indicated that the anticomplementary property arose only after heating in some cases, but that it may be present in some "active" sera. Our results are in agreement with the former concept, but in general have indicated an additive complementary effect with "active" sera rather than any antagonism or synergism. Finally, the finding of Ishizaka *et al*(10) that heat-aggregated gamma globulin fixes complement in the same manner as antigen-antibody complexes suggests that anticomplementary sera act similarly.

On the other hand, serum lacking in detectable C′ activity need not be anticomplementary when heated (Table V). Thus, one can dissociate low C′ levels from anticomplementary activity. The reasons for the decline in C′ levels in systemic lupus erythematosus and glomerulonephritis is not known, but may include *in vivo* fixation, decreased production, increased breakdown or loss, or presence of an inhibitor(11). The lack of anticomplementary activity of sera with low levels of C′ may be presumed to exclude the presence of an inhibitor in these sera. Such an inhibitor, however, might be bound to one or more of the C′ components and unavailable for reactivity with exogenous C′.

Conclusion. The probit transformation for the plotting of immune hemolysis produced by measured amounts of fresh human serum was found to be suitable for titration of complement. Serum from a patient with a high level of C′ activity was found to become highly anticomplementary when heated to 56°C for 30 minutes, but inactivation by heating for 30 minutes at 52°C or below produced little anticomplementary activity in this serum. Addition of an equal quantity of 9% bovine serum albumin prior to heating also prevented the expression of the anticomplementary activity. Ability of serum to become highly anticomplementary as a result of heating is not necessarily associated with diminished activity of its endogenous complement. Conversely, sera with low levels of C′ may not become anticomplementary as a result of heating.

1. Davis, B. D., Kabat, E. A., Harris, A., Moore, D. H., *J. Immunol.,* 1944, v49, 223.

2. Kellett, C. E., *Lancet,* 1936, v2, 1262.

3. Ellis, H. A., Felix-Davies, D., *Ann. Rheum. Dis.,* 1959, v18, 215.

4. Silverstein, A. M., *Blood,* 1960, v16, 1338.

5. Laurell, A. B., Nilssson, U., *Acta Path. et Microbiol. Scand.,* 1963, v59, 79.

6. Kent, J. F., Fife, E. H., *Am. J. Trop. Med. and Hyg.,* 1963, v12, 103.

7. Muschel, L. H., *Am. J. Clin. Path.,* 1957, v27, 453.

8. Fisher, R. A., Yates, F., *Statistical Tables for Biological Agricultural and Medical Research,* Hafner Pub. Co., Inc., 1957, 64.

9. Norgaard, O., *Acta Path. et Microbiol. Scand.,* 1950, v27, 811.

10. Ishizaka, T., Ishizaka, K., Borsos, T., *J. Immunol.,* 1961, v87, 433.

11. Kabat, E. A., Mayer, M. M., *Experimental Immunochemistry,* Chas. C Thomas, Publisher, 1961, 235.

Received June 19, 1964. P.S.E.B.M., 1964, v117.

Comparison of Measurements of Renal Function by an External Monitoring Technique and Renal Clearances. (29562)

JEROME B. BLOCK, RICHARD E. RIESELBACH, CARL J. BENTZEL AND DAVID P. RALL
Clinical Pharmacology and Experimental Therapeutics Service, Medicine Branch, and the Radiation Branch, National Cancer Institute, N.I.H., Bethesda, Md.

Recently there has been increasing use of I^{131}-labelled organic acids for evaluating renal function by external counting techniques (1-7). Clinical evidence of renal disease appears to correlate qualitatively with tracings obtained by monitoring over the renal areas following injection of I^{131}-iodohippurate. However, no studies have attempted to correlate quantitative data obtained by external monitoring with glomerular filtration rate or renal plasma flow measured by conventional clearance techniques.

In this report the relationship of the rate of renal uptake of I^{131}-labelled iodohippurate to renal clearance of inulin and para-amino hippurate was studied in patients with normal renal function and patients with renal insufficiency.

Material and methods. Renal function studies were performed on 18 patients with acute leukemia, chronic myelogenous leukemia, myeloma, or miscellaneous solid tumors. None of these patients had detectable unilateral renal disease. In each study measurements of glomerular filtration rate and renal plasma flow were determined by standard clearance methods employing C^{14}-labelled inulin(8) and sodium para-amino hippurate (PAH)(9). Studies were performed in the fasting state and under conditions of maintained water diuresis. Urine was obtained through an indwelling urinary bladder catheter and clearance periods were terminated with injection of air to insure complete bladder emptying. A constant infusion pump was employed in all clearances, and study periods varied from 10-20 minutes. Venous blood was sampled mid-way through each clearance period. Plasma PAH levels from 1.5-3.0 mg% were achieved in those studies. Clearance values used in this report represent the mean value of at least 3 consecutive clearance periods.

Thirteen patients were studied by means of an external monitoring technique 24 to 96 hours following standard inulin and PAH clearance studies. The external monitoring technique has previously been described, employing I^{131}-labelled iodopyracet(3,10); however, in the present study 0.3 μc per kilogram of I^{131}-labelled iodohippurate* was injected as the tagged compound. No additional "carrier" compound was employed in these patients. None of these patients demonstrated clinical or laboratory evidence of changes in renal function in the period intervening between renal function measurements by clearance techniques and the external monitory studies nor had changes in chemotherapy been instituted.

Following intravenous administration of I^{131}-iodohippurate, renal radioactivity was monitored by 2 NaI (Th) crystal scintillation detectors† placed over the renal areas. Separate count rate meters, employing direct writing recorders, graphed changes in renal radioactivity with time. The tracings obtained were manually replotted on semilogarithm paper and a rate of renal uptake of I^{131}-labelled iodohippurate (T 1/2) was derived as previously described(3,10).

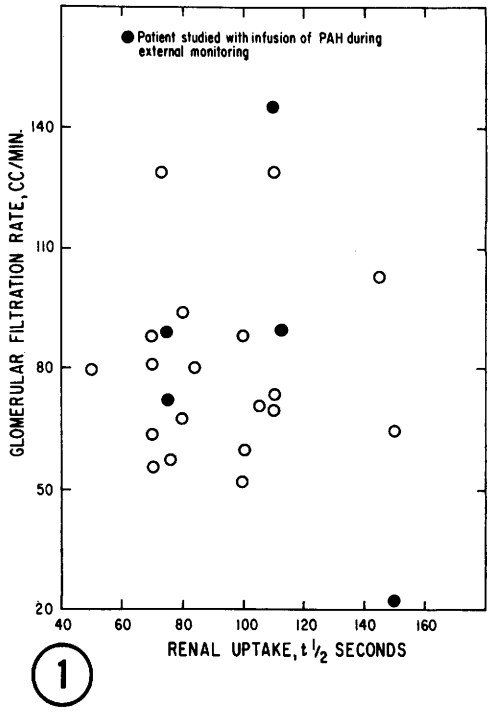
Five other patients were studied immediately following clearance measurements. In these patients, to insure persistent levels of I^{131} iodohippurate, an intravenous infusion of para-aminohippurate (10 to 15 mg/min) was maintained during the studies with the labelled compound.

Results. As may be seen in Fig. 1 and 2 and in Table I, no correlation was apparent between the derived T 1/2 renal uptake rate of I^{131}-labelled iodohippurate and measurements of either the renal blood flow ($r = .001$) or glomerular filtration rate ($r = -.07$). No improvement in correlation was apparent in the patients where I^{131}-hippurate studies were performed during an infusion of PAH (Table I). In several patients studied sequentially for several months, alterations in renal function were noted by clearance techniques but were not detected by the external monitoring method (Table I, patients C.W., J.R., P.K. and W.H.).

Discussion. I^{131}-labelled iodopyracet, administered with a small "carrier" dose of the stable compound had been found useful in detecting unilateral renal functional impairment(3); I^{131}-labelled iodohippurate, administered alone, is now generally used for external monitoring studies because of minimal hepatic uptake of para-amino hippurate and fewer hypersensitivity reactions(1-7). Similar tracings of renal radioactivity are obtained with either method(11), and the techniques have gained considerable support as a screening procedure largely for detection of

* Obtained from Squibb Laboratories, New Brunswick, N. J. All studies performed within one week of shipment.

† Nuclear-Chicago Corp., Chicago, Ill.



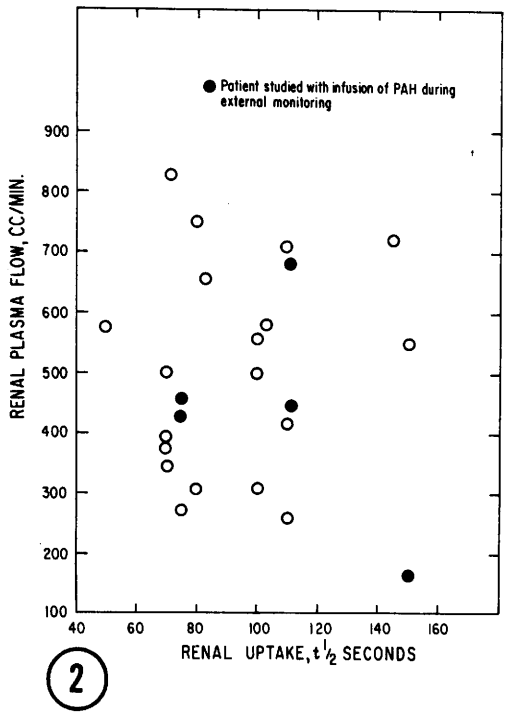


FIG. 1. Relationship of T 1/2 renal uptake of I^{131}-labelled iodohippurate to glomerular filtrate rate.
FIG. 2. Relationship of T 1/2 renal uptake of I^{131}-labelled iodohippurate to renal blood flow.

TABLE I. Comparison of Renal Uptake of I^{131}-Iodohippurate and Renal Clearances.

Patient	Diagnosis	T 1/2 uptake, sec	Clearance: P-amino-hippurate, cc/min	Clearance: Inulin, cc/min
V.H.	Myeloma	150	550	65
D.W.	Acute leukemia	100	309	53
C.W.	Chronic myel. leuk.	100	558	88
C.W.	*Idem*	50	582	80
C.W.	"	70	501	56
C.W.	"	100	500	60
O.T.	Myeloma	110	265	75
G.F.	"	70	375	64
J.R.	Acute leukemia	75	275	58
J.R.	*Idem*	110	410	70
A.F.	"	80	750	94
R.C.	Chronic myel. leuk.	70	392	82
E.B.	*Idem*†	80	301	69
J.G.	Carcinoma of colon	70	348	88
M.C.	Chronic myel. leuk.	110	712	131
P.K.	Acute leukemia	72	828	128
P.K.	*Idem*	145	717	103
W.H.	"	82	651	81
W.H.	"	105	583	71
D.W.*	Carcinoma of ovary	75	422	72
M.T.*	Carcinoma of breast	75	452	90
G.J.*	Myeloma	150	165	22
A.D.*	Carcinoma of breast	112	675	92
C.M.*	Hepatoma	110	446	145

* Radioisotope studies performed during constant infusion of p-amino hippuric acid.
† This patient also had pyelonephritis.

unilateral renal disease in hypertensive patients.

The derived uptake rate (T 1/2) has been demonstrated to be reproducible in the same patient and not influenced by alterations in urine flow(12). Calculations of T 1/2 renal uptake have correlated well with the 30-minute excretion of the tagged compound(3). Other methods of treatment of the tracings obtained by external monitoring have also correlated well with the 30-minute excretion of I^{131}-iodohippurate(2,13) but the reproducibility of these methods have not been established. It has also been demonstrated that renal blood flow measurements with I^{131}-labelled iodohippurate yield quantitatively similar values to simultaneously determined p-amino hippurate measurements(4,14,15). It was, therefore, thought that this technique

of quantitatively evaluating the curves obtained by monitoring renal radioactivity might afford quantitative information related to standard clearance techniques.

The correlation coefficient between the T 1/2 renal uptake of I^{131}-iodohippurate and inulin or PAH clearance was low. Thus, quantitative information relating to glomerular filtration rate or renal blood flow could not be based upon data derived from monitoring techniques as determined in this report (T 1/2 uptake). However, inspection of the curves obtained usually agrees qualitatively with clearance measurements, that is, patients with low clearance rates had slow renal uptake and delayed excretion of I^{131}-iodohippurate. This observation agrees with the report of Schwartz and Madeloff(16).

Several factors may be responsible for these results. It appears unlikely that protein binding of I^{131}-iodohippurate limited its renal excretion as no improvement in correlation with renal blood flow was apparent with the simultaneous use of p-amino hippurate, in an effort to competitively reduce the binding of the iodohippurate. It has recently been shown that perirenal tissue radioactivity may significantly influence the characteristics of the curves obtained by external monitoring (17-19) and in fact alter the apparent rates of renal uptake(20). Where renal function is impaired and the kidneys are unable to concentrate the labelled compound used, tissue background is of increased importance as an artifact in external monitoring(12). In such situations also, errors in placement of the renal monitoring devices become more significant.

It does not seem likely that the results in our patient group (patients with diffuse renal disease) would differ significantly from results obtained in a study of patients with unilateral renal disease and hypertension. The 30-minute excretion of tagged compounds, which has been shown to correlate with external monitoring techniques in patients with hypertension(3) probably reflects both glomerular filtration and renal blood flow but, judging from this study, is not a quantitative measure of either.

Summary. Measurements of renal function in patients with diffuse renal disease by clearance techniques did not correlate quantitatively with measurements derived from an external monitoring technique using I^{131}-iodohippurate. Simple inspection of the curves obtained by monitoring over the renal areas grossly correlated with renal clearance studies.

We wish to express our appreciation to Dr. William Kiser for his cooperation in these studies.

1. Nordyke, R. A., Tubis, M., Blahd, W. H., *J. Lab. and Clin. Med.,* 1960, v56, 438.

2. Meade, R. C., Shy, C. M., *J. Urol.,* 1961, v86, 163.

3. Block, J. B., Hine, G. J., Burrows, B. A., *Circulation,* 1960, v22, 913.

4. Burbank, M. K., Tauxe, W. N., Maher, F. T., Hunt, J. C., *Proc. of Staff Meetings of Mayo Clinic,* 1961, v36, 372.

5. Tauxe, W. N., *ibid.,* 1961, v36, 684.

6. Herron, G., Barbour, B. H., *Angiology,* 1961, v12, 352.

7. Magnusson, G., *Acta Med. Scand.,* 1962, v171, (Suppl.), 378.

8. Cotlove, E., *Fed. Proc.,* 1955, v14, 32.

9. Smith, H. W., Finkelstein, N., Oliminosa, L., Crawford, B., Graber, M., *J. Clin. Invest.,* 1945, v24, 388.

10. Block, J. B., Hine, G. J., Burrows, B. A., *J. Lab. and Clin. Med.,* 1956, v56, 110.

11. Whitley, J. E., Witcofski, R. L., Meschan, I., *Radiology,* 1961, v76, 464.

12. Block, J. B., Burrows, B. A., *J. Lab. and Clin. Med.,* 1960, v56, 463.

13. Hirakawa, A., Corcoran, A. C., *J. Lab. and Clin. Med.,* 1963, v61, 795.

14. Gott, F. S., Pritchard, W. H., Young, W. R., MacIntyre, W. J., *J. Nucl. Med.* 1962, v3, 480.

15. Meschan, I. M. D., Hosik, T., Schmid, H. A., Watts, B. S., *ibid.,* 1963, v4, 70.

16. Schwartz, F. D., Madeloff, M. S., *J. Urol.,* 1962, v87, 249.

17. Klapproth, H. J., Hirakawa, A., Corcoran, A. C., *ibid.,* 1962, v87, 77.

18. Pircher, F. J., Carr, E. A., Patno, M. E., *J. Nucl. Med.,* 1963, v4, 117.

19. Pircher, F. J., Wegst, A. W., Dodson, V. N., *ibid.,* 1963, v4, 45.

20. Farmelant, M. H., Burrows, B. A., *Clin. Res.,* 1963, v11, 240.

Received June 22, 1964. P.S.E.B.M., 1964, v117.