Session II

Chairman Professor Leon I Goldberg

Chairman's Introduction

by Professor L I Goldberg
(*University of Chicago*)

As Professor Schröder is not here, we will begin this session with Professor Schoeppe's paper, and there will be an additional speaker at the end, Professor Rapin.

I want to make one comment about dosage because everyone seems to be misinterpreting what I said. When I talk about a small dose of dopamine, I am talking about congestive heart failure. There I am very much afraid of increasing afterload. In a patient with shock we titrate the dose until the right pressure level is reached, until arrhythmias occur, or until the urine flow decreases. But it is essential that the dose should be titrated. I think one point that Dr Thompson made very clearly was that different patients respond to different doses. This is the same in the dog: some dogs produce vasoconstriction with a very small dose of dopamine, and some need a very large dose. I think that there is biological variability as far as receptors are concerned, and with patients in shock there are all kinds of things that vary: perhaps the muscles are not responding so well. Perhaps we can discuss this later if we have further time, since many people have asked me about this. I did not say that there is any limit on the dose of dopamine. I was merely trying to emphasize that in a patient with congestive heart failure, particularly someone who has had myocardial infarcts in the past, one has to go very slowly in order not to increase the afterload. In shock it is a different situation.

Effects of Dopamine on Kidney Function

by Professor W Schoeppe
(*Department of Internal Medicine, Johann Wolfgang Goethe University, Frankfurt on Main*)

The effects of dopamine on the kidney and various renal functions are well documented in the literature. From experimental and clinical data it can be shown that dopamine dilates the renal arteries within a well defined dosage range and this is followed by an increase in renal blood flow, in urinary volume, and in excretion of sodium and potassium. The glomerular filtration rate is only moderately raised, if at all. In a dosage range above 6.5–7.0 μg/kg per min these effects will be less pronounced, or even reversed. Table 1 shows the changes that take place in the different dosage ranges.

Some of the results on single renal functions in man and the changes during the administration of dopamine are listed in Table 2 for GFR and renal plasma or blood flow.

On the basis of these results, it can be concluded that an increase in renal blood flow in healthy subjects is usually accompanied by an increase in the glomerular filtration rate. Several studies showed increased sodium excretion without any change in the total renal blood flow. Other mechanisms, such as redistribution of intra-renal blood flow or a direct action on the tubular reabsorptive process, have been considered to be responsible for the natriuresis.

In our studies, we were interested in the effects of dopamine in patients with impaired renal function. The group studied comprised 5 male and 6 female patients, aged 16–56 years, with chronic pyelo- or glomerulo-nephritis. Under standard clearance conditions, dopamine was infused at a rate of 2.5–3.5 μg/kg per min. During the collection periods of 20 minutes constant hydration was maintained.

As previously reported in the studies of Orme *et al.* (1973), the glomerular filtration rate increased in all patients with impaired renal function (Table 3), from a mean of 51 to 58 ml/min. After the infusion was stopped, GFR decreased again in 5 patients and increased further in one. The effective

Table 1

Effects of dopamine in different concentrations on renal haemodynamics, volume and cation excretion

	Dosage (μg/kg per min)		
	1.5–6.5 (100–500●)	7.0–14 (500–1000●)	15 (1000●)
Renal vasculature	Dilatation	Dilatation not further increased	Beginning contraction
Renal blood flow	++	+	=−
Cortical	++	+	=−
Medullary	++	++	=
GFR	=−+	=−+	=
Urinary flow	++	+	=−
Sodium excretion	++	+	0
Potassium excretion	(+)	(+)	0
●μg/min			

Table 2

Changes of filtration rate and effective renal plasma flow (renal blood flow during administration of dopamine

GFR (ml/min)				*Effective renal plasma flow (ml/mIn)*			
n	*Control*	*Dopamine*	*P*	*Control*	*Dopamine*	*P*	*Author*
7	109	136		507	798		McDonald *et al.* (1964)
6	102±4	108±13	–	782±102	1161±210	<0.005	Ramdohr *et al.* (1972)
20	100±30.6	138±62.5	<0.005	676±267	1209±691	<0.001	Rosenblum *et al.* (1972)
8	31.2±20.2	42.8±26.8	<0.01	129.8±115.4	173.1±164.3	<0.05	Orme *et al.* (1973)
7	30.8±9	41.8±11	–	160.9	265		Ramdohr *et al.* (1973)
10	114±23	105±23	–	459±116	680±290	<0.02	Abrahamsen *et al.* (1974)
11	110±25	112±41	<0.45	600±137	840±370	<0.025	Jax *et al.* (1975)
15	75±17	92±18	<0.05	360±111	542±133	<0.001	Nadjmabadi *et al.* (1975)
11	51±30	58±34	<0.05	211±109	278±158	<0.0025	Vlachoyannis *et al.* (1976)

renal plasma flow rose significantly from 211 ±109 to 278 +158 ml/kg per min during dopamine infusion. The filtration fraction showed a slight reduction from 24 to 22%. The excretion of sodium and potassium was also significantly different from the pre-infusion period. Sodium clearance increased from 1.4±0.8 to 3.4±3.8 ml/min, and sodium excretion changed from 203±413 mol/l per min to 503±309, and was thus more than doubled. The potassium clearance rose moderately from 11.6±4.0 to 15.7±5.3 ml/min. There was a marked increase in urine volume from a control value of 2.0±1.2 ml/min to 6.0±4.4 ml/min. The tubular rejection fraction of sodium rose from 3.2±2.1% before dopamine to 5.8±2.8%.

During dopamine treatment, plasma cyclic AMP concentration rose from 26.5±7.4 nmol/l to 30.4±9.2 nmol, a difference which was statistically significant. Total cyclic AMP excretion also increased significantly during dopamine infusion. This increase could be related to the renal excretion of plasma cyclic AMP as well as to the component of renal origin (nephrogenic fraction). The increments in the fractions were from 1.2 to 1.6 nmol/min, or 36%, for the renal excretory elimination and from 2.0 to 3.0 nmol/min, or 47%, for the nephrogenic component.

Table 3

Effects of dopamine in patients with impaired renal function

	Control	*Dopamine*	*P*
C_{In}●	51±30■	58±34	<0.05
C_{PAH}●	211±109	278±158	<0.0025
C_{osm}●	2.3±0.9	4.4±1.9	<0.0025
C_{H_2O}●	−0.25±0.7	+1.66±2.5	n.s.
V●	2.0±1.2	6.0±4.4	<0.01
FF(%)	24±6	22±7	<0.05
C_{Na}●	1.4±0.8	3.4±1.8	<0.0025
U Na V (μval/min)	203±113	503±309	<0.0025
Tr_{Na}(%)	3.2±2.1	5.8±2.8	<0.0025
CK●	11.6±4.0	15.7±5.3	<0.0025

●ml min^{-1} 1.73m^2
■mean ± s.d.

These studies show that intravenous administration of dopamine at doses of 2.5–3.5 μg/kg per min produces effects on renal function in patients with renal disease qualitatively comparable to those seen in healthy subjects. We found a simultaneous rise of cyclic AMP concentration in plasma and urine. We observed an increase in renal blood flow, exceeding that of GFR, but less

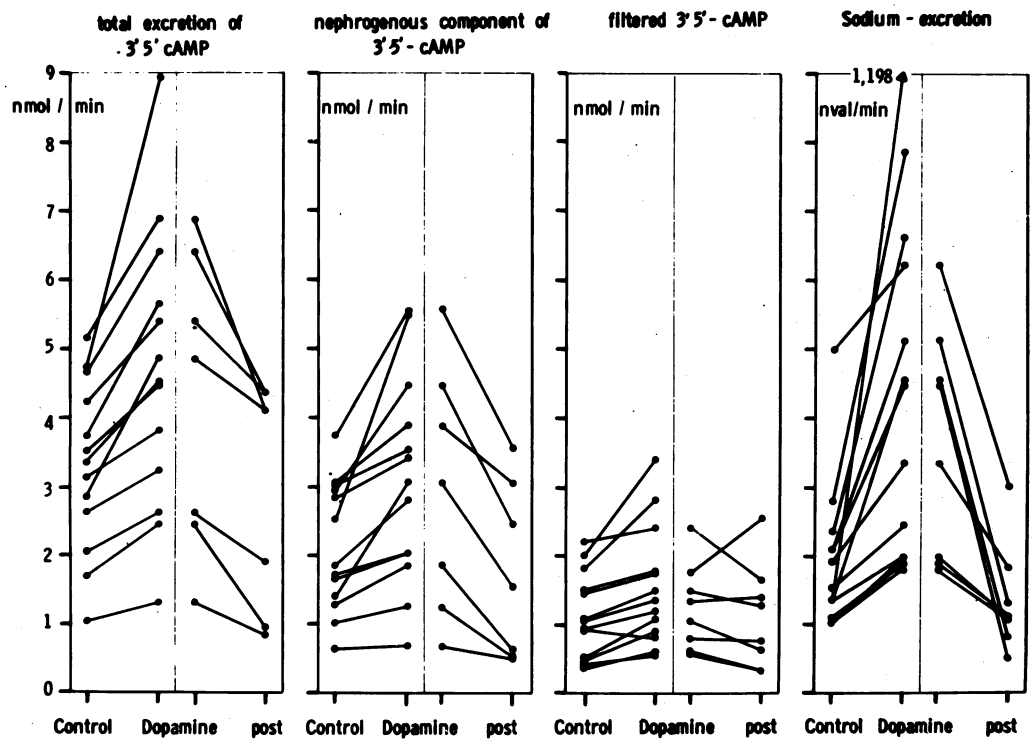

Fig 1 *Change in cyclic AMP and sodium excretion produced by dopamine 2.5–3.5 μg/kg per min*

than that described in healthy persons. In agreement with others, sodium excretion showed a marked increase of 179%. In healthy subjects, McDonald *et al.* (1964) describe an increase in sodium excretion of 234%. The mechanism of natriuresis during dopamine treatment has been widely discussed by many investigators. Evidence has been presented that dopamine has a direct tubular effect. Others suggested that intrarenal vascular changes are responsible. Our results show an increased activity of the adenylate-cyclase-cyclic AMP system during the dopamine infusion, demonstrated by the increased plasma concentration and total urinary excretion of cyclic AMP. It seems possible that the increased nucleotide concentration in plasma is caused by the effects of dopamine in different organs mediated via ß-receptors. The increased cyclic AMP excretion is, however, not due merely to the higher load of filtered nucleotide with subsequent renal excretion, but also to an increase of the nephrogenous component (Fig 1). This is an indication of activated adenylate cyclase in the tubular cells.

In these experiments, there was a positive correlation between sodium rejection and percentage increase of the nephrogenous component of excreted cyclic AMP (Fig 2). Vasodilation in the kidney and natriuresis are the most striking effects of dopamine on renal function. The natriuresis is independent of the tubular load. Sodium rejection increases from all control levels, although the response seems less pronounced in advanced renal failure.

Smaller sodium reabsorptive rates have been thought either to be due to a direct tubular effect of dopamine or to be a consequence of a hæmodynamic redistribution process in renal blood flow. According to this hypothesis, medullary blood flow would increase absolutely (as cortical flow), but relatively more than the blood flow in the cortex. According to the work of Early & Friedler (1966), increased medullary blood flow results in a reduced tonicity of the renal medulla. Flow rates within the tubular system increase especially in the loop of Henle, leading to an overall reduction of sodium reabsorption in the ascending limb. On the other hand, reduced tonicity in the medulla results in the formation of a hypotonic urine. Tonicity of urine therefore decreases together with an increase of sodium excretion.

It has also been shown by several investigators that these postulated changes in distribution of renal blood flow do take place when dopamine is given. The data of Augustin *et al.* (1975) confirm those of Hollenberg *et al.* (1973) and Breckenridge

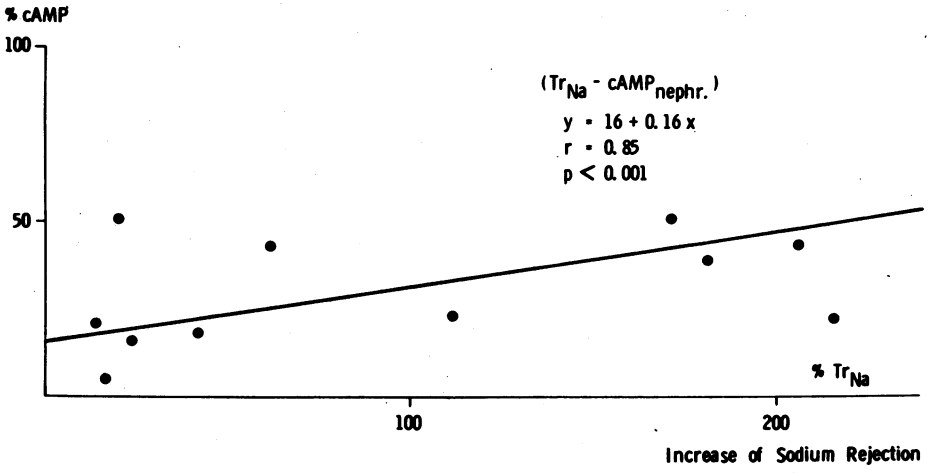

Fig 2 *Correlation between sodium rejection and the increase of the nephrogenous component of excreted cAMP*

et al. (1971). Dopamine causes an increase of total renal blood flow with relative changes of the different fractions in favour of a more than proportional increase of medullary blood flow. This is a dose-dependent effect. Within the range up to 8 μg/kg per min, sodium excretion rises with increments in medullary blood flow. Brotzu (1970) described a similar dissociation when chlorpromazine antagonized dopamine-induced vasodilation.

Our results of an increased excretion of nephrogenous cyclic AMP also indicate that natriuresis is not only flow-dependent. Augustin *et al.* (1975) found significantly higher cyclic AMP concentrations in the renal medulla after dopamine, an observation which seems to be consistent with the idea that sodium excretion is regulated predominantly in this area. It has been assumed that dopamine-specific receptors are also predominantly localized there. Whether it is stimulation of the adenyl-cyclase cyclic AMP system at the receptor sites in the blood vessel, with subsequent AMP effect on sodium reabsorption, or a direct tubular effect of dopamine which causes the fall in sodium reabsorption remains to be elucidated. A concomitant anti-ADH effect cannot be excluded although this would not explain the increase in cyclic AMP excretion.

From the clinical point of view, the observations on dopamine effects in the kidney deserve some comment, irrespective of the basic mechanisms eliciting changes in blood flow or sodium excretion, the changes are interpreted as positive. However, we still do not know how these may be modified by disease. This is illustrated in Table 4.

The group of patients was divided into those with a GFR above and those with GFR below 60 ml/min. There are differences in the activation of adenyl-cyclase cyclic AMP system and also in the effects on sodium excretion. A striking difference can be found in the formation of osmotically free water. It has been reported that the effect of dopamine in hypertensive patients differs from that in normotensive subjects. Cortical compartment I fraction was measured in the series of Augustin *et al.* (1975), using the ^{133}Xe washout technique. The result of hypertensives was 75%, much lower than the 89% fraction in normal subjects. Similar results have been published by Breckenridge *et al.* (1971) and Hollenberg *et al.* (1973). Higher resistance in cortical vessels may account for this difference.

Dopamine exerts a more pronounced effect in raising cortical blood flow, as long as increased vascular resistance is of functional origin. In cases with morphological changes in the vessels (r. phro-

Table 4

Mean values of 2 patient groups with moderately and severely impaired renal function defined by GFR (C_{In}). Dopamine effects are listed for changes in urine volume, cAMP excretion, tubular rejection fraction of sodium and free water clearance

	Group 1	*Group 2*
n	6	5
C_{In} (ml min^{-1}) 1.73m^{-2}	75	21
Urine flow (ml min^{-1})	2.24	1.75
Dopamine effects:		
Urine flow (ml min^{-1})	8.47	3.05
Excretion cAMP nephrogenic (nmol min^{-1})	3.89	1.86
cAMP nephrogenic/ml/GFR	0.05	0.08
Δ % of control	+68	+21
Tubular rejection of Na (% of filtered load)	5.6	6.04
Δ % of control	196	51
C_{H_2O} ml/min^{-1}	+2.9	+0.14

sclerosis) Hollenberg *et al.* (1973) reported an inverse relationship between the initial vascular resistance and the renal vasodilator response to dopamine. By analogy, the pathophysiological mechanisms of impending acute renal failure with vasoconstriction in the cortex and increase in PRA may be regarded as an indication for the therapeutic use of dopamine. Oliguric states of prerenal acute renal failure may frequently prove reversible. Advanced states of tubular necrosis, of course, can never be reversed by an attempt to increase renal blood flow pharmacologically.

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DISCUSSION

Professor Goldberg (*Chairman*): May I ask a question? The cyclic AMP changes were very interesting. Have you studied the effects of other drugs such as isoproterenol on cyclic AMP, or is this specifically a dopamine phenomenon?

Professor Schoeppe: No, we have not studied this with isoproterenol, so I cannot comment.

Professor Goldberg: We tried dopamine in acute tubular necrosis and were rather disappointed. To me this is a most difficult situation, because many patients will diurese with no treatment after a certain period of time. The question I have is whether you are willing to use dopamine in a situation that might clear up on its own? Let us say a patient comes in with acute tubular necrosis, reason unknown, oliguric, or anuric: would you be willing to try dopamine, or what do you use for therapy in such cases?

Professor Schoeppe: We generally use dopamine now. Of course, you have to exclude the intrarenal acute tubular necrosis, such as may be caused by poisoning. Especially where the renal failure is due to shock, or even a state of low blood pressure over a longer period – for instance, in surgical procedures – a reduction of urine flow is an alarming warning of impending renal failure. In such cases we use dopamine all the time, and we prefer it even to the use of osmotic diuretics and furosemide.

However, I have to stress the point that this is a problem of careful clinical control, and keeping close watch on the concentrations used. We would not dare to go higher than this 20 μg/kg. If after some hours there is no effect, then stop it and dialyse. This is much better. But as an attempt to see whether the renal vessels react, I would always prefer to use dopamine.

Dr D J Robson (*London*): Our own experience in using dopamine in oliguria following surgical shock has been disappointing. We have in general not employed it until we have had a reasonably stable circulation, with a mean blood pressure of 80, and in general a situation where we felt that we ought to be getting urine and were not. Then we have added dopamine to therapy and have, in fact, been disappointed.

What I should like to ask is, what are we doing wrong? Or have other people the same disappointing experience in this particular situation? We have not been convinced that, in this admittedly difficult and complicated situation, we have managed to produce urine with dopamine when we were not getting it otherwise.

Professor Schoeppe: I can only repeat what I have said: we are not disappointed at all, but I think it is a problem of philosophy. If a diagnosis of acute renal failure is made, we must try to recognize those patients who are oliguric after events which might lead to renal failure and the need for dialysis. Of course, there will be no success – I think we are agreed on that – if anuria is already present, and has been for some time. In general dopamine cannot work in this situation. This does not exclude its use as a pilot study to see how far the patient's condition has already progressed. I do not know when you get your patients. We are often lucky in that we are confronted with the problem early, while the patients are still excreting, while they have some urine flow. However, all the data suggest that, if you do not use a therapeutic procedure like this, you will end up having to dialyse the patient.

We used to use furosemide and osmotic diuretics, and we have now compared these results with those obtained in about 40 patients on dopamine. This is not a controlled trial, of course, but so far we have had success in about one-third more of the patients on dopamine than with those on furosemide or osmotic diuretics only.

However, I have to stress that this refers to an early stage of acute renal failure. It may be you do not call this acute renal failure, but histology in some cases does show dilated tubules.

Dr J Zaroslinski (*Chicago*): I think that the period of time which elapses between onset of symptoms and treatment with dopamine is very important. We found in an analysis of survivors and non-survivors that the time between onset of shock and initiation of treatment was critical. If treatment with dopamine were initiated within four hours or less of onset of symptoms, survival of the shock episode was approximately 47%, but if it was delayed beyond 16 hours, the survival was rather low and disappointing – perhaps 17%. So I think that, as a general rule, the longer you wait the less apt you are to obtain a satisfactory therapeutic response.

Professor Dollery (*London*): I wonder if I can ask a question of Dr Schoeppe or, if he cannot answer it, anyone else who can. That is whether there is virtue in combining treatment with dopamine and with saralasin or other angiotensin 2 antagonists in patients with acute tubular necrosis. As you will know, some of the people who are interested in the intrarenal role of renin believe that this may play a part in tubular necrosis. Therefore, if it does – and I am not sure that it does, but some of the arguments seem quite reasonable – then the two agents together might have more effect than either one alone.

Professor Schoeppe: We have no experience with the combination of dopamine and saralasin, but I am reluctant to combine them because we do not see very much increase of renin in these cases. There are reports about an increase of renin, but whether it works intrarenally nobody knows, and in our series the extrarenal concentrations were not so impressive as some reports say. In this series we had no change at all, but this does not answer your question on acute failure.

Professor Goldberg: Has anyone had experience with those two drugs?

Dr W L Thompson (*Cleveland, Ohio*): In dogs the combination of dopamine and saralasin is remarkably effective in antagonizing at least one type of renal vasoconstriction. Amphotericin B, 2.5 μg/kg given over 20 minutes intravenously, causes a profound reduction of renal blood flow, glomerular filtration rate, and urine flow in barbiturate-anæsthetized dogs.

Dopamine alone partly antagonizes the renal vasoconstriction, but it maintains glomerular filtration to a lesser extent. Saralasin alone has even less effect. Given together, however, dopamine and saralasin antagonize the renal vasoconstricting effects of amphotericin B, and maintain renal blood flow, glomerular filtration, and urine flow at control levels. We are continuing these studies to define the mechanism of this action in dogs and patients.

I should like to compliment Dr Schoeppe on his paper and ask him about his last figure in which he showed, in the patients who had a relatively high GFR, 60 ml/min and more, that after dopamine there was an increase in free water clearance of more than 2 ml/min, and I think the total urine flow would be around 8 ml/min in those patients. Those patients must have been water loaded. Were they given furosemide by any chance?

Professor Schoeppe: No, no furosemide.

Dr Thompson: But they were water loaded?

Professor Schoeppe: They were water loaded.

Dr Thompson: Have you made observations in patients who were not water loaded? Because I am not sure that answers the question about ADH antagonism.

Professor Schoeppe: No, not yet. We are doing this at the moment.

Dr Thompson: It is difficult to know if the 60% of patients who were anuric during therapy with

noradrenaline or isoprenaline and who then made urine during dopamine were spared lasting renal damage. In dogs the postischæmic kidney is perfused better with dopamine, in contrast to the opposite effect of furosemide, but we have been unable to study renal perfusion and glomerular filtration in anuric patients.

There is another effect of dopamine that is quite prominent, and that is potentiation of the diuretic action of furosemide in patients who are hypoperfused. We have studied patients with glomerular filtration rates of less than 10 ml/min in the presence of severe liver failure (often with coma) or chronic renal failure. Such patients are often refractory to large doses of furosemide (1000 to 3000 mg/24 hours intravenously). In many such patients small doses of dopamine (2 to 10 μg/kg per min) have produced a massive diuresis in combination with furosemide when neither drug alone was effective. We believe that there is a critical level of glomerular filtration and tubular perfusion for the effect of the loop diuretics, and that augmenting renal perfusion by the dopaminergic action (in doses that have little effect on heart rate or mean arterial pressure) may move the patient over a threshold and facilitate the diuretic effects.

There are two important points I wish to stress. First, I do not believe these data prove protection from or reversal of acute renal failure. Second, I do not think diuresis is an important aspect of the treatment of chronic renal failure except for short-term management of fluid and electrolyte imbalance.

Professor Goldberg: There is one paper by Metalle in the literature which showed that patients who were oliguric for a number of reasons did not respond to mannitol, did not respond to dopamine, and did not respond to furosemide, but did respond to all three drugs together. However, like you, I have never known whether it is beneficial for a patient to have urine or not. It always makes me feel better when my patient is having a urine flow and I think nephrologists prefer it.

Dr Dollery and I have had experience of infusing acetylcholine directly into the renal artery of patients with BUNs of about 200 with end-stage renal failure, and finding a doubling of renal blood flow. The question is, where is the blood going? I think that this is something we are going to have to learn, particularly in the non-shock situation. I think it is probably better if we can avoid the kind of study where they clamp one renal artery for a certain period of time, and afterwards find that this kidney seems to respond better to mannitol. I think that we need more data to determine whether, in fact, this treatment prevents renal failure.

Do you have any feeling about this, that with urine flow the patient is less likely to have renal failure than if he is anuric?

Professor Schoeppe: Yes, of course. I think that this is, as I said, a difference in philosophy. When do we speak of renal failure? One observation on which I agree with Dr Thompson is that we see a striking difference in the potentiation of dopamine by furosemide given beforehand. This is certainly true in patients with liver disease. When they are in a state in which they no longer put out urine in the necessary volume the increase brought about by dopamine is striking.

I have not made any such observations of potentiation on the shock patients. I do not see an increase whether furosemide is given or not. Perhaps there is a difference in the ADH, which is certainly different in the liver patients. I think that it has to do with the ADH, but we have not measured it.