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APPENDICES

APPENDIX

A. Composition and Preparation of Mobile Phase for HPLC

B. Standard Curve Determination

C. Equations

D. Figures about TDx^{R} Analyzer, Nomogram and Dosing Chart

APPENDIX A

Composition and Preparation of Mobile Phase for HPLC

Mobile phase composes of mixture of methanol : water (3.26 : 1 by vol) containing 2 gm Tripotassium Ethylenediaminetetraacetate (Tripotassium EDTA) per liter and adjusted until pH 6.5 with Ethylenediaminetetraacetic Acid (EDTA acid). It must be freshly prepared.

The preparation procedure is as follow.

1. Dissolve 2 gm Tripotassium EDTA in 234.8 ml distilled water. Adjust pH to 6.5 with EDTA acid. Add methanol HPLC grade 765.2 ml. Mix well and protect from evaporate.

2. Filter through HA 0.5 um membrane filter with suction filtration.

3. Degas the mobile phase using a sonifier for 15-20 minutes.

APPENDIX B

Standard Curve Determination

The typical standard curve data and the curve for gentamicin concentrations in pooled serum are presented in Table 18 and Figure 14, respectively.

Table 18 Typical Standard Curve Data of Gentamicin Concentrations in Pooled Serum Estimated Using Linear Regression[1]

Standard No	Concentration (ug/ml)	Peak area (G/G)	Inversely estimated[2] Concentration (ug/ml)	% Theory[3]
1	0	0	0	0
2	1	54039	0.9605	96.05
3	2	105996	1.9399	96.99
4	4	229912	4.2758	106.89
5	8	421222	7.8821	98.53
			Mean	99.62
			SD	4.96
			CV	4.98%

1. $r^2 = 0.998$

2. Inversely estimated concentration

$$= \frac{\text{Peak area} - \text{Intercept}}{\text{slope}}$$

3. % Theory

$$= \frac{\text{Inversely estimated concentration}}{\text{known concentration}} \times 100$$

4. Coefficient of variation (CV)

$$= \frac{SD}{\text{mean}} \times 100$$

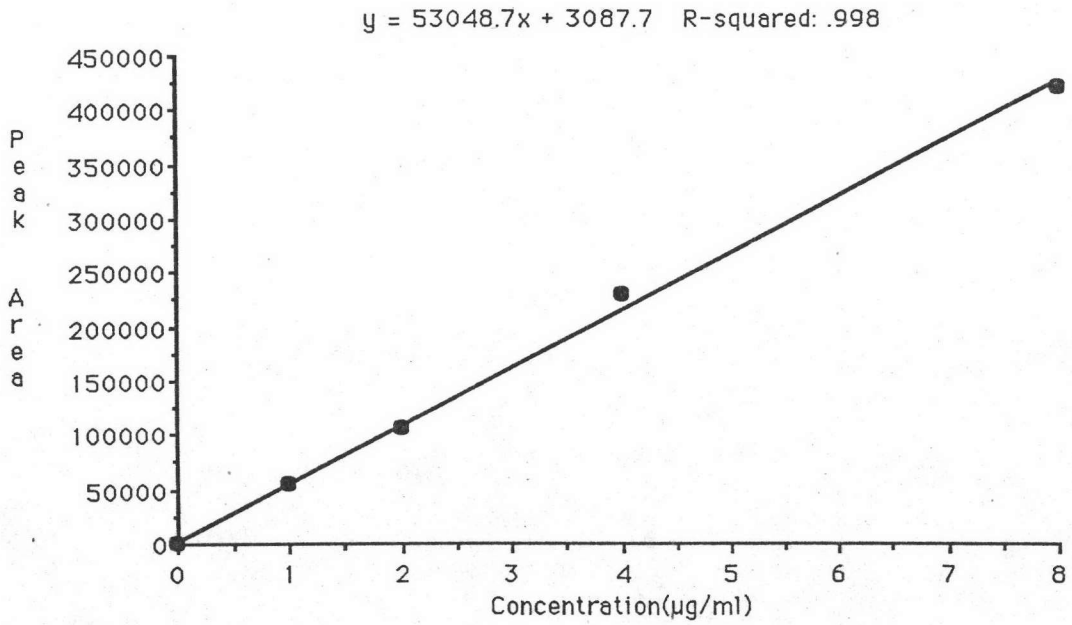


Figure 14 Typical Standard Curve of Gentamicin Concentration in Human Serum.

APPENDIX C

Equation 1 :

$$\text{IBW (male)} = 50 + (\text{height in inches} - 60)(2.3) \quad \text{kg}$$

Equation 2 :

$$\text{IBW (female)} = 45.5 + (\text{height in inches} - 60)(2.3) \quad \text{kg}$$

Equation 3 :

$$\text{CrCl (male)} = \frac{(140-\text{age}) \times \text{BW(kg)}}{72 \times \text{Scr(mg/dl)}} \quad \text{ml/min}$$

Equation 4 :

$$\text{CrCl (female)} = \left[\frac{(140-\text{age}) \times \text{BW(kg)}}{72 \times \text{Scr(mg/dl)}}\right](0.85) \quad \text{ml/min}$$

Equation 5 :

$$Vd = \frac{MD(1 - e^{-Kelt'})}{Kel\ t'\left(Cpmax_{ss} - Cpmin_{ss}\ e^{-Kelt'}\right)} \quad L/kg$$

Equation 6 :

$$Cpmax_{ss} = \frac{MD(1 - e^{-Kelt'})}{Kel\ Vd\ t'\ (1 - e^{-Kel\tau})} \quad \mu g/ml$$

Equation 7 :

$$Cpmin_{ss} = Cpmax_{ss}\ e^{-Kel(\tau - t')} \quad \mu g/ml$$

Equation 8 :

$$\tau = t' + \frac{(-1)}{kel} \ln\left[\frac{Cpmin_{ss}}{Cpmax_{ss}}\right] \quad \text{hour}$$

Equation 9 :

$$MD = \frac{t'\ Kel\ Vd\ Cpmax_{ss}\ (1 - e^{-Kel\tau})}{(1 - e^{-Kelt'})} \quad mg$$

Equation 10 :

$$MD = \frac{t' \; Kel \; Vd \; Cpmin_{ss} \; (e^{Kel\tau} - 1)}{(e^{Kelt'} - 1)} \quad mg$$

Equation 11 :

$$Cpost_{ss} = Cpmax_{ss} \; e^{-Kel(t - t')} \quad \mu g/ml$$

Equation 12 :

$$Kel = 0.01 + 0.0024 \; (CrCl) \quad hour^{-1}$$

$$Vd = 0.26 \quad L/kg$$

Equation 13 : (Ref. 62)

$$Kel = \frac{-1}{\tau} \left[\ln \left(\frac{Cpmin_{ss} Vd}{Dose + Cpmin_{ss} Vd} \right) \right] \quad hour^{-1}$$

$$Vd = 0.26 \quad L/kg$$

Equation 14 :

$$t_{1/2} = \frac{0.693}{Kel} \quad hour$$

Equation 15 :

$$Ccr \text{ or } CrCl = \frac{Ucr \times V}{Scr \times 1440} \quad ml/min$$

Symbol

BW = Body Weight (kg)

IBW = Ideal Body Weight (kg)

TBW = Total Body Weight (kg)

CrCl = Creatinine Clearance, Ccr (ml/min)

Scr = Serum Creatinine (mg/dl)

Vd = Volume of Distribution (L/kg)

Kel	=	Elimination Rate Constant
MD	=	Maintenance Dose
$Cpmax_{ss}$	=	Peak Concentration at Steady-State (μg/ml)
$Cpmin_{ss}$	=	Trough Concentration at Steady-State (μg/ml)
$Cpost_{ss}$	=	Concentration at the Time after Drug Infusion had finished (μg/ml)
t'	=	Duration of Infusion Time (hour)
	=	Time of Dosing Interval (hour)
t	=	The Period Time after Drug Infusion had finished
$t_{1/2}$	=	Half-life
Ucr	=	Urinary Creatinine Concentration (mg/dl)
V	=	Total Volume of Urine in 24 Hours (ml)

APPENDIX D

Figures about TDx^{R} Analyzer, Nomogram and Dosing Chart

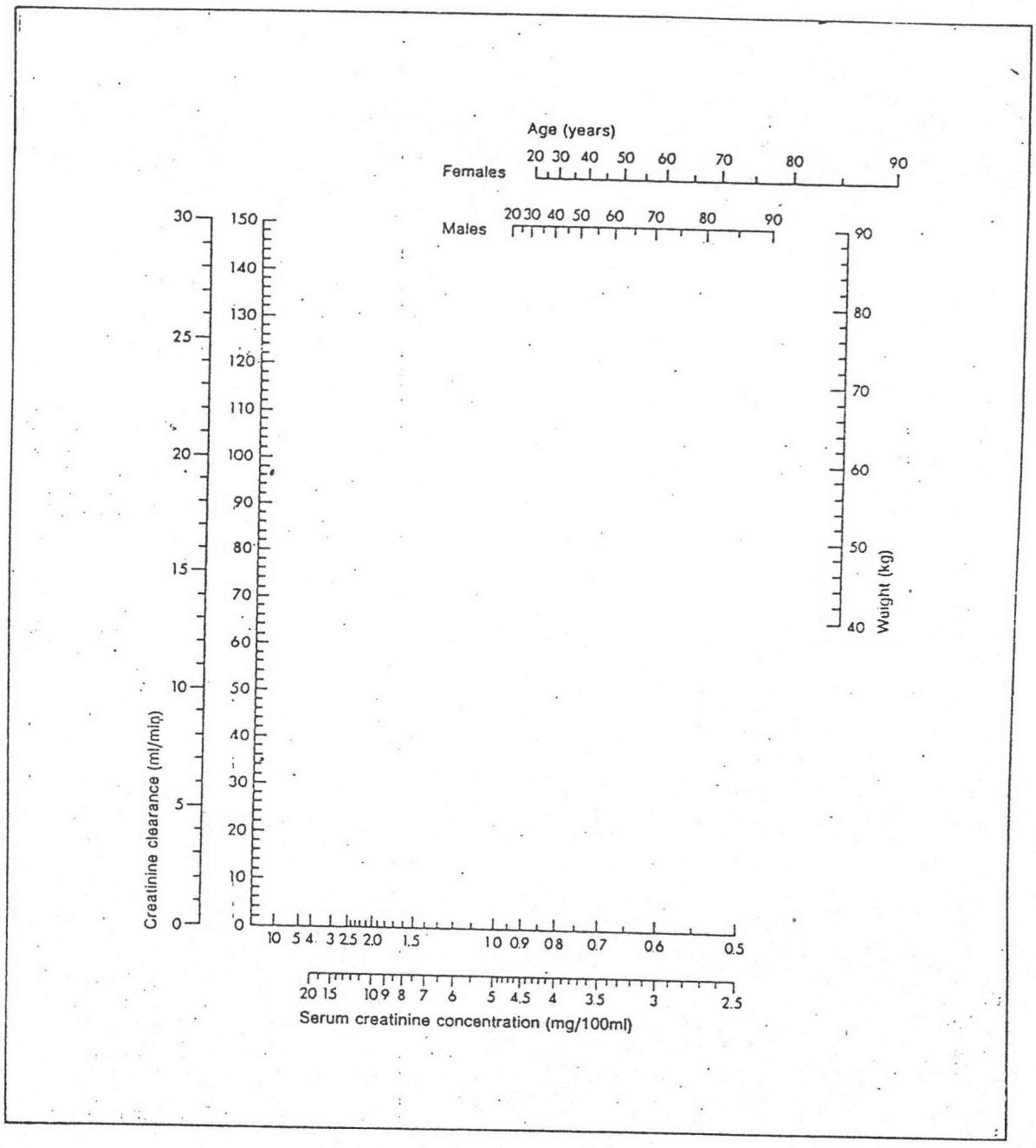


Figure A Bjornsson's Nomogram

Nomogram for estimating creatinine clearance from serum creatinine concentration in adults.

Use of the Nomogram :

Step 1 : Define a point where lines perpendicular to the axes for the individual patient's age (sex) and body weight cross.
Step 2 : Draw a line connecting this point and the origin.
Step 3 : For any given serum creating concentration, a corresponding creatinine clearance is determined by this line.

Use the outer scales for serum creatinine concentrations higher than 2.5 mg/100 ml.

Figure B The TDx^{R} Analyzer System Uses Fluorescence Polarization Immunoassay Technology to Measure Therapeutic Drug and Hormone Levels.

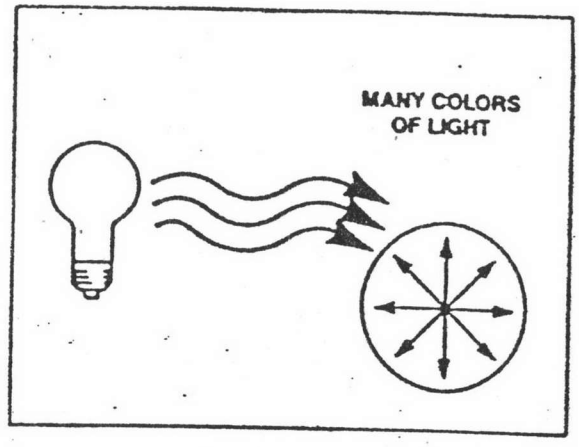


Figure B.1 The light source emits light of different wavelengths or colors with random spatial orientation.

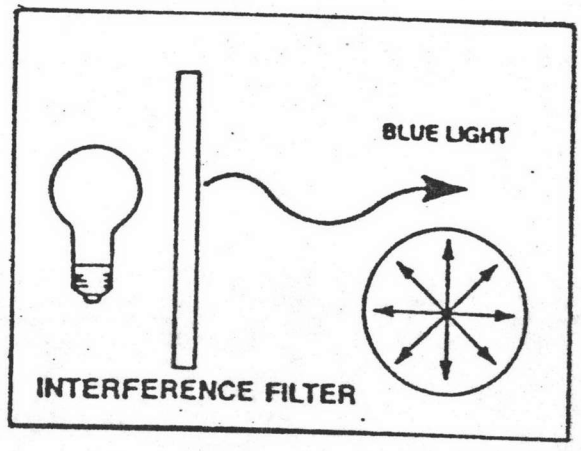


Figure B.2 An interference filter is placed in front of the light source to filter out a single wavelength of blue light.

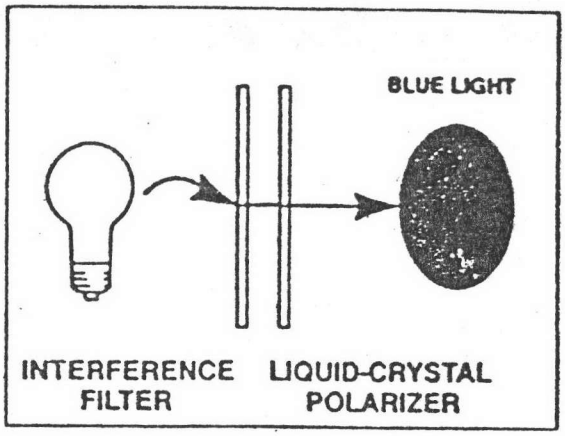


Figure B.3 In the TDx^{R} Analyzer System, this monochromatic light is then passed through a liquid crystal polarizer, and the end result is a single plane of blue light.

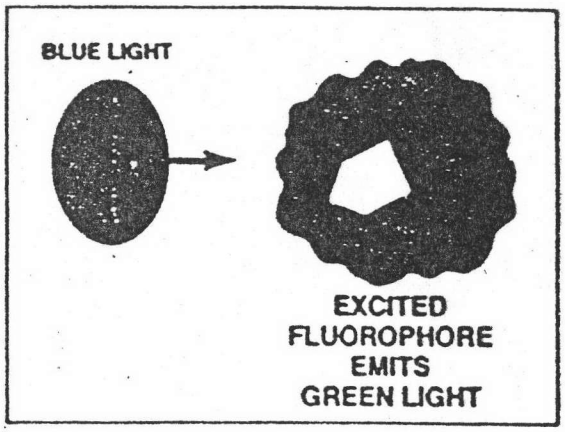


Figure B.4 When a tracer, or fluorophore, is excited with this plane polarized blue light, it is raised to an excited state where it remains, for a split second, before it emits light of a different energy level and wavelength (green light).

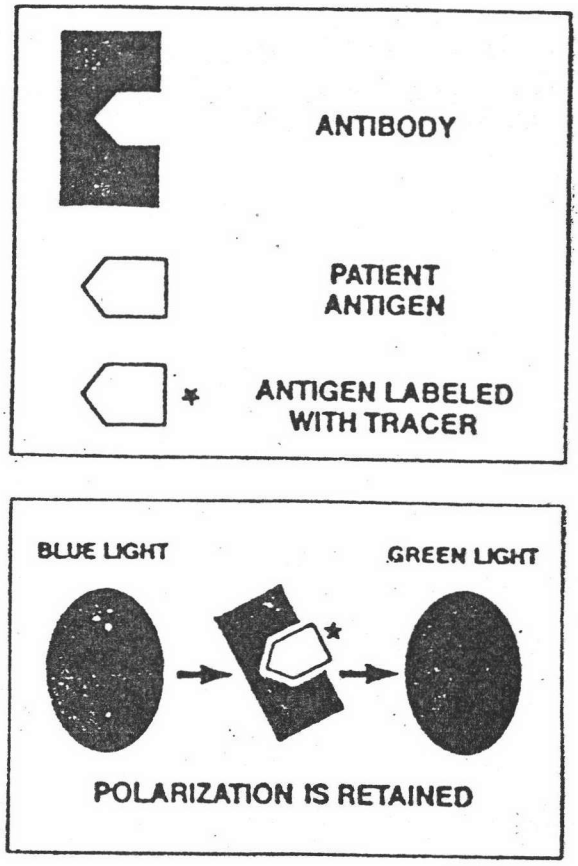


Figure B.5 By definition, if the fluorophore is fixed in solution, an example being if it is bound to a very large antibody molecule, the emitted green light will be in the same plane as the blue excitation light. In other words, polarization is retained.

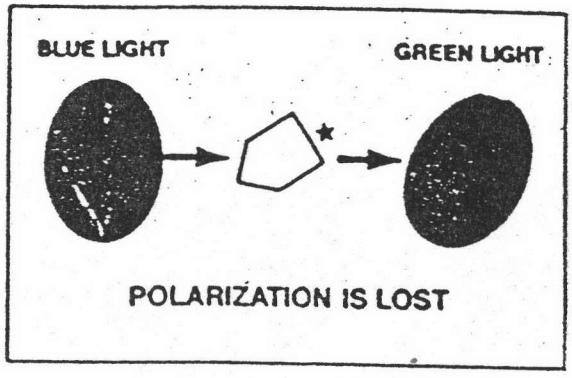


Figure B.6 Conversely, if the fluorophore is free to rotate, an example being a very small free tracer molecule that is not bound, the emitted green light will be in different plane than the blue excitation light. Or, polarization is lost.

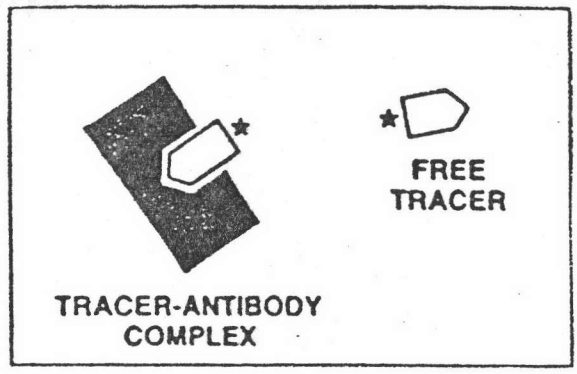


Figure B.7 When competitive binding occurs, the tracer-antigen complex becomes a part of the very large antibody molecule; the free tracer is small in comparison.

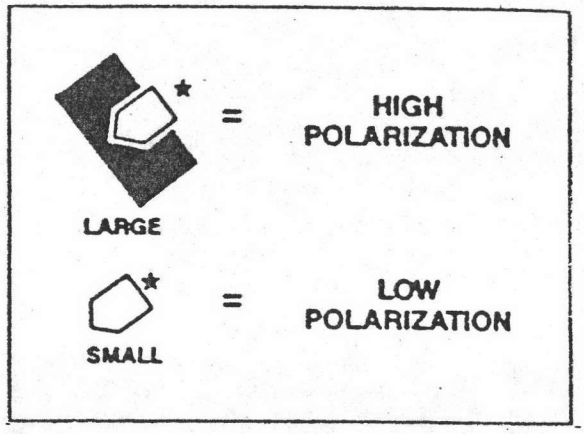


Figure B.8 Because of the rotational properties of molecules in solution, the degree of polarization is directly proportional to the molecule. That is, polarization increases as molecular size increases.

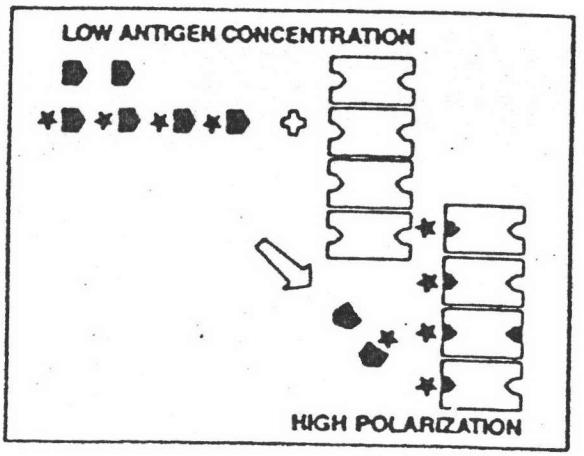


Figure B.9 So, if a patient sample contains a low concentration of antigen, after the competitive binding reaction reaches steady-state, there will be very high bound tracer in the reaction mixture. Therefore, polarization will be high.

LOW CONC ANTIGEN → HIGH BOUND TRACER → HIGH POLARIZATION

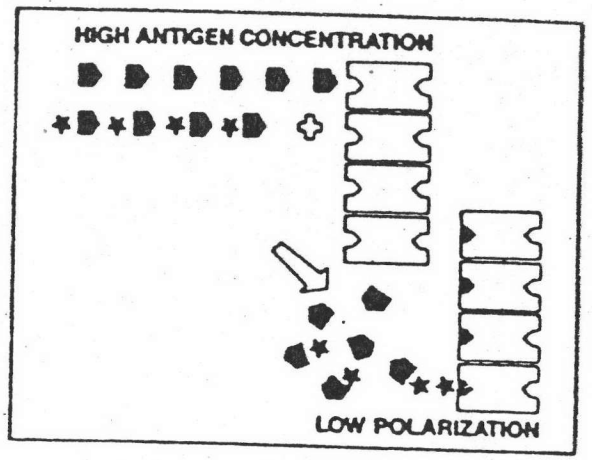
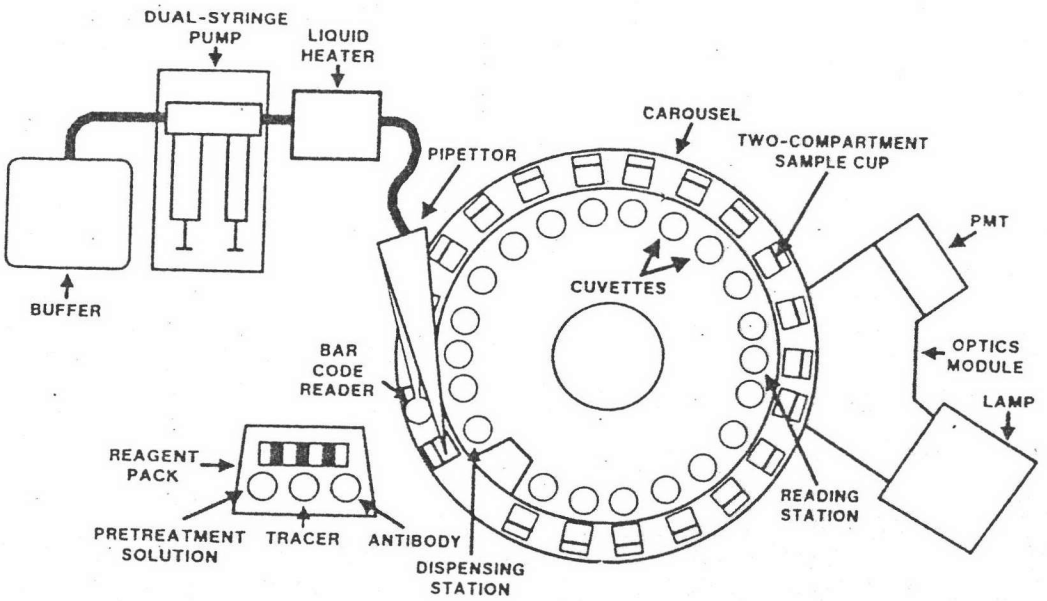


Figure B.10 Conversely, if there is high concentration of antigen in the sample being analyzed, after the competitive binding there will be a low number of tracer molecules bound to the antibody, most tracer molecules will be free to rotate in the reaction mixture. So, polarization will be low.

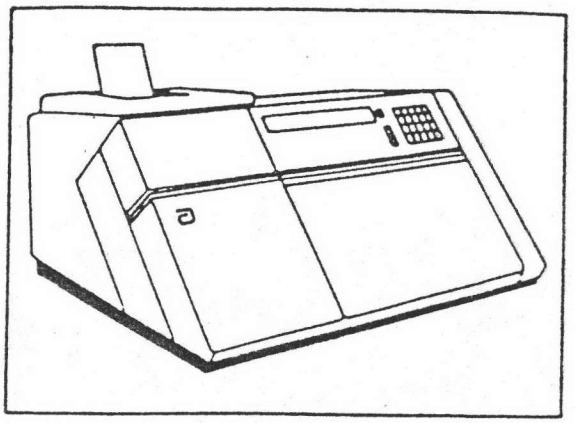
HIGH CONC ANTIGEN → LOW BOUND TRACER → LOW POLARIZATION

Figure C The TDx^{R} Analyzer



1: The major components of the totally automated, bench-top, fluorescence polarization analyzer
PMT, photomultiplier tube

2:



DATE : 01/23/90
TIME : 12:34:12

SERIAL # : 14001
ASSAY : GENTAMICIN

CALIBRATION

VOL = 1.00
REFS = 1
GAIN = 20

CONC = UG/ML

I.D.		NET P	NET I	BLANK I
1	A	191.35	5785.2	95.0
2	B	184.06	5966.4	90.8
3	C	161.43	5959.1	93.6
4	D	129.28	6211.1	92.7
5	E	97.52	6327.4	91.8
6	F	82.23	6354.0	91.3

I.D.	CONC	AVGP	FITP	PERR
A	0.00	191.35	191.35	0.00
B	0.50	184.06	184.77	-0.71
C	1.50	161.43	160.87	0.56
D	3.00	129.28	129.48	-0.20
E	6.00	97.52	97.62	-0.10
F	10.00	82.23	82.15	0.08

RMSE = 0.33

SAMPLES

LOC	CONC	NET P	BLK I
7	8.11 HI	87.55	95.81
8	4.43	110.43	93.54
9	1.20	168.23	97.23

Figure D Therapeutic Drug or Hormone Batch Calibration Printout

1. GENTAMICIN

1.1	SPL VOL	1.0
1.2	SPL REP	1
1.3	LOLIM	0.00
1.4	HILIM	8.00
1.5	CAL VOL	1.0
1.6	CAL REP	2
1.7	CONC A	0.00
1.8	CONC B	0.50
1.9	CONC C	1.50
1.10	CONC D	3.00
1.11	CONC E	6.00
1.12	CONC F	10.00
1.13	UNITS	0
1.14	CRV FIT	2
1.15	MX DEV	5.0
1.16	MN POLA	170.0
1.17	MN SPAN	100.0
1.18	MODE	1
1.19	GAIN	20
1.20	MX BKG	1600.00
1.21	MN TR	4177
1.22	C DATE	11/30/89
1.23	C TIME	12:18:37

DATE : 12/15/89
TIME : 10:33:27
SERIAL # : 14001
ASSAY : GENTAMICIN

CAROUSEL : 1

SPLVOL = 1.00
REPS = 1
GAIN = 20
CALIB.DATE : 11/30/89
CALIB.TIME : 12:18:37

CONC = UG/ML

SAMPLES

LOC	CONC	NET P	BLK I
1	0.85	175.32	101.70
2	3.64	116.21	101.70
3	1.00	170.86	88.54
4	4.01	111.68	85.26
5	0.23	191.13	89.98
6	4.09	110.72	90.47
7	1.93	149.67	92.80

Figure E Gentamicin Concentration Batch Sample Printout

AMINOGLYCOSIDE DOSING CHART

1. Select Loading Dose in mg/kg [IDEAL WEIGHT] to provide peak serum levels in range listed below for desired aminoglycoside.

AMINOGLYCOSIDE	USUAL LOADING DOSES	EXPECTED PEAK SERUM LEVELS
Tobramycin Gentamicin	1.5 to 2.0 mg/kg	4 to 10 µg/ml
Amikacin Kanamycin	5.0 to 7.5 mg/kg	15 to 30 µg/ml

2. Select Maintenance Dose (as percentage of chosen loading dose) to continue peak serum levels indicated above according to desired dosing interval and the patient's corrected creatinine clearance.

		PERCENTAGE OF LOADING DOSE REQUIRED FOR DOSAGE INTERVAL SELECTED		
C(c)cr (ml/min)	half life† (hrs)	8 hrs	12 hrs	24 hrs
90	3.1	84%	-	-
80	3.4	80	91%	-
70	3.9	76	88	-
60	4.5	71	84	-
50	5.3	65	79	-
40	6.5	57	72	92%
30	8.4	48	63	86
25	9.9	43	57	81
20	11.9	37	50	75
17	13.6	33	46	70
15	15.1	31	42	67
12	17.9	27	37	61
10*	20.4	24	34	56
7	25.9	19	28	47
5	31.5	16	23	41
2	46.8	11	16	30
0	69.3	8	11	21

*Calculate corrected Creatinine Clearance C(c) cr as:

C(c) cr male = 140-age/serum creatinine
C(c) cr female = 0.85 x C(c) cr male

†Alternatively, one half of the chosen loading dose may be given at an interval approximately equal to the estimated half life.

‡Dosing for patients with C(c) cr≤10 ml/min should be assisted by measured serum levels.

Figure F Aminoglycoside Dosing Chart

VITAE

Miss Kanogwan Saerekul was born on September 17, 1962, in Yala, Thailand. She graduated with a Bachelor Degree of Science in Pharmacy in 1984 from the Faculty of Pharmacy, Prince of Songkhla University Haddyai, Songkhla, Thailand. Her current position is a staff in Department of Pharmacy, Songkhlanakarin Hospital, Faculty of Medicine, Prince of Songkhla University, Haddyai, Songkhla, Thailand.