LETTERS TO THE EDITOR

Re: The Exercise Renogram. A New Approach Documents Renal Involvement in Systemic Hypertension

The work reported by Clorius and Schmidlin appears to have great significance for the diagnosis of renal disease in hypertensive patients (*1*). However, there are serious problems in the data that do not support their conclusions. They state that the hippurate renogram of normal volunteers was not affected by standing or exercise. Very little quantitative data are given to support this conclusion. In fact, their Fig. 3 shows the renograms of one 29-yr-old volunteer, and it is supposed to show no change between studies done in the prone position, standing, or during exercise. Simple inspection of the curves and images in this figure shows an obvious flattening of the third phase of the renogram during exercise and a delay in appearance of the tracer in the urinary bladder.

Their control of exercise seems inadequate, since they state that ergometric resistance was adjusted to the wishes of the patients and that the heart rate had increased at least 20 beats per min. There are no data indicating whether exercise was comparable in each of their groups.

Furthermore, they state that "antihypertensive therapy was noted," but made no note of such therapy in their report. They admit they did not document which drugs were being given to the patients. This is a very important point, because antihypertensive drugs can have marked effects on renal blood flow, either increasing or decreasing it. Alterations in renal blood flow are most likely the explanation for their results. It has been known for many years that marked sympathetic stimulation, e.g., during severe exercise, can decrease renal blood flow almost to zero (*2*). Since hippurate clearance provides a good estimate of renal plasma flow, one would expect abnormalities in the renogram even in normal individuals during exercise (*2*). Standing, exercise, anesthesia, decreased cardiac output, etc., all evoke renal vasoconstriction and decreased renal blood flow, and thus would be expected to reduce hippurate clearance (*3*).

The authors make the astonishing statement that exercise renography is a powerful new tool to study transient tubular dysfunction in the kidney. Most likely the changes they observed were related to changes in renal blood flow, as they later discuss in their paper. Renal blood flow in the normal individual is known to vary greatly from 10% to 30% of the cardiac output, and is different even in the same individual at different times (*2*).

Another problem with the data of Clorius and Schmidlin is that there appears to be a relationship to the ages of the patients, so that abnormal renograms were found in patients with an average age of 44.5. Those hypertensives with normal renograms had an average age of 40.8, and their normal controls averaged 35.9. It is common knowledge that renal function diminishes with age.

One would be well advised to avoid using the exercise renogram as a test for renal dysfunction in systemic hypertension until much more work has been accomplished. The authors' results suggest that renal dysfunction or renal blood flow may be altered by exercise in some hypertensive patients more than in normotensive subjects, but their data are far from convincing. More accurate quantitative measurements of hippurate excretion and renal blood flow must be obtained.

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Reply

We believe that the data we presented support the conclusions drawn (*1*). We felt justified to suggest: (a) that exercise renography appears to be a powerful new approach to study transient tubular dysfunction of the kidney; (b) that initial results with the exercise renogram suggest renal involvement in essential hypertension; and (c) that our results may help to explain the contradictory reports on the value of renography in evaluating patients with hypertension.

The lack of quantitative data is criticized. Clearance examinations would have been most helpful and would have given us the opportunity to assess the extent of the perfusion abnormality. However, the results of clearance examinations, or of computer-generated numerical data, are not needed to demonstrate the existence of the phenomenon itself. The appearance of tracer in the bladder offers an acceptable estimate for the tissue transit time of the tracer, barring obstruction or dehydration (*2*). The parenchymal tracer retention will also permit the demonstration of a hippurate transport disturbance.

We do not agree with Dr. Shreiner that our normals demonstrated exercise-mediated shifts in hippurate transport. I assume, of course, that posture- or exercise-induced change refers to alterations that progress from normal to abnormal. The reproduction of the sequential images, shown in Fig. 3 of our paper, may have caused confusion. The reproduced images do not clearly show tracer in the bladder in the 4th minute during the exercise examination. The tracer appearance in the bladder was not delayed, and was unchanged between the prone and standing examinations. We also believe that most nuclear medicine specialists would classify the three renograms of Fig. 3 as normal.

We have carried out a computer classification of the renograms using discriminant analysis. This evaluation has shown that the computer classified practically all renograms in agreement with the previous evaluation.

The adequacy of our control of exercise is questioned. We tried to avoid the pitfalls of selection, and chose to examine all patients referred for evaluation of hypertension if they were hypertensive at the time of presentation. We thus adjusted exercise to achieve

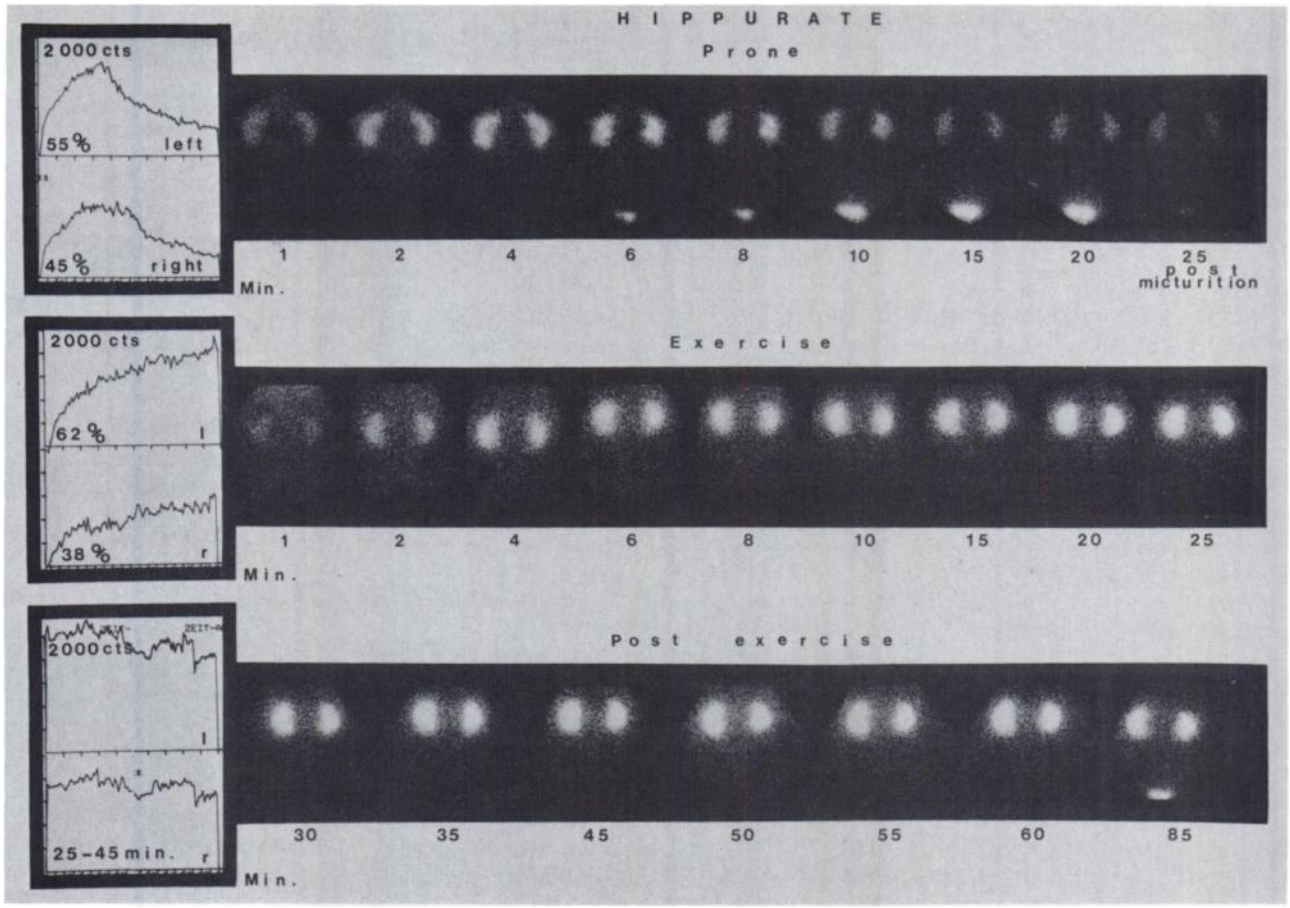

FIG. 1. Renograms and sequential scintigrams of 48-yr-old hypertensive patient, examined both in prone position and during exercise. Sequence of examinations shows that exercise can initiate pronounced changes of tracer kinetics. Underlying vascular response appears inappropriate relative to stimulus. Prone examination demonstrated that left kidney contributed 55%, right kidney 45% of total function. Parenchymal tracer transport was slightly delayed. Exercise initiated massive disturbance of tracer kinetics. Note tissue retention of tracer and its lack of excretion into bladder during 20-min examination. Extended observation period demonstrated that tracer excretion into bladder had failed to occur at 60 min–40 min after termination of exercise. Late image at 85 min identified radiohippurate in bladder. Lower time-activity curves contain artifacts due to movement from one foot to other.

a similar response in pulse rate. The mean pulse-rate data observed in each group during prone, standing, and exercise renography were presented, and were shown to be similar for normals and hypertensives.

Antihypertensive therapy has been noted. The results have not been evaluated. At this time we have no evidence that antihypertensive drugs, or drug combinations, can effectively provoke or eliminate the positive exercise renogram.

While Dr. Shreiner agreed with us that the observed disturbance of hippurate transport is probably the result of altered blood flow, he questioned the postulated cause-effect relationship that we presented. Dr. Shreiner, citing Guyton, pointed out that very strong sympathetic stimulation can result in reduced glomerular blood flow and pressure, so "that the urinary output can fall to zero for as long as 5 to 10 min" (*3*). As was noted, four patients demonstrated such prominent delay in the tracer's tissue transit that no excretion was seen during the 20-min examination. Thus 14% of our exercise positives demonstrated a far more pronounced response than that described by Guyton. On the other hand, our patients and controls remained comfortable during exercise. We therefore have no reason to suspect very strong sympathetic stimulation in our patients. Moreover, we failed to observe delay, or cessation, of urine flow in the control group. We are observing a vascular response in hypertension that is inappropriate for the exercise stimulus and could not be demonstrated in normals.

I believe that Dr. Shreiner partly misunderstood us. We do not claim to have rediscovered autoregulation of renal blood flow. Anxiety, standing, anesthesia, exercise, and anoxia can cause renal vasoconstriction (*4*), and we know this. The physiologic vasoconstriction due to anxiety, standing, or exercise is not intensive enough to result in highly pathologic renograms. Again we would like to point out that our controls failed to show the renographic changes seen in the hypertensive population (Fig. 1). Furthermore it should be remembered that we demonstrated bilateral renal dysfunction in two hypertensive populations when we examined patients in the standing position (*1*,*5*). The perfusion abnormality appears, once more, to be excessive with respect to any probable sympathetic stimulation. We therefore do not agree with Dr. Shreiner that one would expect the demonstrated types of renographic abnormalities in normals during exercise; indeed we failed to observe it. One need only consider the result of inappropriate arteriolar constriction on the function of the loop of Henle, and on the inner medulla, to conclude that standing or light work must never cause perfusion alterations that result in exercise-positive, highly pathologic renograms. We expect partial clarification from GFR and ERPF measurements at rest and during exercise.

Dr. Shreiner points out that renal blood flow varies from 10% to 30% of cardiac output. This only demonstrates the importance

of adequate autoregulation in the normal kidney. GFR should not be altered by 30% in normals! Please note that the physiologic decrease in GFR and ERPF due to age cannot be used to explain the results of our study. The expected mean age-dependent difference in GFR between each of the three groups would be 4 ml/min. The ERPF would differ by about 25 ml between each group (*6*). Lastly, age is not known to cause the described swings in renal blood flow.

At this time we remain excited about the use of the renogram in hypertension. We do not know enough about the observed hippurate transport disturbance and the postulated vascular responses to recommend the procedure for routine patient evaluation. We are convinced, however, that the conclusions drawn from our study were justified. We believe that research-oriented nuclear medicine specialists should re-evaluate the gamma-camera radiorenogram in the patient with hypertension.

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Unexpected Breast Uptake of Tc-99m PIPIDA

A 21-yr-old man was admitted to the hospital after sustaining an abdominal stab wound. Significant medical history revealed that he was a transvestite and was taking a large but undisclosed quantity of conjugated estrogens. Physical examination, apart from the obvious abdominal trauma, revealed marked breast-tissue development bilaterally with no evidence of surgical implants, inflammation, or trauma. At laparotomy the liver and the head of the pancreas were found lacerated. During the immediate postoperative period, the patient became febrile and his serum bilirubin became elevated to 5-6 mg/dl (normal, 0.2-1.2). In addition there was a fall in the hematocrit to 19% requiring multiple blood transfusions.

Hepatobiliary scintigraphy, after injection with 7 mCi of Tc-99m-tagged *p*-isopropyl iminodiacetic acid (PIPIDA), was done with a large-field-of-view camera. This demonstrated bowel activity by 10 min, but no visualization of the gallbladder within 3 hr. Of note was the unexpected and persistent localization of the radiopharmaceutical in both breasts (Fig. 1).

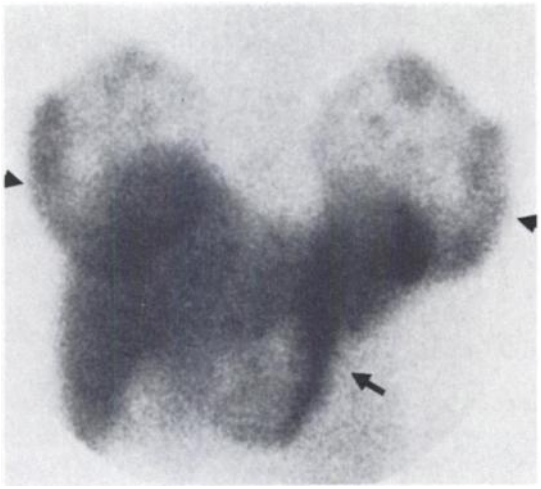

FIG. 1. Hepatobiliary scintigram, 3 hr after injection of 7 mCi of Tc-99m PIPIDA, demonstrating tracer uptake in both breasts (top arrows). Bottom arrow points to loop of displaced bowel secondary to prior surgery.

Celiac angiography revealed a faint blush in the area of the superior pancreaticoduodenal artery, suggesting a pseudoaneurysm. A second abdominal surgical exploration demonstrated a fistula between the superior pancreaticoduodenal artery and the common bile duct. Intraoperatively there was no evidence of acute cholecystitis. The remaining hospital course was complicated by the development of serum hepatitis, with eventual recovery.

This is an unusual report of breast localization of a Tc-99m-labeled N-substituted iminodiacetic acid (IDA) as an incidental finding during hepatobiliary scintigraphy. The mechanism of this breast uptake of Tc-99m PIPIDA is unknown, but it is probably related to exogenous hormonal stimulation. Potential mechanisms, singly or in combination, for uptake of Tc-99m PIPIDA in the hormonally stimulated (male) breast include:

1. Coincidental affinity of breast hormone receptors for the agent.
2. Lipophilicity of the agent.
3. Alterations of the radiopharmaceutical by in vivo ligand-exchange reactions (perhaps estrogen-influenced).
4. Presence of radiopharmaceutical impurities not detected by routine chromatography.
5. IDA chelating (possibly associated with increased lactoferrin present in stimulated breast tissue) (*1*).

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