Gentamicin Pharmacokinetic Changes in Induced Acute Canine Nephrotoxic Glomerulonephritis†

J. EDMOND RIVIERE,^{1*} GORDON L. COPPOC,¹ EDWARD J. HINSMAN,² AND
WILLIAM W. CARLTON³

*Department of Veterinary Physiology and Pharmacology,¹ Department of Veterinary Anatomy,² and
Department of Veterinary Microbiology, Pathology and Public Health,³ School of Veterinary Medicine,
Purdue University, West Lafayette, Indiana 47907*

Received 26 November 1980/Accepted 10 June 1981

Most clinical schemes used to adjust gentamicin dosage regimens in renal insufficiency assume that the volume of distribution remains constant. The purpose of this investigation was to determine the pharmacokinetic parameters of gentamicin (two-compartment open model) before and at two points during the acute phase of experimentally induced nephrotoxic (injection of anti-glomerular basement membrane antibody) glomerulonephritis in beagle dogs. Disease was verified by decreased 24-h creatinine clearance, increased 24-h urinary protein excretion, and characteristic immunofluorescent, light- and electron-microscopic lesions. After disease induction, the concentration of drug in serum at time zero (C_p^0) was significantly decreased and the volume of the central compartment (V_c) and the volume of distribution ($V_{d(are)}$) were increased in all treated dogs. These findings suggest that the assumption of unchanged volume of distribution in acute glomerulonephritis could lead to a serious overestimation of serum drug concentration.

Studies of the pharmacokinetics of gentamicin in various mammalian species have demonstrated a serum elimination half-life of 1 to 2 h, renal elimination, and a serum concentration-time profile described by an open two-compartment pharmacokinetic model (4, 5, 18). Other investigators have reported an extended, slow, terminal elimination phase ("washout phase") with a half-life of approximately 150 h. This can be detected in experiments conducted over 2 to 3 weeks and, in part, represents the well documented renal cortical accumulation of gentamicin observed in all species thus far studied (19, 27, 31). Most investigations have shown negligible serum protein binding (11, 15). Because of its primarily renal elimination route, accumulation of gentamicin occurs in renal insufficiency, requiring adjustments. Numerous schemes have been reported (6, 21, 28). Most of these methods assume that the volume of distribution of this drug is comparable to that found in patients with normal renal function and attempt to correlate serum elimination half-life with creatinine clearance. The pathophysiological state of the patient's renal disease process is not entered into the formula.

An increased volume of distribution has been reported in some studies of aminoglycoside dis-

position in patients with renal insufficiency (12, 23, 30). In addition, volume of distribution varied widely in surgical patients with normal renal function (34). Many investigators have demonstrated poor correlation between actual and predicted gentamicin serum concentrations (1, 2, 14, 25). The correlation improved when both half-life of elimination and volume of distribution were calculated on an individual patient basis (26).

This report describes the effects of acute renal failure on certain pharmacokinetic parameters of gentamicin using acute anti-glomerular basement membrane (anti-GBM)-induced glomerulonephritis in the dog as an animal model.

MATERIALS AND METHODS

Animals and study design. Ten healthy male beagle dogs, 5 months of age, were used (Marshall Research Animals, Inc., North Rose, N.Y.). All animals were vaccinated against the common canine diseases. Indwelling cannulae were aseptically implanted into the right jugular veins. Dogs were housed in individual metabolism cages in a controlled environment. Experiments were conducted according to the schedule outlined in Table 1. Gentamicin pharmacokinetic experiments consisted of administering gentamicin sulfate (Gentocin, Schering Corp., Bloomfield, N.J.) at a dose of 10 mg/kg of body weight as an intravenous bolus to each dog and collecting blood samples through the jugular cannula at 0, 5, 10, 20, 30,

† Journal paper no. 8327, Agriculture Experiment Station, Purdue University, West Lafayette, IN 47907.

TABLE 1. Study design

Group	Treatment ^a	No. of dogs	Renal function tests (day of study)			Gentamicin pharmacokinetic expt (day of study)		
			Pre	Phase I	Phase II	Pre	Phase I	Phase II
A	Anti-GBM Serum	4	0, 1	7, 8	17, 18	1	8	18
B	Control	4	0, 1	7, 8	17, 18	1	8	18
C	Normal rabbit serum	2	0, 1	7, 8	17, 18			

^a Specified treatment was administered on day 3.

40, 50, 60, 90, 120, 180, 240, 300, and 360 min after drug administration. Gentamicin doses were calculated on the basis of weights determined in each phase of the study. Treatments were administered to all dogs on day 3 of the study and consisted of either anti-GBM antiserum (group A) or normal rabbit serum (group C). Dogs (group B) not receiving anti-GBM or normal rabbit serum served as kinetic controls for group A.

The experimental design employed for statistical analysis of this data was a factorial model with repeated measurements over time. Treatment effects were tested using analysis of variance. Groups A and B, the groups given gentamicin, were included in this analysis. Group C was not included and served as a control on the method of glomerulonephritis induction.

Experimental nephrotoxic glomerulonephritis. Four kidneys were obtained from two living adult beagle dogs, and GBMs were prepared by the modified method of Krakower and Greenspon (16). Briefly, freshly removed kidneys were perfused for 2 h with sterile 0.85% NaCl (4°C). Renal cortex was removed by dissection, minced into fine pieces, and gently passed through a 120-mesh stainless-steel sieve (United Surgical Supplies, Inc., Port Chester, N.Y.). This tissue brei was collected in saline, poured through a 60-mesh sieve, and centrifuged at $300 \times g$ for 10 min. This sediment was suspended in saline and allowed to settle undisturbed for 30 min. Centrifugation, suspension, and settling were repeated until phase contrast microscopy at $100\times$ demonstrated all glomeruli were free of parietal capsules and at least 90 of 100 objects counted were glomeruli. This sediment was suspended in 1 M NaCl and sonicated for 7 min at 20,000 cps and 102 W/cm² with a Biosonik III sonicator (Bronwill Scientific Inc., Rochester, N.Y.). The sonicated suspension containing GBM was centrifuged at $500 \times g$. The sediment was washed and then brought to a final concentration of 0.1 mg/ml with sterile water. This solution was mixed and homogenized with an equal volume of complete Freund adjuvant (Difco Laboratories, Detroit, Mich.). Two sets of subcutaneous injections of this material were given 3 weeks apart, at four sites for each set of injections, into rabbits at a dose of 20 mg of GBM per rabbit per treatment. Three weeks after the last injection, rabbits were anesthetized and exsanguinated, and blood samples were pooled. Serum was obtained and stored in sterile vials at -90°C until used. Four dogs (group A) were intravenously inoculated with a total of 0.7 ml of this rabbit anti-GBM serum per kg in two divided doses 2 h apart. Two dogs (group C) were inoculated with normal rabbit serum according to the same schedule and

served as controls for the specificity of the glomerulonephritis.

Renal function tests. Renal function was estimated in all dogs according to the schedule in Table 1. Clearances of creatinine (24 h) were determined as were 24-h urinary protein excretion, hematocrit, and serum concentrations of protein, creatinine, and urea nitrogen.

Postmortem evaluation. At the termination of the experiment on day 19, dogs were killed with sodium pentobarbital and necropsied. Renal tissue samples were collected and prepared in the following manner. For light microscopy, tissue was fixed in 10% (vol/vol) neutral buffered Formalin, embedded in paraffin, sectioned, and stained in hematoxylin and eosin. For transmission electron microscopy, samples were fixed by immersion overnight in cold 0.08 M phosphate-buffered (pH 7.3) 2% (vol/vol) paraformaldehyde and 2.5% (vol/vol) glutaraldehyde, postfixed in 2.5% (wt/vol) osmium tetroxide in 0.08 M phosphate buffer (pH 7.3), dehydrated, and embedded in epoxy resin. For immunofluorescence studies, tissue blocks were frozen in liquid nitrogen, sectioned, and mounted on glass slides. They were incubated for 45 min at 37°C with a 1:10 dilution, in phosphate-buffered saline, of fluorescein-conjugated swine anti-rabbit immunoglobulin G (IgG), rabbit anti-dog IgG, and rabbit anti-dog C3 antibodies (Bio-Rad Laboratories, Richmond, Calif.). Sections were then examined by fluorescence microscopy.

Pharmacokinetic analysis. Serum samples were assayed in duplicate for gentamicin using a double-antibody gentamicin ¹²⁵I radioimmunoassay procedure (Rianen ¹²⁵I RIA kit, New England Nuclear Corp., Boston, Mass.). Gentamicin serum concentrations were fitted for each dog, by means of a nonlinear least-squares regression routine, to a two-compartment, open, pharmacokinetic model of the form: $C_p = Ae^{-\alpha t} + Be^{-\beta t}$, where C_p is the concentration of drug in serum at time t , A and B are intercept terms, α is the distribution rate constant, and β is the elimination rate constant.

Parameters determined in these analyses were used to calculate the pharmacokinetic rate constants (k_{el} , k_{12} , k_{21}), the volume of the central compartment (V_c), the volume of distribution ($V_{d(area)}$), the body clearance of gentamicin (Cl_B), the beta-phase elimination half-life ($t_{1/2}$), and the concentration of drug at time zero (C_p^0) (9, 29).

RESULTS

An examination of preliminary clinical laboratory values (Table 2) indicated that dogs in

TABLE 2. Clinical laboratory data for dogs over the three phases of the study^a

Dog group	Hematocrit (%)	Total protein (g/dl)	Serum creatinine (mg/dl)	Serum urea nitrogen (mg/dl)	Urine protein excretion (mg/24 h)	Creatinine clearance (ml/min per kg)
A (anti-GBM serum)						
Pre	34 ± 2	6.1 ± 0.3	0.5 ± 0.0	15 ± 4	19 ± 10	3.62 ± 0.60
Phase I	30 ± 4 ^b	5.6 ± 0.2	0.6 ± 0.0	16 ± 2	198 ± 206	1.89 ± 0.60 ^{b,c}
Phase II	30 ± 4	6.2 ± 0.7	0.6 ± 0.1	20 ± 1 ^{b,c}	48 ± 74	1.89 ± 0.60 ^{b,c}
B (control)						
Pre	38 ± 4	5.5 ± 0.7	0.4 ± 0.1	12 ± 3	59 ± 13	4.09 ± 0.59
Phase I	40 ± 1	5.4 ± 0.4	0.4 ± 0.1	12 ± 5	70 ± 11	3.54 ± 0.23
Phase II	37 ± 5	5.7 ± 0.5	0.4 ± 0.1	14 ± 4	100 ± 21	3.62 ± 0.60
C (normal rabbit serum) ^d						
Pre	46 ± 2	5.3 ± 0.2	0.4 ± 0.1	12 ± 4	45 ± 2	3.33 ± 0.07
Phase I	45 ± 0	5.7 ± 0.1	0.5 ± 0.1	17 ± 4	38 ± 14	3.47 ± 0.18
Phase II	46 ± 0	5.4 ± 0.3	0.5 ± 0.1	14 ± 3	54 ± 26	3.25 ± 0.12

^a Results expressed as mean ± standard deviation.^b Significantly different ($P < 0.05$) from the corresponding phase in group B.^c Significantly different ($P < 0.05$) from the Pre value within group.^d Group not included in statistical analysis.

group A and B did not differ significantly ($P > 0.05$) prior to treatment. Note that the Pre hematocrit values of group C were greater than those of groups A and B, and, that the Phase I values were different between groups A and B. Since no trends within any group were evident and since all values were within normal ranges, these differences were not judged to be clinically significant.

Within group A dogs receiving anti-GBM antiserum, creatinine clearance significantly decreased ($P < 0.05$) in Phases I and II, and serum urea nitrogen significantly increased in Phase II. These values were different when compared both within and between groups. There was also a trend for 24-h urinary protein excretion to increase in group A, although this was not statistically significant. No changes from Pre values occurred in the control group B. Immunofluorescence microscopy at the termination of the study demonstrated linear deposits of canine IgG, C3, and rabbit IgG in the glomeruli of all anti-GBM-treated dogs. Light microscopy was marked by capillary wall thickening (wire-loop formation), glomerular swelling, and hypercellularity. Transmission electron microscopy demonstrated focal, segmental GBM thickening, mesangial cell proliferation, and linear, subendothelial deposits of poorly electron-dense material in all dogs given anti-GBM antibody. The absence of changes in renal functional parameters in the group C dogs receiving normal rabbit serum supports the microscopic evidence for induction of a pure anti-GBM glomerulonephritis.

Serum concentrations of gentamicin in all phases of the study were adequately described by the two-compartment model as judged by error sums of squares and residual plot analyses.

An examination of the Pre values between group A and B dogs (Table 3) demonstrated no significant differences ($P > 0.05$) except for weight and an increased α value in group A. Notably, volume parameters were not different between groups. There was no significant change ($P > 0.05$) over time in any pharmacokinetic parameter within the control group B.

Within group A, which received anti-GBM antiserum, the $t_{1/2}$ remained relatively stable, whereas k_{e1} of individual animals changed in direct relation to creatinine clearance ($R^2 = 0.98$, $P < 0.01$). Analysis of variance detected significant ($P < 0.05$) differences due to disease (Phase I and II versus Pre values) in C_p^0 , V_c , and $V_{d(areal)}$; C_p^0 decreased, but V_c and $V_{d(areal)}$ increased. In addition, these parameters were significantly ($P < 0.05$) different from corresponding values in the control group B.

The standard deviation of the parameter values within group A for Phase I and II were greater than those for the control period. This could be attributed to the inherent variability of the host immunological response since the progression of pathological changes in glomerulonephritis is dependent on the immune system. This variability did not obscure the findings reported here since it was of lesser magnitude than the overall changes observed.

DISCUSSION

An acute glomerulonephritis was induced in all dogs of this study given anti-GBM serum as judged by decreased creatinine clearance, a trend toward increased urinary protein excretion, and characteristic light microscopic, immunofluorescent, and electron microscopic lesions. These findings were similar to those reported by other investigators studying the path-

TABLE 3. Comparison of pharmacokinetic parameters for gentamicin after administration of a single intravenous bolus (10 mg/kg) to dogs^a

Dog group	Body wt (kg)	C_p^0 (μ g/ml)	α (min^{-1})	β (min^{-1})	$t_{1/2}$ (min)	k_{e1} (min^{-1})	k_{12} (min^{-1})	k_{21} (min^{-1})	V_c (liters/100 kg)	V_d (area) (liters/100 kg)	Cl_B (ml/min per kg)
A (anti-GBM serum)											
Pre	6.2 $\pm$ 0.6 ^b	52.1 $\pm$ 1.9	0.121 $\pm$ 0.017 ^b	0.011 $\pm$ 0.002	63 $\pm$ 8	0.022 $\pm$ 0.003	0.048 $\pm$ 0.006	0.062 $\pm$ 0.009	19.2 $\pm$ 0.7	37.7 $\pm$ 2.9	4.2 $\pm$ 0.70
Phase I	6.5 $\pm$ 0.7 ^b	34.3 $\pm$ 1.5 ^{b,c}	0.141 $\pm$ 0.021	0.010 $\pm$ 0.003	58 $\pm$ 14	0.019 $\pm$ 0.006	0.055 $\pm$ 0.007	0.077 $\pm$ 0.006	29.2 $\pm$ 1.3 ^{b,c}	53.0 $\pm$ 4.1 ^{b,c}	5.4 $\pm$ 1.55
Phase II	6.4 $\pm$ 0.6 ^b	36.9 $\pm$ 8.3 ^c	0.075 $\pm$ 0.047	0.010 $\pm$ 0.003	69 $\pm$ 18	0.019 $\pm$ 0.002	0.031 $\pm$ 0.010	0.036 $\pm$ 0.019	28.1 $\pm$ 6.1 ^c	53.5 $\pm$ 23.1 ^{b,c}	5.17 $\pm$ 0.90
B (control)											
Pre	10.0 $\pm$ 0.1	47.7 $\pm$ 11.5	0.076 $\pm$ 0.007	0.010 $\pm$ 0.003	61 $\pm$ 4	0.018 $\pm$ 0.002	0.019 $\pm$ 0.003	0.050 $\pm$ 0.009	22.0 $\pm$ 5.6	30.1 $\pm$ 3.4	3.44 $\pm$ 0.38
Phase I	9.9 $\pm$ 0.5	50.5 $\pm$ 8.3	0.081 $\pm$ 0.103	0.010 $\pm$ 0.002	69 $\pm$ 5	0.016 $\pm$ 0.005	0.012 $\pm$ 0.003	0.063 $\pm$ 0.078	20.2 $\pm$ 3.4	35.8 $\pm$ 5.9	3.33 $\pm$ 0.66
Phase II	10.2 $\pm$ 1.0	48.0 $\pm$ 17.7	0.083 $\pm$ 0.046	0.014 $\pm$ 0.002	52 $\pm$ 8	0.018 $\pm$ 0.001	0.010 $\pm$ 0.002	0.069 $\pm$ 0.034	22.8 $\pm$ 7.3	34.7 $\pm$ 4.1	4.66 $\pm$ 0.69

^a Results expressed as mean $\pm$ standard deviation.^b Significantly different ($P < 0.05$) from the corresponding phase in group B.^c Significantly different ($P < 0.05$) from the Pre value within group.

ogenesis of anti-GBM glomerulonephritis in dogs (22, 33).

The volume of distribution of gentamicin in dogs with glomerulonephritis significantly increased as determined by C_p^0 , V_c , and $V_{d(\text{area})}$. Since $V_{d(\text{area})}$ changed in the opposite direction of that predicted solely from a decrease in k_{e1} (7, 8, 13), a pathophysiological increase in the volume of distribution occurred in the induced acute glomerulonephritis.

If significant changes of volume occur in acute glomerulonephritis, then dosage adjustment regimens should take these into account. Altered volume of distribution could partially explain the unpredictability of gentamicin serum concentrations observed by various investigators (1, 2, 14, 25). As reported previously, aminoglycoside volume of distribution was increased in some patients with renal insufficiency (12, 23, 30). Gill and Kern reported an increase in volume of distribution of gentamicin in ascitic patients (10). Pennington et al. have reported lower serum gentamicin concentrations in endotoxin-induced fever in dogs, possibly attributable to shifts in body fluid compartments (24).

It is possible that the present volume changes are due to increased tissue binding of drug. Gentamicin tissue binding has been demonstrated by Kunin (17). Another speculation is that vasoactive factors released by the immunological events occurring in the glomerulus (20, 32) could alter peripheral drug distribution.

The change in volume of distribution is similar to the expansion of extracellular fluid volume during the evolution of nephrotoxic glomerulonephritis in rats as recently reported by Bennett and Glasscock (3). They observed significant increases in exchangeable sodium in young rats as glomerulonephritis proceeded. Decreased creatinine clearance was closely correlated with these changes.

Two other factors must also be considered. First, this study did not quantitate the effect of glomerulonephritis on tissue accumulation during the washout phase because the study was too short. Secondly, stable renal failure was not present, indicated by changing serum creatinine and serum urea nitrogen concentrations. This scenario is often present in the clinical setting and is difficult to account for in dosage regimen calculations.

It must also be considered that the volume changes observed in the present study are a function of the pathophysiological changes present in glomerulonephritis and may not be found in other models of renal failure. In fact, it would appear that this was the major pharmacokinetic change present in this study. Most studies of

aminoglycoside disposition in renal insufficiency do not include a variable related to the pathophysiological state of the disease, but instead correlate kinetic changes solely with decreased glomerular filtration rate.

The use of laboratory models is well established as a means of clarifying preliminary results from clinical studies. The model presented here is especially reasonable because it is initiated and characterized by changes resembling those associated with clinical disease. Use of this model allowed determination of all pharmacokinetic parameters in the same animals before and after disease induction. The model produced consistent pathophysiological changes in each animal and appears to be excellent for studying pharmacokinetics in renal glomerular disease under controlled conditions. This model and the results presented represent a beginning in the direction of correlating changes in drug pharmacokinetics to specific pathophysiological disease states rather than solely to decreases in glomerular filtration rate.

ACKNOWLEDGMENT

This work was supported in part by the Indiana Dog Tax.

LITERATURE CITED

- Barza, M., R. B. Brown, D. Shen, M. Gibaldi, and L. Weinstein. 1975. Predictability of blood levels of gentamicin in man. *J. Infect. Dis.* 132:165-174.
- Barza, M., and M. Lauerman. 1978. Why monitor serum levels of gentamicin? *Clin. Pharmacokin.* 3:202-215.
- Bennett, C. M., and R. J. Glasscock. 1979. Glomerular hemodynamics and permselectivity in experimental glomerular disease, p. 159-172. *In* P. Kincaid-Smith, A. J. F. d'Apice, and R. C. Atkins (ed.), *Progress in glomerulonephritis*. John Wiley & Sons, Inc., New York.
- Chiu, P. J. S., A. Brown, G. Miller, and J. F. Long. 1976. Renal extraction of gentamicin in anesthetized dogs. *Antimicrob. Agents Chemother.* 10:277-282.
- Chung, M., R. Costello, and S. Symchowicz. 1980. Comparison of netilmicin and gentamicin pharmacokinetics in humans. *Antimicrob. Agents Chemother.* 17:184-187.
- Dettli, L. 1974. Drug dosage in patients with renal disease. *Clin. Pharmacol. Therap.* 16:274-283.
- Gibaldi, M., and D. Perrier. 1972. Drug distribution and renal failure. *J. Clin. Pharmacol.* 12:201-204.
- Gibaldi, M., and D. Perrier. 1972. Drug elimination and apparent volume of distribution in multicompartment systems. *J. Pharmaceut. Sci.* 61:952-954.
- Gibaldi, M., and D. Perrier. 1975. *Pharmacokinetics*. Marcel Dekker, Inc., New York.
- Gill, M. A., and J. W. Kern. 1979. Altered gentamicin distribution in ascitic patients. *Am. J. Hosp. Pharm.* 36:1704-1706.
- Gordon, B. C., C. Regamy and W. M. Kirby. 1972. Serum protein binding of aminoglycoside antibiotics. *Antimicrob. Agents Chemother.* 2:214-216.
- Gyselynyck, A., A. Forrey, and R. Cutler. 1971. Pharmacokinetics of gentamicin. Distribution and plasma and renal clearance. *J. Infect. Dis.* 124(Suppl):70-76.
- Jusko, W. J., and M. Gibaldi. 1972. Effects of change in elimination on various parameters of the two compartment open model. *J. Pharmaceut. Sci.* 61:1270-1273.
- Kaye, D., M. E. Levison, and E. D. Labovitz. 1974. The unpredictability of serum concentrations of gentamicin: pharmacokinetics of gentamicin in patients with normal and abnormal renal function. *J. Infect. Dis.* 130:150-154.
- Kozak, A. J., D. N. Gerding, L. R. Peterson, and W. H. Hall. 1977. Gentamicin intravenous infusion rate: effect on interstitial fluid concentration. *Antimicrob. Agents Chemother.* 12:606-608.
- Krakower, C. A., and S. A. Greenspon. 1951. Localization of the nephrotoxic antigen within the isolated renal glomerulus. *Arch. Pathol.* 51:629-639.
- Kunin, C. M. 1970. Binding of antibiotics to tissue homogenates. *J. Infect. Dis.* 121:55-64.
- Leroy, A., G. Humbert, G. Oksenhendler, and J. P. Fillastre. 1978. Pharmacokinetics of aminoglycosides in subjects with normal and impaired renal function. *Antimicrob. Agents Chemother.* 25:163-180.
- Luft, F. C., and S. A. Kleit. 1974. Renal parenchymal accumulation of aminoglycoside antibiotics in rats. *J. Infect. Dis.* 130:656-659.
- Merrill, J. P. 1974. Glomerulonephritis. *N. Engl. J. Med.* 290:257-266, 313-319, 374-381.
- Michelson, P. A., W. A. Miller, J. F. Warner, L. W. Ayers, and H. G. Boxenbaum. 1976. Multiple dose pharmacokinetics of gentamicin in man. Evaluation of the Jelliffe nomogram and the adjustment of dosage in patients with renal impairment, p. 207-245. *In* L. Z. Benet (ed.), *The effect of disease states on drug pharmacokinetics*. American Pharmaceutical Association, Washington, D. C.
- Movat, H. Z., D. D. McGregor, and J. W. Steiner. 1961. Studies of nephrotic nephritis. II. The fine studies of the glomerulus in acute nephrotoxic nephritis of dogs. *Am. J. Clin. Pathol.* 36:306-321.
- Pechere, J. C., R. Dugal, and M. M. Pechere. 1978. Pharmacokinetics of netilmicin in renal insufficiency and haemodialysis. *Clin. Pharmacokin.* 3:395-406.
- Pennington, J. E., D. C. Dale, H. Y. Reynolds, and J. D. MacLowry. 1975. Gentamicin sulfate pharmacokinetics. Lower levels of gentamicin in blood during fever. *J. Infect. Dis.* 132:270-275.
- Reymann, M. T., J. A. Bradac, C. G. Cobbs, and W. E. Dismukes. 1979. Correlation of aminoglycoside dosages with serum concentrations during therapy of serious gram-negative bacillary disease. *Antimicrob. Agents Chemother.* 16:353-361.
- Sawchuck, R. J., D. E. Zaske, R. T. Cipolle, W. A. Wargin, and R. G. Strate. 1977. Kinetic model for gentamicin dosing with the use of individual patient parameters. *Clin. Pharmacol. Ther.* 21:362-369.
- Schentag, J. J., and W. J. Jusko. 1977. Renal clearance and tissue accumulation of gentamicin. *Clin. Pharmacol. Ther.* 22:364-370.
- Tozer, T. 1974. Nomogram for modification of dosage regimens in patients with chronic renal function impairment. *J. Pharmacokin. Biopharm.* 2:13-28.
- Wagner, J. G. 1975. *Fundamentals of clinical pharmacokinetics*. Drug Intelligence Publications, Inc., Hamilton, Ill.
- Welling, P. G., A. Baumuller, C. C. Lau, and P. O. Madsen. 1977. Netilmicin pharmacokinetics after single intravenous doses to elderly male patients. *Antimicrob. Agents Chemother.* 12:328-334.
- Whelton, A., G. Carter, T. J. Craig, H. H. Bryant, D. V. Herbst, and W. G. Walker. 1978. Comparison of the intrarenal disposition of tobramycin and gentamicin: therapeutic and toxicologic answers. *J. Antimicrob. Chemother.* 4(Suppl. A):13-22.
- Wilson, C. B., and F. J. Dixon. 1976. The renal response to immunological injury, p. 838-940. *In* B. M. Brenner

- and F. C. Rector (ed.), The kidney. W. B. Saunders Co., Philadelphia.
33. **Wright, N. G., H. Thompson, and H. J. C. Cornwell.** 1973. Canine nephrotoxic glomerulonephritis. A combined light, immunofluorescent and ultrastructural study. *Vet. Pathol.* **10**:69-86.
34. **Zaske, D. E., R. J. Cipolle, and R. J. Strate.** 1980. Gentamicin dosage requirements: wide interpatient variations in 242 surgery patients with normal renal function. *Surgery* **87**:164-169.