of these explanations is that renin is released into blood as a result of acute renal failure. It will follow, however, if this is so, that renin does not produce the vasoconstriction which is known to occur in the vascular territory through which it passes during its release from the kidney (alternatively it will be necessary to postulate that the vasoconstriction is not the cause of acute renal failure). This hypothesis also fails to explain, other than as a coincidence, the finding of histological lesions in renin-rich zones of the kidney, the

susceptibility of patients with high levels of renin to acute renal failure, and the fact that most of the known stimuli to renin can provoke acute renal failure when sufficiently intense. In our view these are serious objections. Similar objections apply also to a second hypothesis in which renin and acute renal failure are provoked together but independently of each other by a single mechanism. For these reasons we favour a third explanation: that renin is directly involved in a pathological sequence of changes leading to acute renal failure. We do not mean by this that renin is involved in all cases or at all stages of acute renal failure; rather that it contributes in greater or less degree at an early or late stage to the renal vasoconstriction which is generally believed to play a major part in acute renal failure. The hypothesis is based on circumstantial evidence which cannot by itself establish the case. It also derives some support from the weakness inherent in alternative hypotheses. The points on which it is particularly vulnerable include ambiguity about the conversion of angiotensin I within the kidney, the inability of injected angiotensin always to produce acute renal failure, and the lack of information about levels of renin and angiotensin II in glomerular blood during the development of acute renal failure. Nevertheless, for reasons which we have discussed, these points do not necessarily represent strong evidence against our proposal.

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REFERENCES

Akinkugbe, O. O., Brown, W. C. B., and Cranston, W. I. (1966). *Clinical Science*, **30**, 409.

Bálint, P., Châtel, R., Fekete, A., and Forgács, I. (1964). *Clinical Science*, **26**, 471.

Bank, N., Mutz, B. F., and Aynedjian, H. S. (1967). *Journal of Clinical Investigation*, **46**, 695.

Biber, T. U. L., *et al.* (1968). *American Journal of Medicine*, **44**, 664.

Black, D. A. K., and Williams, R. T. (1962). *Quarterly Journal of Medicine*, **31**, 57.

Britton, K. E. (1968a). *Lancet*, **2**, 329.

Britton, K. E. (1968b). *Lancet*, **2**, 632.

Brown, J. J., Davies, D. L., Lever, A. F., and Robertson, J. I. S. (1963). *Lancet*, **2**, 278.

Brown, J. J., Davies, D. L., Lever, A. F., Robertson, J. I. S., and Tree, M. (1964a). *Biochemical Journal*, **93**, 594.

Brown, J. J., Davies, D. L., Lever, A. F., and Robertson, J. I. S. (1964b). *Journal of Physiology*, **173**, 408.

Brown, J. J., Davies, D. L., Lever, A. F., and Robertson, J. I. S. (1964b). J. I. S. (1965). *Journal of Physiology*, **176**, 418.

Brown, J. J., Davies, D. L., Lever, A. F., and Robertson, J. I. S. (1966a). *Postgraduate Medical Journal*, **42**, 153.

Brown, J. J., Davies, D. L., Lever, A. F., Robertson, J. I. S., and Verniory, A. (1966b). *Journal of Physiology*, **182**, 649.

Brown, J. J., *et al.* (1970a). To be published.

Brown, J. J., Davies, D. L., Johnson, V. W., Lever, A. F., and Robertson, J. I. S. (1970b). *American Heart Journal*. In press.

Brun, C., and Munck, O. (1957). *Lancet*, **1**, 603.

Brun, C., and Munck, O. (1964). *Progress in Surgery*, **4**, 1.

Bull, G. M., Joekes, A. M., and Lowe, K. G. (1950). *Clinical Science*, **9**, 379.

Bull, G. M., Joekes, A. M., and Lowe, K. G. (1955). *Lancet*, **2**, 1152.

Byrom, F. B. (1937). *Journal of Pathology and Bacteriology*, **45**, 1.

Byrom, F. B. (1964). *British Journal of Experimental Pathology*, **45**, 7.

Byrom, F. B., and Pratt, O. E. (1959). *Lancet*, **1**, 753.

Cameron, J. S., Ogg, C., and Trounce, J. R. (1967). *Lancet*, **1**, 1188.

Carriere, S., Thorburn, G. D., O'Morchoe, C. C. C., and Barger, A. C. (1966). *Circulation Research*, **19**, 167.

Clute, K. F., and Fitzgerald, G. W. (1948). *Canadian Medical Association Journal*, **59**, 426.

Cook, W. F. (1968). *Journal of Physiology*, **194**, 73P.

Cook, W. F., Gordon, D. B., and Peart, W. S. (1957). *Journal of Physiology*, **135**, 46P.

Cook, W. F., and Pickering, G. W. (1959). *Journal of Physiology*, **149**, 526.

Daniel, P. M., Peabody, C. N., and Prichard, M. M. L. (1952). *Quarterly Journal of Experimental Physiology*, **37**, 11.

Daniel, P. M., Prichard, M. M. L., and Ward-McQuaid, J. N. (1954). *Journal of Physiology*, **124**, 106.

De Champlain, J., Genest, J., Veyratt, R., and Boucher, R. (1966). *Archives of Internal Medicine*, **117**, 355.

de Wardener, H. E. (1963). *The Kidney*. London, Churchill.

Domenet, J. G., and Evans, D. W. (1969). *Quarterly Journal of Medicine*, **38**, 117.

Eigler, F. W. (1967). *Klinische Wochenschrift*, **45**, 23.

Faarup, P. (1968). *Acta Pathologica Microbiologica Scandinavica*, **72**, 109.

Finckh, E. S. (1962). *Lancet*, **2**, 330.

Finckh, E. S., Jeremy, D., and Whyte, H. M. (1962). *Quarterly Journal of Medicine*, **31**, 429.

Fisher, E. R. (1961). *Laboratory Investigation*, **10**, 707.

Flanigan, W. J., and Oken, D. E. (1965). *Journal of Clinical Investigation*, **44**, 449.

Gömöri, P., Zolnai, B., Nagy, Z., Jakab, I., and Mészáros, A. (1964). *Acta Medica Academiae Scientiarum Hungaricae*, **20**, 169.

Goormaghtigh, N. (1937). *Comptes Rendus des Séances de la Société de Biologie et ses Filiales*, **124**, 293.

Goormaghtigh, N. (1942). *Bulletin de l'Académie Royale de Médecine de Belgique*, **7**, 194.

Goormaghtigh, N. (1944). *La fonction Endocrine des Artérioles Rénales*. Louvain, Fonteyn.

Goormaghtigh, N. (1945). *Proceedings of the Society for Experimental Biology and Medicine*, **59**, 303.

Goormaghtigh, N. (1947). *American Journal of Pathology*, **23**, 513.

Henry, L. N., Lane, C. E., and Kashgarian, M. (1968). *Laboratory Investigation*, **19**, 309.

Heptinstall, R. H. (1966). *Pathology of the Kidney*. Boston, Little Brown.

Herbertson, B. M., and Kellaway, T. D. (1960). *Journal of Pathology and Bacteriology*, **80**, 87.

Hess, R., and Gross, F. (1959). *American Journal of Physiology*, **197**, 869.

Hollenberg, N. K., *et al.* (1968). *Medicine*, **47**, 455.

Horster, M., and Thurau, K. (1968). *Pflügers Archiv fur die gesamte Physiologie des Menschen und der Tiere*, **301**, 162.

Hosie, K. F., *et al.* (1970). *Clinical Science*. In press.

Houssay, B. A., Braun-Menendez, E., and Dexter, L. (1942). *Annals of Internal Medicine*, **17**, 461.

Jaenike, J. R. (1967). *Journal of Clinical Investigation*, **46**, 378.

Kempczinski, R. F., and Caulfield, J. B. (1968). *Nephron*, **5**, 249.

Klaus, D., and Heizmann, A. (1967). *Klinische Wochenschrift*, **45**, 657.

Kokot, F., and Kuska, J. (1969). *Nephron*, **6**, 115.

Kovalevskii, G. V. (1963). *Federation Proceedings*, **23**, Translation Suppl., p. 312.

Lauler, D. P., and Schreiner, G. E. (1958). *American Journal of Medicine*, **24**, 519.

Lloyd-Thomas, H. G., Balme, R. H., and Key, J. J. (1962). *British Medical Journal*, **1**, 909.

McKenzie, J. K., Ryan, J. W., and Lee, M. R. (1967). *Nature*, **215**, 542.

Massani,, Z. M., Finkielman, S., Worcel, M., Agrest, A., and Paladini, A. C. (1966). *Clinical Science*, **30**, 473.

Masson, G. M. C., Corcoran, A. C., and Page, I. H. (1952). *Archives of Pathology*, **53**, 217.

Merrill, J. P. (1960). *Annual Review of Medicine*, **11**, 127.

Ng, K. K. F., and Vane, J. R. (1968). *Nature*, **218**, 144.

Nickel, J. F., Gagnon, J. A., and Levine, L. (1963). *Journal of Applied Physiology*, **17**, 83.

Oken, D. E., Arce, M. L., and Wilson, D. R. (1966). *Journal of Clinical Investigation*, **45**, 724.

Oliver, J., MacDowell, M. C., and Tracey, A. (1951). *Journal of Clinical Investigation*, **30**, 1307.

Papper, S., and Vaamonde, C. A. (1968). *Annals of Internal Medicine*, **68**, 958.

Penner, A., and Bernheim, A. I. (1940). *Archives of Pathology*, **30**, 465.

Phillips, R. A., *et al.* (1946). *American Journal of Physiology*, **145**, 314.

Pickering, G. W., and Prinzmetal, M. (1940). *Journal of Physiology*, **98**, 314.

Pomeranz, B. H., Birtch, A. G., and Barger, A. C. (1968). *American Journal of Physiology*, **215**, 1067.

Powers, S. R., Boba, A., and Stein, A. (1957). *Surgery*, **42**, 156.

Ruiz-Guiñazú, A., Coelho, J. B., and Paz, R. A. (1967). *Nephron*, **4**, 257.

Scarff, R. W., and Keele, C. A. (1943). *British Journal of Experimental Pathology*, **24**, 147.

Schnermann, J., Nagel, W., and Thurau, K. (1966). *Pflügers Archiv für die gesamte Physiologie des Menschen und der Tiere*, **287**, 296.

Schröder, E. (1970). *Deutsche Medizinische Wochenschrift*. In press.

Schroeder, H. A. (1949). *Journal of the American Medical Association*, **141**, 117.

Sevitt, S. (1959). *Lancet*, **2**, 135.

Shear, L., Kleinerman, J., and Gabuzda, G. J. (1965). *American Journal of Medicine*, **39**, 184.

Sheehan, H. L., and Moore, H. C. (1952). *Renal Cortical Necrosis and the Kidney of Concealed Accidental Haemorrhage*. Oxford, Blackwell Scientific publications.

Smith, K., Browne, J. C. M., Shackman, R., and Wrong, O. M. (1968). *British Medical Bulletin*, **24**, 49.

Sundsfjord, J. A. (1969). *Lancet*, **2**, 807.

Teschan, P. E., and Lawson, N. L. (1966). *Nephron*, **3**, 1.

Thiel, G., Wilson, D. R., Arce, M. L., and Oken, D. E. (1967). *Nephron*, **4**, 276.

Thurau, K. (1964). *American Journal of Medicine*, **36**, 698.

Thurau, K. (1969). *Proceedings of the IV International Congress on Nephrology*, p. 129.

Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J., and Prichard, M. M. L. (1947). *Studies on the Renal Circulation*. Oxford, Blackwell.

Truniger, B., Rosen, S. M., and Oken, D. E. (1966). *Klinische Wochenschrift*, **44**, 857.

Tu, W. H. (1965). *Circulation*, **31**, 686.

Ueda, H., Tagawa, H., Ishii, M., and Kaneko, Y. (1967). *Japanese Heart Journal*, **8**, 156.

Vander, A. J. (1965). *American Journal of Physiology*, **209**, 659.

Vander, A. J., and Geelhoed, G. W. (1965). *Proceedings of the Society for Experimental Biology and Medicine*, **120**, 399.

Vaughn, D. L., Bersentes, T., Kirschbaum, T. H., and Assali, N. S. (1967). *American Journal of Obstetrics and Gynecology*, **99**, 208.

Walker, J. G., Silva, H., Lawson, T. R., Ryder, J. A., and Shaldon, S. (1963). *Proceedings of the Society for Experimental Biology and Medicine*, **112**, 932.

Waugh, D., and Pearl, M. J. (1960). *American Journal of Pathology*, **36**, 431.

Wilson, D. R., Thiel, G., Arce, M. L., and Oken, D. E. (1967). *Nephron*, **4**, 337.