

PARTIAL ACTIVITY OF THE KIDNEY AND THE "ALL OR NOTHING" PRINCIPLE.*

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IN the ordinary example of chronic general nephritis, which comes to inspection as a contracted granular kidney, it is uncommon, perhaps unknown, to find all the stages of glomerular sclerosis. One of the most striking and significant of the anatomical changes is that in any one kidney the glomeruli are divisible into groups, each of which shows one stage in the process of obliteration. There may be a certain number of intact (normal or hypertrophied) glomeruli, a second group in which the annular overgrowth occupies one-quarter of the glomerular area, and a third in which the glomerulus is represented by a hyaline mass. The whole series of gradations from the normal state to complete obliteration can be seen only in combined pictures from several cases. The natural inference from this is that the primary destructive lesion occurs in attacks, and that in each attack only a certain proportion of the glomeruli are involved.

It may be assumed that the destructive agent reaches the kidney in the blood: whether it originally affects the glomeruli or the tubules is immaterial; for the destruction of either involves the secondary degeneration of the other. A focal or selective action of a poison reaching the kidney by the blood-stream seems to be capable of only two interpretations. Either all parts of the kidney are not receiving an equal quantity of blood or different parts have at any one time different susceptibilities to the poisonous agent. These two alternatives are not mutually exclusive. The association of local vasodilation with functional activity is universal and there are many reasons for thinking that as a rule active cells are more liable to toxic action than resting cells. The process of poisoning is one of interaction between the cell and the poison rather than the impact of an external agent on the cell. If there is a stagnation of blood in any part, the time for this interaction is correspondingly increased.

In the special case of the kidney, this association of susceptibility and activity is illustrated in the necrosis produced by agents such as corrosive sublimate or uranium nitrate. Cells are damaged in limited

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segments of proximal convoluted tubules; these areas differ with different poisons (Suzuki (1912¹)). This suggests that the cells which are killed by an adequate amount of the sublimate or the chromium salts are those whose business it is to deal with the excretion of these poisons. The connection of a similarly limited area of convoluted tubule epithelium with the excretion of iron has long been known in pernicious anæmia. It has recently been demonstrated by Stieglitz (1921²) after the experimental injection of iron salts into the blood-stream. The lesser susceptibility of resting cells is illustrated by the resistance of hibernating animals to colchicine, abrin, etc. (Hausmann (1906³⁵)), and to trypanosome infection (Blanchard et Blatin (1907³)).

The resting cells then will be less liable to be poisoned, partly on account of their inherently lower activity and partly because they will receive a smaller quantity of blood than the active cells.

This hypothesis of the association of susceptibility and activity as applied to the distribution of kidney lesions involves the assumption that during average normal activity some parts are active and some resting. Bowditch (1871⁴) formulated the proposition that if the frog's heart responds at all to an induction shock it responds with the greatest contraction of which the muscle is at the time capable. This fundamental principle of "all or nothing" has since been extended to other excitable tissues, such as muscle* (Lucas (1909⁵)) and nerve (Gotch (1902,⁶ Adrian, 1912, 1913⁷)). Bayliss (1915⁸) and also Metzner (1907⁹) have indicated the necessary consequence that glands which receive their normal stimuli through the nervous system should show the same phenomenon.

A few casual observations on the medulla of the adrenal glands, the pancreas, the salivary glands and the glandular portion of the pituitary body have given suggestive results. Elliott (1913¹⁰) has shown that the myelinated fibres from the splanchnic nerves "seem to branch and run directly to the nests of chromaffine cells" in the adrenal glands. It has also been shown that these cells discharge adrenalin as a direct result of excitation of the splanchnic nerves, which supply these glands. Elliott (1913¹¹) says that "it may be that the sympathetic ganglion cells and the medullary or paragan-glion cells were once identical and that the liberation of adrenalin was once an essential part of the nervous impulse." The principle of "all or nothing" in the case of nervous impulse is clearly established; and this would lead one to the necessary conclusion, that the distribution of medullary cells stimulated to activity by nervous impulses would exhibit a focal distribution. It is well recognised that the cortex of

* The objections of Hartree and Hill (*Journ. of Physiol.*, 1921, vol. lv. p. 404) are unconvincing. They appear to assume that all the units in a muscle are exactly similar to one another—an untenable *a priori* proposition—and that under all conditions their mechanism is the same.

the suprarenals empties its load of lipoid in zones, whereas in the medulla the cells empty out in groups or nests of cells. Thus even on continued splanchnic nerve stimulation, when almost all the medullary cells look empty there may still be found some cells loaded with secretory granules. These appearances were specially well seen in the slides exhibited by Cramer at the meeting of the Physiological Society on February 18, 1922, and also in figures 1, 2, 3, of his article (1919¹²). On repeating his technique it was possible in normal "resting" glands to find areas of cells filled with fine grey granules lying side by side with islets of clear cells. In response to stimulation of the gland, by exposing mice to varying degrees of cold, larger areas of clear cells were observed; but even in these specimens there were nests of cells loaded with the grey granules. The cells containing secretory granules in the acini of submaxillary serous glands show a similar arrangement (Müller (1912¹³)). Also the acini in the pancreas of healthy rabbits examined for Altmann's granules often showed a grouping together of the granule-containing cells, lying adjacent to empty acini. The eosinophile cells in the glandular portion of the pituitary body (pars anterior) show an arrangement, which is very suggestive, especially if the two varieties of cells are taken as different phases of activity, or "two different physiological conditions" of the same cells (P. T. Herring (1908¹⁴)). It seems likely that the principle is applicable to practically all the tissues of the body.

Marey (1885¹⁵) found that the frog's heart will not respond to an external stimulus during a contraction, and that its excitability is low at the beginning of relaxation, and progressively increases until it reaches its normal level soon after the end of relaxation. This "refractory period" has also been demonstrated in skeletal muscle (Lucas 1908⁵), nerve (Gotch and Burch (1899¹⁶)) and sense organs (Adrian and Lucas (1912¹⁷)). It is appropriately described by Gotch (1900¹⁸) as a "general phenomenon of living substance."

Along these lines we find a rational explanation of the fact that each organ of the body has more substance than is necessary to do its normal amount of work. This "reserve force" is present in the normal state and is also found in atrophy and hypertrophy (Boycott (1914¹⁹)). It can be assumed that all the units of which an organ is composed are not active during moderate activity of the organ; that those which are active are doing as much work as they are capable of; that the total activity of the organ varies with the number of units which are active; and that each period of activity is followed by a refractory period and an interval of rest. On this basis the units take duty, as it were by rotation, and at any one moment some are in the active state, others in the completely refractory period, others in the relatively inexcitable phase which follows it. With increasing strengths of stimulation, successive groups are brought into action, first those whose active spell is most remote and lastly those in which it is most

recent. It is by this means that a larger number of units than are usually necessary are kept in efficient working order.

The anatomical basis of these units, except in the case of nerve and striped muscle fibre, is unknown; in these they are the nerve fibre and the muscle cell. In secreting glands the unit might be a cell, an acinus, a group of acini or even a part of a cell. In the liver all the evidence points to each lobule behaving like the others; and the zones of the lobules are the probable units. If this organ has to deal with a moderate excess of destroyed red corpuscles, the iron occurs only in the outer zone; in more extreme cases the middle zone is also engaged. In the kidney, it is possible that each glomerulo-tubal system is a unit. The human kidneys contain nearly two millions of these units. During moderate activity of this organ—which gives over the whole twenty-four hours about 1 c.c. of urine per minute—only a proportion (perhaps about 10 to 20 per cent.) of these units are in action at any one time. When on violent stimulation some 18 to 20 c.c. per minute are excreted, as by Priestley (1916²⁰) and by Macallum and Benson (1909^{20a}), then a much larger proportion of these units is acting; and it is possible that when Greenwood excreted 135 c.c. in five minutes (Hill and Greenwood (1907²¹)) all these units were thrown into simultaneous activity.

The relation between the number of active units during submaximal stimulation and the total activity of the organ can only be determined from the relation of the existing to the maximal activity. Except for the specialised excitable tissues, the durations of the active phase and the refractory period are not known.

The line along which objective evidence bearing on these considerations can be obtained is the discovery of anatomical evidence of activity of some units during moderate activity, and of all units during extreme action of an organ. I have sought for such evidence in the kidney.

Krogh (1919²²) in his recent work has shown that many capillaries in normal organs are at any one moment closed and out of action. Similarly, on examining a series of sections of the healthy kidney cortex, it is noticeable that all the glomerular capillaries are not equally distended with blood. Some glomeruli appear quite full, whereas others are almost empty. It is very difficult to explain this histological finding as a post-mortem phenomenon. A similar lack of uniformity is also observed in the glomerular circulation in the living animal. The renal circulation in frogs can be observed under appropriate conditions during four to five hours. The best results were obtained by the method described by Leonard Hill (1921²³) and Richards (1922²⁴). The kidney of a frog under urethane (about 0.25 c.c. of 25 per cent. solution) is exposed through a lumbar incision and, after retracting the abdominal walls, held in place by a cover-glass; a strong beam of light from a small arc lamp, or preferably a 100 watt Mazda lamp, is focussed on the surface of the kidney; through a one-inch objective

many glomeruli are plainly visible. Selecting a group at the edge of the kidney (where it is thinner and more transparent) the blood is seen circulating briskly through the tortuous glomerular capillaries. In the course of a few minutes, the circulation in a certain number of these glomeruli either gradually or sometimes abruptly comes to a stop. It stops either with the glomerular capillaries still full of blood, in which case the blood column in these capillaries may remain stationary, or it may oscillate, apparently with the heart-beat, or the capillaries become empty and the glomeruli gradually disappear from view. In the course of another few minutes, the circulation recommences in these glomeruli, and is arrested in others. Owing to the thickness of the capsule, and the presence of pigment in the mammalian kidneys, it was found impossible to repeat these observations on mice and I was unable to confirm Ghiron's (1913²⁵) statements.

It was thought that if there were any difference in the glomerular circulation, its existence would be detected on injection of particulate material intravenously or in the carotid arteries. Any such difference might indicate a difference of activity in the glomeruli or in the kidney units. Starch granules of various kinds, pigeon's red-blood cells, stained rabbit's red-blood cells (Butterfield in Bolton (1921²⁶)) and milk, were injected in the ear vein or carotid artery of rabbits which were killed after intervals of one to fifteen minutes. The kidneys, fixed whole, were examined in serial sections. These experiments did not lead to any definite evidence, mainly owing to the uncertainty of assuring myself as to the presence or absence of individual particles in all of the consecutive serial sections.

Injections of emulsions of easily recognisable micro-organisms (staphylococcus and sarcinæ) were next attempted. It was found that the cocci which were arrested in the glomerular capillaries, were embedded in little masses of clot, confirming the findings of Teale and Bach (1920²⁷). As these small thrombi were very variable in size, their presence in the capillaries could not have served as an indication of the patency or the contrary of the capillaries.

Experiments with a yeast (6 to 8 μ) gave rather indeterminate results (Table I.), but appeared to show that the glomeruli were certainly not all in the same state of circulatory activity at any one moment.

TABLE I.
No. of Yeast Cells in Glomeruli

	Weight.	Amount of Yeast Emulsion.	Time.														Total Yeast Cells.
				0	1	2	3	4	5	6	7	8	9	10	11	12	
R. 33	1875	10 c.c.	3 mins.	Glomeruli	16	14	6	4	4	4	2	86
R. 32	2350	20 c.c.	3 mins.		15	4	5	6	7	2	3	2	2	..	2	..	162

About one-third of the glomeruli show no arrested cells, but it is not clear that the results are not largely due to chance distribution.

A more direct method of obtaining an evidence of the focal secretory activity of the kidney consisted in observing the distribution of easily recognisable substances, eliminated by the healthy kidney, after their introduction in the blood-stream.

For this purpose three different kinds of substances were employed.

I. Iron Salts.

The use of iron in investigations of the mechanism of renal activity is quite old. The advantages are that it is normally excreted by the kidneys in minute quantities even by healthy individuals. In diseases accompanied by considerable blood destruction, *e.g.*, pernicious anæmia, its quantity is greatly increased. It also forms salts whose presence can be detected by a delicate colour-precipitation reaction (prussian blue).

The latest addition to the time-worn discussion on "secretory and filtration" theories of the kidney is the work of Stieglitz, who has tried to unravel this problem by reintroducing the use of iron in his experiments. He has incidentally noticed that "in some tubules the cells were heavily laden, while in others the cells did not contain any iron at all." "Those tubules containing iron were grouped together." Kolbert (1883²⁸) records similar findings for iron retained in the kidneys, and suggests that the difference in the tubules is due to a difference in the phases of activity of these tubules.

Using a solution of iron-ammonium citrate (green scales) in doses of about 0.4 grms. per kilo body weight and killing the animals after three to five minutes, I obtained a good demonstration of the presence of iron-containing particles in the cells of the convoluted tubules. In alcohol fixed specimens I was unable to demonstrate the presence of iron histologically in the capsules of the corresponding glomeruli. It is therefore possible that the uneven distribution of iron indicates the selective action of certain tubules in the secretion of iron, or that the iron was present in the units of the kidney which were functionally active at the particular moment when the animal was killed.

II. Carmine.

The route of elimination, by the kidney, of various dyes introduced in an animal has long been studied. Suzuki came to the conclusion that "carmine is excreted by the glomeruli in large part and some of it escapes through the convoluted tubules." Carmine dissolved in lithium carbonate solution was found to be the most suitable dye. It is not converted into colourless salts during its passage in the body, and after intravenous injection the granular staining is readily obtained in the convoluted tubules.

In my experiments, in most cases all the glomerular capsules took on a faint pink stain (as observed in thick sections). Some glomeruli

showed "worm-cast" like deposits of stain in their capillaries (below, p. 423). This appearance was noticeable even in fresh unfixed, frozen sections. On washing out the blood through a canula fixed in the arch of the aorta, with a 6 per cent. gum-arabic saline solution these casts were not washed out.

Three illustrative experiments are quoted below.

Five c.c. of warm 10 per cent. carmine B.D.H. dissolved in 1 per cent. lithium carbonate solution were injected in the rabbit's ear vein. The rabbits were killed half a minute after the removal of the injection needle. Renal vessels were ligatured, and kidneys fixed whole in 10 per cent. formalin. Sections 150 μ thick were cut on a freezing microtome. The sections were stained with methyl green and dehydrated in graded strengths of alcohol, cleared in cedarwood oil and mounted in canada balsam. With this technique it was possible to see through the whole thickness of a glomerulus and its capsule with a 16 mm. and even with a 4 mm. objective.

TABLE II.

R. 46	2200 g.	5 c.c.	$\frac{1}{2}$ min.
Almost all the glomerular capsules took on a faint pink stain.			
R. 48	2050 g.	5 c.c.	$\frac{1}{2}$ min.
"Worm-cast" like masses in glomerular capillaries, also a faint pink stain of glomerular capsules.			
		Masses.	No. of Glomeruli.
		+ + +	9
		+ +	27
		+	37
		Nil	27
			<hr/> 100
The sign " + " = masses present.			
R. 50	1800 g.	5 c.c.	$\frac{1}{2}$ min.
Washed out with about 300 c.c. of 6 per cent. gum-arabic saline solution from the aorta.			
			No. of Glomeruli.
Faint colour of capsule only			32
Colour + Masses			53
Masses only in capillaries			11
Nil			4
			<hr/> 100

The extent and the retention of the stain do not run *pari passu* with the functional activity of the units. The staining of the capsule after it has once taken place, would persist even though the glomerulus may pass on to the inactive phase. Suzuki and Aschoff (1912²⁹) have also pointed out that the granular staining in the convoluted tubules has nothing to do with the secretion of the dye.

These experiments only show that at any one particular moment all the glomeruli are not alike, at least so far as concerned their circulation, as some of them contained the "worm-cast" like deposits of stain and others did not.

III. Hæmoglobin.

The normal kidney is practically impermeable to plasma proteins. It eliminates other proteins reaching it by the blood-stream. Thus the hæmoglobin when freed in the blood escapes through the kidney quite rapidly. Ponfick (1875³⁰) showed that when the amount of injected hæmoglobin solution reaches its threshold limit it was excreted quantitatively by the kidney. Adami (1885³¹) and later Ribbert (1913³²) showed that when laked blood is injected into the rabbit's ear vein, the kidneys excised after five minutes and hardened, hæmoglobin can be demonstrated in the capsules of the glomeruli. After ten minutes the hæmoglobin is still present in the glomerular capsule, but has mostly passed down in the tubules of the kidney.

If the kidneys are fixed in boiling water, the hæmoglobin in fresh unstained thick sections is found coagulated into a yellowish reticular crescent, distending the space round the glomerular tuft. Sections stained with eosin and counter-stained with methyl green showed these masses of hæmoglobin clearly. A few preliminary experiments are quoted below.

Fresh blood from rabbits, received in 10 per cent. citrate solution. Washed red-blood cells centrifuged and laked with saponin in a few cases, but in most with distilled water. Stromata of broken red-blood cells centrifuged out with high speed centrifuge till a transparent clear solution was obtained. Strong salt solution added to bring up the salt content to 0.9 per cent. Hæmoglobin percentage on Haldane's hæmoglobinometer between 50 and 60. Solution injected in the ear vein of rabbits. Kidneys fixed in boiling water for five minutes (formalin or sublimate fixation gives much less clear pictures).

TABLE III.

	Weight.	Amount of Hb. Solution.	Time.	Remarks.
R. 34	1880	10 c.c.	Inst.	No Hb. crescents in glomerular capsule.
31	2500	"	1 min.	"
32	2350	"	5 min.	Hb. crescents present. " Hb. also in tubules.
25	2320	"	15 min.	Very few crescents present, mostly in tubules.
35	2120	15 c.c.	1½ min.	Hb. crescents present.
21	1950	20 c.c.	10 min.	"
22	1890	"	20 min.	No Hb. " crescents found. Hb. present in large quantities in tubules.

Of these, serial sections 10 μ thick were cut in paraffin from R. 32 and R. 35; 50 adjacent glomeruli reconstructed after staining with hæmotoxylin and eosin showed the distribution of hæmoglobin given in Table IV.

TABLE IV.

	Weight.	Amount.	Time.	Amount of Hb. in Glomeruli.		
				+	Tr.	Nil.
R. 32	2350	10 c.c.	5 min.	20	9	21 = 50
35	2120	15 c.c.	1½ min.	12	17	21 = 50

The signs + and Tr. are arbitrary.

+ = a lot of Hb. Tr = a trace.

Barratt and Yorke (1912³³) demonstrated that laked blood, freed from the stroma of broken blood cells, was not poisonous to animals. Some of my experiments confirm these observations. Rabbits showed no visible ill-effects after 20 c.c. injections of stroma-free hæmoglobin solution. In three cases these injections were repeated six to seven times after intervals of four to six days. From this it may be assumed that during the period of the experiments quoted below (which never lasted more than twenty minutes) the injected material did not impair the kidney function, but that the presence of hæmoglobin in any particular glomerular capsule pointed to its functional activity.

Using thick frozen sections (about 150 μ) and analysing 100 adjacent glomeruli in each case, the results were as follows:—

TABLE V.

	Weight.	Hb.	Time.	++	+	Tr.	Nil.
R. 54	2875	10 c.c.	5 min.	...	3	13	84
55	2900	15 c.c.	"	...	11	10	79
57	2210	15 c.c.	"	...	10	10	80
61	1825	15 c.c.	"	2	10	6	82
58	2265	15 c.c.	8 min.	...	7	4	89

If these experiments could be interpreted as evincing the "partial" activity of the kidney, then increasing the excretory activity of the kidney by a preceding dose of a diuretic (which is parallel to increasing the load on a contracting muscle) ought to increase the number of glomeruli showing these hæmoglobin crescents, still perhaps leaving some empty.

The results of diuretic experiments are given in Table VI.

TABLE VI.

		Diuretic . . . $\left\{ \begin{array}{l} 3 \text{ c.c. of } 5 \text{ per cent. salt solution.} \\ 2 \text{ c.c. } 5 \text{ per cent. caffeine sod. benzoate. (B.P.)} \end{array} \right.$					
	Weight.	Time after Diuretic.	Hb.	Time.	++	+	Tr. Nil.
R. 56	2890	10 min.	10 c.c.	5 min.	15	27	6 52
62	2225	"	15 c.c.	2 min.	51	28	... 21
63	1925	"	"	4 min.	3	11	3 83
59	1945	"	"	5 min.	2	3	9 86

The only conclusion to be derived from these experiments is that the various units of which the kidney is composed are not all active during moderate activity of the organ. In other words, the exigencies of everyday life during health demand the activity of only a proportion of the kidney units, at any particular moment; that the active units are active to their utmost limit; that whenever the amount of work to be accomplished is increased, this is met with by an increased number of units being thrown into activity and not by an increased activity of the active units.

The uniform activity of all the units in the two kidneys has so far been tacitly assumed, and I have not discovered any reference to the

contrary view except in the suggestions of Hermann (1859³⁴) and of Kobert (1887²³). Richards (1922²⁴) has stated this principle clearly in the case of frog's kidney in his lecture, but full details of his work are not yet available.

The exact mechanism by which this "selective or focal" activity is maintained in the kidneys is still open to speculation. Richards has suggested that it is probably obtained by local vaso-constriction of afferent and efferent glomerular capillaries, thus arresting the circulation in the particular glomerular tufts. Regardless of the view held about the function of the convoluted tubules (secretory or absorptive) it is evident that the arrest of circulation through the glomerular tufts would for the time being arrest or affect the activity of the tubules which derive their blood supply through these tufts. This view would explain the appearances observed in the living frog kidney, also the distribution of iron, in groups of convoluted tubules. It might further explain the "worm-cast" like deposits of carmine in a certain number of glomerular capillaries, on the assumption that in these glomeruli the circulation is arrested by a constriction of the efferent vessels.

It is possible that the "tonus" of the capillaries described by Krogh (1919-20²²) may be the regulating mechanism. In his observations on frog's tongue and also the skeletal muscle, he has arrived at strikingly similar conclusions. To quote his words, "Every capillary must alternately open and close; and in the resting tissue (tongue) which is very poorly supplied with blood, the position of open capillaries must be continuously changing, with the result that the whole tissue is uniformly irrigated when considered over a period of sufficient length."

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