RENAL FUNCTION IN AGED SUBJECTS

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INTRODUCTION

CHANGES of the renal function with advancing years have been studied by many investigators, and by many different methods. The estimation of urea concentration in the blood, of the specific gravity of the urine as an expression of the concentrating ability of the kidney tubules, of the capacity to eliminate water, and of urea clearance have all been used, whilst some investigators have relied upon phenolsulfonphthalein and other dyes to test the excretory power of the kidney. The invariable conclusion has been that with advancing years the renal function decreases.

More recently, the clearance methods introduced by Homer Smith have been used by Shock (1946) and Hilden (1943) to investigate, in greater detail, the changes in renal function which accompany old age.

It has previously been pointed out (*e.g.* Olbrich (1947), Stewart 1948), that there is great difficulty in dissociating the effects of age itself from those of the disabilities and diseases which so commonly accompany old age; the results obtained by Shock and by Hilden illustrate this difficulty as do those to be reported in this paper. An attempt will, however, be made to discuss how far the "abnormalities" of renal function observed are to be ascribed to hypertension.

METHODS

Subjects.—We have investigated 50 subjects aged 60 years and upwards of whom 36 were males and 14 were females. All were ambulant, and free from gross organic disease.

Shock (1946) stipulates that a "normal" aged person is one who has a clinical history indicating the absence of, and is free from, clinical signs of cardiovascular or renal disorders, has a blood pressure less than 150 systolic and 90 diastolic, has no albumin, sugar, red cells or casts in the urine, has a specific gravity of the urine greater than 1020 after 14 hours of water restriction, has no marked prostatic hypertrophy, is easily catheterised and has minimal peripheral sclerosis.

Among our subjects these criteria of the "normal aged" could not be completely obtained as only very few cases with a systolic blood pressure less than 150 could be found, and the connotation of the term "minimal peripheral sclerosis" varies according to the investigator. In all cases, however, the urine was free from sugar, albumin, blood and casts; there was no marked prostatic hypertrophy and, as already stated, there were no clinical signs of gross organic disease.

We have therefore divided our subjects into two groups—those with a high systolic and an essentially normal diastolic pressure (*i.e.* not exceeding 100 mm. Hg.) and those with a high systolic and a high diastolic pressure. The blood pressure measurements were taken repeatedly under basal conditions, and the figures given are the average readings for each individual, at least ten measurements having been taken for each subject.

In the first group we have included 10 males investigated by the continuous infusion method and 9 investigated by the method of single intravenous injection. The average blood pressure of the subjects investigated by the infusion method was 169/91 (with a range of 215-120 and 100-75), and the average age was 72 (with a range of 65-80 years). The average blood pressure of the subjects investigated by the single injection method was 198/95 (with a range of 265-160 and 100-80), and the average age was 73 (with a range of 65-83 years).

The second group contained 16 males who were investigated by the drip infusion method and 11 males and 14 females investigated by the single injection method. The average blood pressure of the males investigated by the infusion method was 209/118 (with a range of 260-160 and 140-105), and the average age was 77 (with a range of 69-87 years). For the subjects to whom the single injection method was applied the average blood pressure was 209/119 (with a range of 250-160 and 140-106), and the average age was 74 (with a range of 62-91 years).

Nine young males served as normal controls for the single injection method. They were patients who suffered from lumbago, neurasthenia or some minor type of alimentary disorder. Their average blood pressure was 119/75 (with a range of 130-110 and 85-65), and their average age was 30 (with a range of 20-39 years).

Preparation of Subject.—All subjects were afebrile and all were investigated under post-absorptive conditions in the early morning. Fluid was given freely during the evening before the test. In the early morning, at 6.0 a.m., 1000 c.c. of water or weak tea was given and this was followed by about 150 c.c. of water every ½-1 hour during the period of investigation. This process of hydration achieved a free urinary flow, the average for all subjects being 7 c.c. per min. with a range of 1 c.c. to 29 c.c. per min.

Blood pressure and body temperature were measured during the test.

Techniques.—The experimental methods and analytical techniques were those described by the authors in a previous paper (Olbrich, Ferguson, Robson and Stewart, 1950).

The clearance estimations of inulin and diodone were calculated for each period by the formula UV/P, and that for the tubular excretory mass by the formula $U_D V - (P_D \times C_{In} \times FW)$. All values were reduced to the standard of 1·73 sq. m.

Results

Table I gives the results of the measurements of inulin clearance, diodone clearance and tubular excretory capacity for diodone, those obtained by the infusion method being separated from those obtained by the single injection method (though many subjects were tested by both methods). The aged subjects are divided into the two groups previously described—those with diastolic blood pressure not greater than 100 mm. mercury, and those with diastolic pressure above 105 mm. The first (relatively low diastolic pressure) group consisted entirely of males; the second included both men and women who, however, were grouped together since the number of men submitted to the single injection test was very small and it has been shown (Goldring and Chasis, 1944) that no significant sex differences exist.

TABLE I

Summary of Results

	Infusion Method.					Injection Method.				
	Age.	No. of Cases.	Mean.	S.D.	S.E.	Age.	No. of Cases.	Mean.	S.D.	S.E.
Inulin Clearance										
Normal young males	...	67	136·0*	21·5	2·6	20-39	9	126·0	16·7	5·6
Aged males, normal diastolic	65-80	10	92·1	15·1	4·8	65-83	9	93·8	23·6	7·9
Aged males, high diastolic, and aged females, high diastolic	69-87	16	76·5	20·0	5·0	69-79 / 62-91	25	77·2	17·6	3·5
Diodone Clearance										
Normal young males	...	61	719*	136	17·4	20-39	9	535	78	26·0
Aged males, normal diastolic	65-80	10	489	112	35·0	65-83	8	419	133	47·0
Aged males, high diastolic, and aged females, high diastolic	69-87	16	326	86	22·0	69-79 / 62-91	22	289	72	15·0
TmD										
Normal young males	...	40	51·8*	8·7	1·4	20-39	8	41·0	7·4	2·6
Aged males, normal diastolic	65-80	10	36·0	5·6	1·8	65-83	8	31·0	5·5	2·0
Aged males, high diastolic, and aged females, high diastolic	69-87	16	25·5	7·5	1·9	69-79 / 62-91	19	21·9	7·0	1·6
Urea										
Normal young males	...	...	...	...	...	20-39	9	82·4 (109%)	23	7·8
Aged males, normal diastolic	65-80	10	64·2 (85%)	16·8	5·3	65-83	8	62·3 (85%)	16	5·7
Aged males, high diastolic, and aged females, high diastolic	69-87	16	57·0 (76%)	20·4	5·1	69-79	20	53·3 (71%)	19	4·2

* Figures for normal young males in infusion method given by Homer Smith (1943).

S.D. = Standard deviation. S.E. = Standard error

The results are compared, in the case of the single injection method, with those from nine healthy men aged 20 to 39 years. For the infusion method it has been necessary to use as " controls " the figures given by Homer Smith (1943) for normal young men.

1. *Diodone Clearance* (*Effective Renal Plasma Flow*).—Both methods show the diodone clearance to be lower in the aged subjects than in the young, and to be still lower in those with definitely high diastolic pressure than in those whose diastolic pressure is normal or nearly so. That the actual figures differ according to the method used is probably due to the fact that when the single injection method is used there is a considerable difference between the concentration of diodone in the venous blood used for analysis and the arterial blood which is supplied to the kidney (Olbrich, Ferguson, Robson and Stewart, 1950). Application of Student's t-test shows the fall from the normal mean of 719 for the infusion method to the mean value of 489 of the aged group with low diastolic pressure to be highly significant ($t = 4{\cdot}65$; for $n = 26$ and probability 0·05, $t = 2{\cdot}056$). In the case of the single injection series, however, where the normal young men have a mean C_D of 535 and the aged men with low diastolic pressure have a mean C_D of 419, the difference is not strictly significant ($t = 2{\cdot}08$: for a probability of 0·05, $t = 2{\cdot}131$). It seems fair to conclude, in spite of this statistical discrepancy (due in part to the difference in method) that the lower diodone clearance in the aged subjects with low diastolic pressure is a real phenomenon. Comparison of the mean figures for diodone clearance in the young normal males with those for aged subjects with high diastolic pressure shows that the latter are lower by about 50 per cent., and irrespective of the method used, this difference is highly significant.

These changes in diodone clearance paralleling increasing age and blood pressure alterations may be interpreted as indicating corresponding changes in effective renal plasma flow if it be accepted that the usual assumption—that the diodone is completely removed from the plasma during one circuit through the kidney—applies equally to the aged and young subjects. Whether or not the assumption is strictly correct, there is no evidence that the two types of subject behave differently. The measurements, taken at their face value, suggest that changes in blood pressure are the dominating factor and that age is of importance in so far as it is accompanied by these changes. The alterations in diodone clearance indicate quantitative changes in the effective renal plasma flow rather than qualitative changes in the renal response.

In the first group of the aged the normal diastolic pressure indicates that the peripheral arteriolar resistance is not increased. The increased systolic pressure indicates only an increased resistance in the preglomerular arterial part of the vascular tree by an intact myocardium ; in this group of subjects a smaller amount of blood reaches the functioning kidney epithelium and therefore a smaller amount of

diodone is excreted per minute. In the second group with high diastolic pressure, where the arteriolar resistance is also increased, the amount of blood reaching the kidney further decreases. In both groups there is a distal reduction of the flow of blood into the kidneys, but there is no evidence that the physiological mechanism of the kidney itself suffers any change in quality.

2. *Inulin Clearance* (*Glomerular Filtration Rate*).—Whichever method of measurement is used, the mean inulin clearance of the aged subjects with low diastolic pressure is only about three-quarters of that of the normal young subjects and the t test shows this difference to be highly significant. The infusion method gives $t = 6{\cdot}28$ (for $P = 0{\cdot}05$, $t = 2{\cdot}038$): the single injection method gives $t = 5{\cdot}55$ (for $P = 0{\cdot}05$, $t = 2{\cdot}120$).

Again irrespective of method, the aged subjects with high diastolic pressure show a mean inulin clearance about 12 per cent. lower than that of the low diastolic pressure group, and this difference is also significant. For the infusion method $t = 2{\cdot}03$ (for $P = 0{\cdot}05$, $t = 2{\cdot}06$) and for the single injection method $t = 2{\cdot}14$ (for $P = 0{\cdot}05$, $t = 2{\cdot}04$).

The agreement between the two methods may be related to the fact that, for inulin, the arteriovenous difference in concentration is very small.

The belief that the inulin clearance measures the glomerular filtration rate depends on the assumption that inulin is neither excreted nor reabsorbed by the tubules. The authors (Ferguson, Olbrich, Robson and Stewart, 1950) have shown this assumption to be probably untrue, but have found that, under the usual experimental conditions the inulin clearance represents a nearly constant proportion (85 per cent.) of the glomerular filtration rate. For comparative purposes, therefore, when absolute figures are not important, the inulin clearance may be accepted as at least an approximate measure of the glomerular filtration rate.

In the aged subjects with low diastolic pressure both the effective renal plasma flow and the glomerular filtration rate are about 30 per cent. less than in normal young men. This indicates that in these groups the available glomeruli are functioning with equal effectiveness. The aged subjects with high diastolic pressure have an effective renal plasma flow about 30 per cent. lower still than those with low diastolic pressure, but their glomerular filtration rate is reduced, on the average, by only about 12 per cent. Hence these aged people with high diastolic pressure produce more glomerular filtrate per minute than would be expected from their renal plasma flow—their available glomeruli are apparently working with increased efficiency.

The rate of glomerular filtration depends partly upon the resultant of the mean arterial pressure, the colloid osmotic pressure of the plasma and the intracapsular pressure, the second and third of these components acting in opposition to the first. In the aged subjects we have studied it may be assumed, since there is no evidence of obstruction

to the urinary flow, that the intracapsular pressure is substantially unaltered. The mean arterial pressure is raised, and the colloid osmotic pressure due to the plasma proteins tends to be lowered in comparison with young normal subjects (Olbrich, 1947). The changes in mean arterial pressure are undoubtedly real, but those in colloid osmotic pressure are not statistically significant. In these circumstances an increase in glomerular filtration rate would be expected, instead of the decrease actually found and it is therefore obvious that other factors play a dominant role.

Homer Smith considers that glomerular filtration is regulated by the interplay between the afferent and efferent vessels and that this is, within limits, independent of the mean arterial pressure. If the afferent vessels are constricted then, other things being equal, less plasma reaches the glomeruli and the amount of filtrate produced in unit time is decreased; this may be supposed to account for the proportionate reduction in diodone and inulin clearance in the aged subjects with normal diastolic pressure. If the efferent vessels are constricted then, other things being equal, plasma is trapped, so to speak, in the glomerular capillaries and the amount of filtrate is increased. In the aged subjects with high diastolic pressure, constriction of the afferent vessels leads to decreased filtration whilst constriction of the efferent vessels produces increased filtration; the resultant is a filtration rate less than in the normal or in the aged subjects with normal diastolic pressure but greater than would be anticipated on the basis of effective renal plasma flow (diodone clearance) alone.

3. *Maximum Tubular Excretory Capacity for Diodone* (T_{mD}).—The T_{mD} is the difference between the total amount of diodone excreted per minute and the amount excreted by glomerular filtration when the tubules are functioning maximally—*i.e.* when the amount of diodone presented to them by the plasma is greater than they can excrete. The amount of diodone presented to the tubules in unit time is governed by the volume of plasma per minute and the concentration of diodone in the plasma. Hence the plasma diodone concentration necessary to demonstrate maximum tubular excretory capacity must vary inversely with the effective renal plasma flow, but provided it is properly adjusted so that the real T_{mD} is obtained, the measurements should not be affected by the renal plasma flow.

This is important, for the aged subjects with low diastolic pressure had a mean T_{mD} about 30 per cent. lower than that of the young "controls" and this difference is about the same as that in effective renal plasma flow. The difference in T_{mD} is highly significant. Using the figures from the infusion method, $t = 5{\cdot}27$ (for $P = 0{\cdot}05$, $t = 2{\cdot}06$); using those from the single injection method, $t = 2{\cdot}85$ (for $P = 0{\cdot}05$, $t = 2{\cdot}15$). The lower T_{mD} in the aged subjects is not merely a reflection of the changes which have produced a reduced plasma flow, but represents either a decrease in the amount of functioning tubular

tissue or a diminution in the efficiency of the tubular epithelium—or perhaps both.

The subjects with high diastolic as well as high systolic pressure had a still lower mean T_{mD} and the difference between them and the low diastolic pressure group was significant. This, also, must indicate change in the actual amount of functioning tubular tissue or in the tubular efficiency. Though it may be a result of defective supply of oxygen and nutrients and may therefore ultimately be due to the reduced renal plasma flow (or to the factors causing this reduced renal plasma flow) it is not merely a direct consequence of this.

4. *Derived Ratios.*—(*a*) $\frac{C_{In}}{C_D}$. The ratio of the inulin clearance (interpreted as equivalent to the glomerular filtration rate) and the diodone clearance (representing the effective renal plasma flow) is termed the *filtration fraction* and indicates the volume of glomerular filtrate formed from each c.c. of plasma perfusing the functioning nephrons.

The figures given in Table II show that, by both methods of measurement, the mean filtration fraction is the same in the aged

TABLE II

Derived Ratios

	Infusion Method.				Injection Method.			
	Mean Value of Ratio.	S.D.	S.E.	No. of Cases.	Mean Value of Ratio.	S.D.	S.E.	No. of Cases.
C_{In}/C_D (Filttation Fraction)—								
Normal young males	19·0*	2·0	0·3	61	23·8	2·8	0·9	9
Aged males, normal diastolic	19·4	3·3	1·0	10	24·3	5·4	1·9	8
Aged males, high diastolic, and aged females, high diastolic	23·9	5·1	1·3	16	27·7	5·3	1·1	22
C_D/T_{mD}—								
Normal young males	14·0*	2·16	0·37	34	13·27	2·4	0·85	8
Aged males, normal diastolic	13·76	1·18	0·37	10	13·35	2·82	1·0	8
Aged males, high diastolic, and aged females, high diastolic	13·49	4·0	1·0	16	14·64	5·6	1·3	19
C_{In}/T_{mD}—								
Normal young males	2·63*	0·34	0·05	40	3·17	0·69	0·25	8
Aged males, normal diastolic	2·60	0·47	0·15	10	3·17	0·66	0·23	8
Aged males, high diastolic, and aged females, high diastolic	3·13	0·9	0·2	16	4·00	1·7	0·4	19

* The infusion method figures given for normal young males are those given by Goldring and Chasis (1944).

subjects with normal diastolic pressure as in the healthy young subjects. [The actual figures yielded by the two methods differ since, for reasons already explained, the figures for C_D are different.] This is simply a statistical confirmation of the statement that the reduction in inulin

clearance shown by the low diastolic pressure group is proportional to the reduction in effective renal plasma flow.

The subjects with high diastolic pressure, have on the average, a higher filtration fraction than the other subjects. The difference is highly significant. The actual mean figures by the infusion method are 23·9 for the high diastolic pressure group, 19·4 for the low diastolic pressure aged subjects, and 19·0 for the healthy young subjects. Student's *t*-test gives, for the difference between 23·9 and 19·4, a value of 2·91 (for $P = 0{\cdot}05$, $t = 2{\cdot}064$; for $P = 0{\cdot}01$, $t = 2{\cdot}797$). The single injection method yields figures of similar significance. These results indicate an apparently greater filtration efficiency in the subjects with high diastolic pressure and, as has been suggested, this may well be attributed to the effect of constriction of the efferent vessels.

(*b*) $\frac{C_D}{T_{mD}}$. The ratio between the effective renal plasma flow and the maximum tubular excretory capacity (or mass) expresses the volume of plasma which may be supposed to be cleared of test substance per unit of functioning tissue.

The mean figures in Table II show, by both methods, that the ratio C_D/T_{mD} is slightly lower for the aged subjects with high diastolic pressure than for those of comparable age but normal diastolic pressure and slightly lower for these latter subjects than for the healthy young men. The differences are very slight and not statistically significant. We do not, therefore, feel justified in regarding them as real, and interpreting them, as Goldring and Chasis (1944) interpret a fall in this ratio, as indicating relative ischæmia.

(*c*) $\frac{C_{In}}{T_{mD}}$. The ratio between the glomerular filtration rate and the maximum tubular excretory capacity (mass) expresses the amount of glomerular filtrate per unit of functioning tubular tissue. In so far as the T_{mD} can be taken as measuring the total functioning tubular mass (although it really represents only the tubular capacity for excreting diodone) the ratio may be considered to give a measure of tubular efficiency in relation to glomerular activity.

The identity of the mean figures for the young "controls" and the aged subjects with normal diastolic pressure suggests, on this basis, that the parallel reductions in inulin clearance and T_{mD} indicate a decrease in the functioning mass of tubular tissue. However, since the relation of excretory capacity for diodone to actual mass of tubular tissue is no more than presumptive, it is not possible to draw this conclusion with certainty and to exclude the possibility of a general reduction in efficiency.

More marked changes in the same direction—decrease of tubular mass or efficiency or both—in the aged subjects with high diastolic pressure is shown by the fact that the mean value of ratio C_{In}/T_{mD} in these subjects is actually increased by about 20 per cent. as compared with the young healthy men, an increase which is statistically significant.

Urea Clearance.—The urea clearance is the resultant of glomerular filtration and tubular activity. The latter is usually supposed to consist of re-absorption since the urea clearance is, in general, considerably lower than would be expected from the glomerular filtration rate alone. The normal maximum urea clearance of 75, associated with a normal inulin clearance of 125 would indicate that about 40 per cent. of the filtered urea is reabsorbed. It is, however, possible that tubular activity is never absolutely unidirectional and that in every case the observed re-absorption or excretion (as the case may be) is really the net result of both absorption and excretion. This is supported by the occasional finding of a urea clearance greater than the inulin clearance simultaneously determined, as occurred in five of the subjects we have investigated. All five had low inulin clearance (42 to 76), but three had urea clearance (68 to 79) within the normal range.

It is evident that the interpretation of urea clearance in relation to the separate components of renal function is not easy. We therefore content ourselves with noting that the mean maximum urea clearance was 82·4 for our normal young men, 62·3 for our old men with normal diastolic pressure, and 53·3 for our old people with high diastolic pressure. These group differences were highly significant and of the same order as the differences in inulin and diodone clearances (with which, however, there was not an exact individual correlation).

General Discussion

Many investigators have claimed to have demonstrated impaired renal function in old age but the extent and type of the deficiency has generally been obscure. For one thing, the concentration tests which were widely used probably did not give a true picture even within their limited compass, because most of the subjects were to some extent dehydrated as compared with young people. Further, it is doubtful whether in old age the absence of vascular change is indeed normal. The vast majority of aged subjects have signs, though not necessarily gross signs, of vascular change and it may even be said that the ageing process is characterised by degenerative vascular changes. It is for this reason that we have abstained from grouping our subjects as normal and abnormal but have classified them merely according to the presence or absence of an increased diastolic blood pressure.

The measurements we have made show that the aged have, generally, a diminished blood supply to the kidney (and probably, for the same reasons, to other organs) and that there are quantitative renal functional changes which are the direct consequence of this. The glomeruli of the aged filter the plasma which is supplied to them with the same efficiency as do those of the young; the young glomeruli receive, however, more plasma per minute. Similarly, the excretory function of the tubular epithelium is not impaired until the arterioles are affected by the sclerosing process.

As has been briefly discussed already, it seems that the observed changes in clearance may be ascribed, in the subjects with normal diastolic pressure to increased resistance affecting the afferent renal vessels, and in those with high diastolic pressure to increased resistance involving both the afferent and efferent vessels. This interpretation, which is consistent with the structural changes described by many workers, also agrees with calculations based on Lamport's (1941, 1943) formula for estimating the afferent and efferent arteriolar resistance to the renal blood flow. This formula cannot be regarded as providing entirely new evidence because it is based on considerations of the mean arterial pressure, the plasma volume as a percentage of whole blood, the filtration fraction (C_{In}/C_D) and the renal blood flow; we have already used some of these factors in reaching our conclusions. However, with this proviso, and without discussing the validity of Lamport's assumptions, the results of the calculations shown in Table III may have some interest. Taken at face value, they indicate that, compared with normal young men, the old men with high systolic but normal diastolic pressure have a considerably increased afferent resistance but little or no increased efferent resistance. In the old people (of both sexes) with increased diastolic as well as increased systolic pressure not only is the afferent resistance still further increased but there is a definite and marked increase in the efferent resistance.

TABLE III

Changes in the Resistance to the Afferent and Efferent Renal Blood Flow, calculated by Lamport's Formula.

	Infusion Method.			Single Injection Method.		
	Afferent Resistance.	Efferent Resistance.	Total.	Afferent Resistance.	Efferent Resistance.	Total.
Normal young . .	18·8	18·2	37·0	32·6	11·6	44·2
Aged :—						
(*a*) Normal diastolic pressure	82·1	10·9	93·0	112·5	20·5	133·0
(*b*) High diastolic pressure	160·0	27·0	160·0	194·5	31·3	225·8

Summary

In 50 subjects, over sixty years of age, inulin clearance, diodone clearance, tubular excretory capacity for diodone and urea clearance have been determined.

The subjects were divided into two groups—those with normal diastolic pressure and those with high diastolic pressure.

Compared with healthy young men, the first group showed a mean decrease of about 30 per cent. in diodone clearance, inulin clearance, and tubular excretory capacity, and about 25 per cent. in urea clearance.

The second group, similarly compared, showed a decrease of 50 per cent. of diodone clearance and tubular excretory capacity, 40 per cent. in inulin clearance, and 35 per cent. in urea clearance.

It is suggested that these results signify no impairment of the glomerular filtration capacity, the changes in inulin clearance merely reflecting the changes in renal plasma flow and being associated with the vascular changes indicated by the blood pressure. Tubular excretory capacity shows some actual impairment but whether by decreased efficiency or actual reduction of the mass of functioning tissue cannot be determined.

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