ANNUAL REPORT (1989-1990)
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REGARDING MORAN FOUNDATION PROJECT #1-88-0028

Cyclosporine: HPLC vs RIA in Individual Patients with Specific Organ Transplants

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During the past year, we have completed our accumulation of new patient data and have since been concentrating on retrospective review and clinicopathologic correlations. Since no additional funds will be necessary for the review process, any remaining money should be returned to the general pool for reallocation.

In reviewing accumulated data, our objectives have been:

1. to determine the patterns of cyclosporine metabolite (MET) formation and concentrations in different kinds of transplant patients;
2. to determine if MET measurements offer any diagnostic or prognostic information regarding a.) toxicity or b.) organ rejection, over that available from more routine biochemical tests.

For purposes of this review, data from the following transplant patients was available:

1. heart (2)
2. kidney (3)
3. liver (5)
4. lung (2)
5. heart-lung (1)
6. bone marrow (3)

REGARDING OBJECTIVE No. 1 (figures 1-17)

It is apparent from reviewing figures 1-17 that there is significant individual pattern specificity regarding the metabolism of cyclosporine, both within as well as between transplant groups, with liver transplant patients showing the greatest variation.

Patients with kidney transplants showed the lowest average level of circulating metabolites, where the concentration was generally no more than 2X that of the parent compound. At the other extreme, in 3 of 5 liver transplant patients, metabolite concentrations were frequently 6-10x greater than the parent compound level, for many weeks to many months post-transplant. The one patient with a heart-lung trans-

plant also showed this latter pattern.

In general, typical metabolite concentrations are as follows: liver/heart-lung > heart/single lung > bone marrow > kidney.

Because of significant individual patient differences in the metabolism of cyclosporine, preliminary pharmacokinetic studies prior to surgery might be useful in determining optimum dosage schedules, at least in selected patients such as liver or heart/lung candidates.

REGARDING OBJECTIVE No. 2a (figure 18-21)

Cyclosporine metabolite concentrations were compared with alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin (BIL) levels in 1 heart-lung and 3 liver transplant patients over a period of 6-20 weeks.

From a review of figures 18 - 21, in each of the patients studied, there appears to be poor correlation between the MET pattern and that of each of the other tests, a view supported by Correlation Coefficient estimates (table 1). This suggests that the metabolites are measuring a different function than each of the other tests. The best correlation occurred with ALP, but even here, it is relatively poor (average = 0.519). However, additional review and perhaps other studies are probably necessary to determine whether Met has any usefulness in diagnosing early cyclosporine toxicity.

TABLE 1
CORRELATION COEFFICIENTS (R-VALUES)
CYCLOSPORINE METABOLITES
VERSUS

Patient	ALT	ALP	BIL
J.C.	.345	.613	.137
L.F.	.198	.376	.353
M.F.	.657	.521	.590
V.N.	.059	.565	.565
Ave.	.315	.519	.411

REGARDING OBJECTIVE No. 2b

The MET concentrations of 4 liver transplant patients were compared with corresponding Interleukin-2 Receptor (IL-2R) levels, the latter assumed to be a reflection of immune activity and apparent host efforts at organ rejection. As one reviews the results (figure 22), no good pattern of correlation appears to be present, and it would appear from this limited group of patients that MET measurements are probably not useful for the early detection of organ

rejection (table 2).

TABLE 2
CORRELATION COEFFICIENT (R-VALUE)
CYCLOSPORINE METABOLITES
VERSUS IL-2R

J.C.	.297
L.F.	.126
M.T.	.145
G.P.	.304
Ave.	.218

In one of the patients (L.F.), MET, ALT, ALP, BIL, and IL-2R were compared with liver biopsy information. Again, from this single patient, useful patterns of correlation are apparently absent (figure 23).

In summary, this study is now complete. Initially, we showed that RIA procedures, utilizing monoclonal, monospecific anti-cyclosporine antibodies, can accurately measure the concentration of the parent compound, Cyclosporine A, producing results that compare favorably with the reference HPLC procedure. In addition, we also measured the concentration of the metabolites of cyclosporine in a representative group of transplant patients to determine their utility in the early recognition of toxicity or organ rejection, a measurement that would appear to have limited usefulness. However, the great diversity of metabolite patterns in individual patients would appear to support the recommendation of some that pharmacokinetic studies be performed pre-transplant as an aid in optimizing the dose of cyclosporine post-transplant.

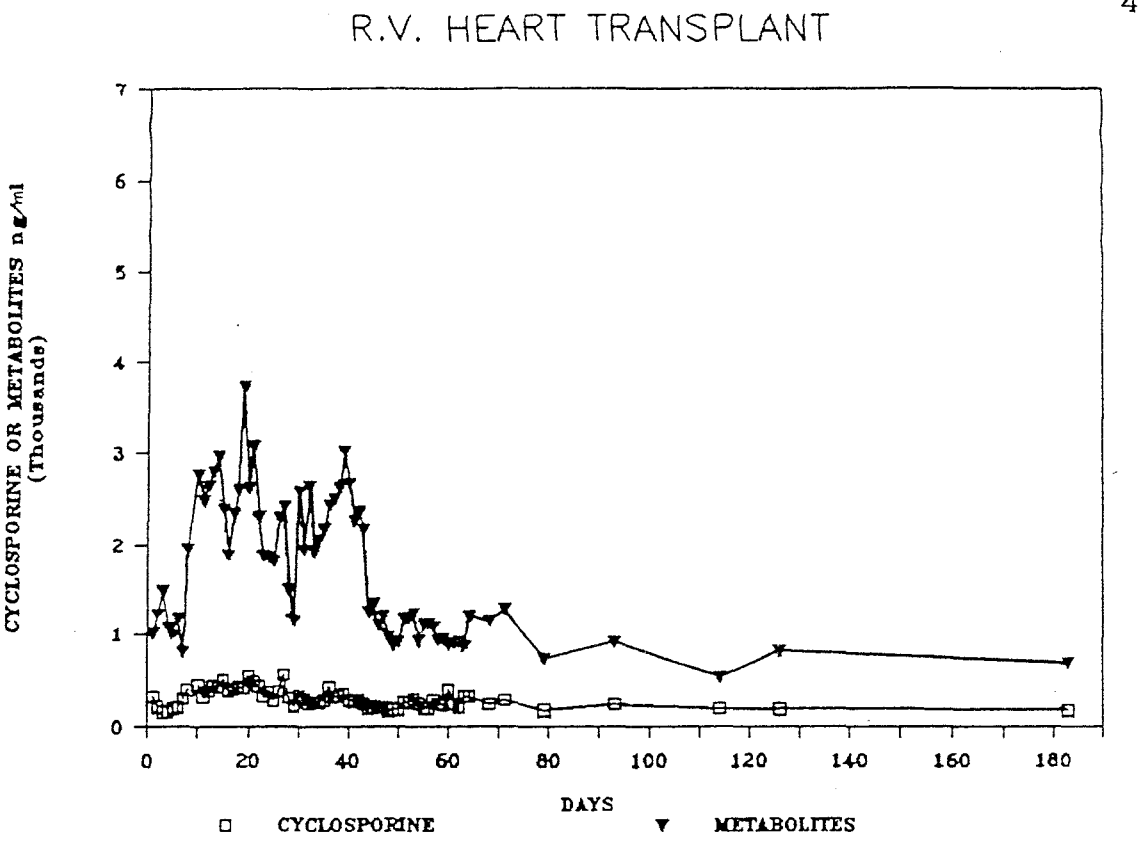


Figure 1

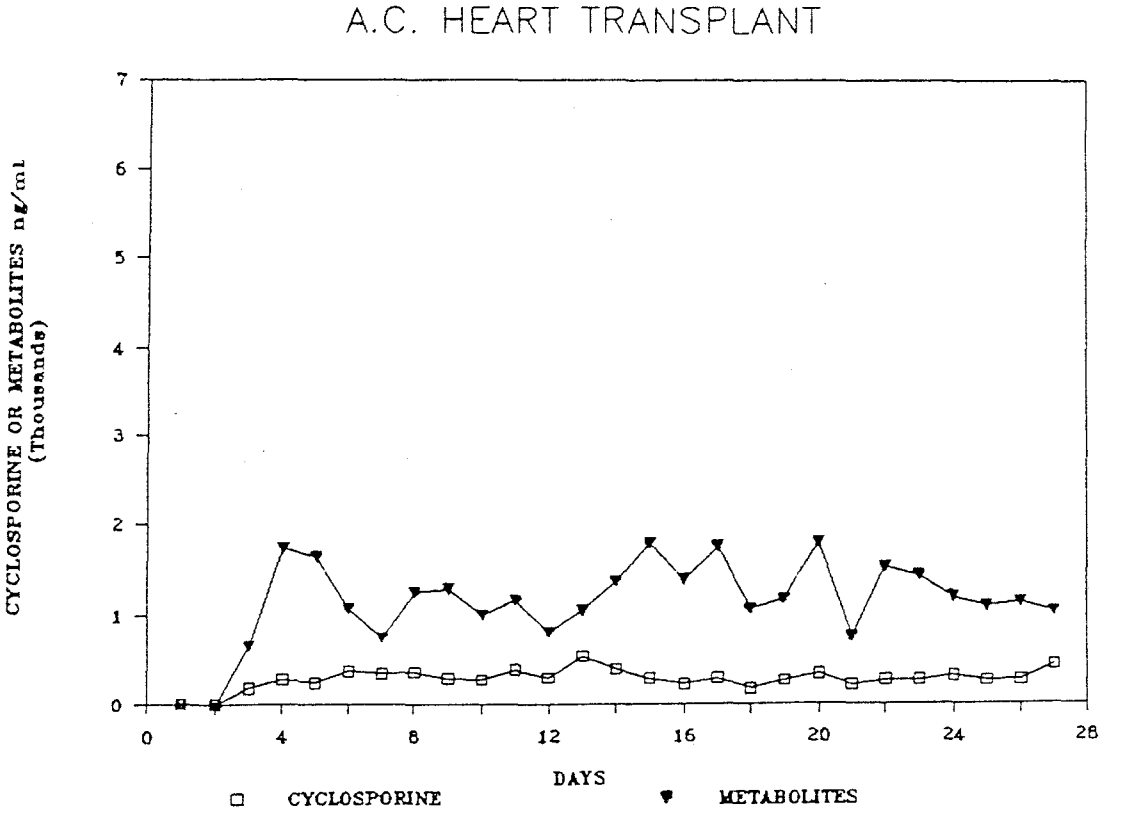


Figure 2

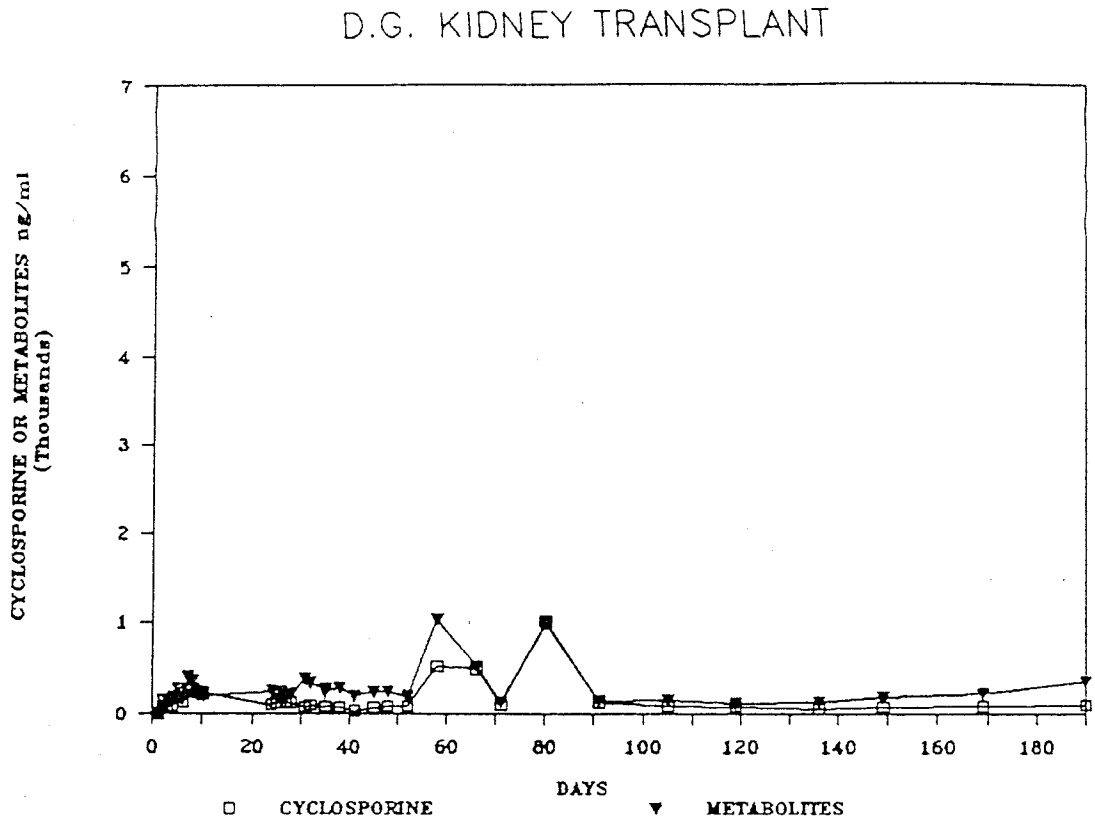
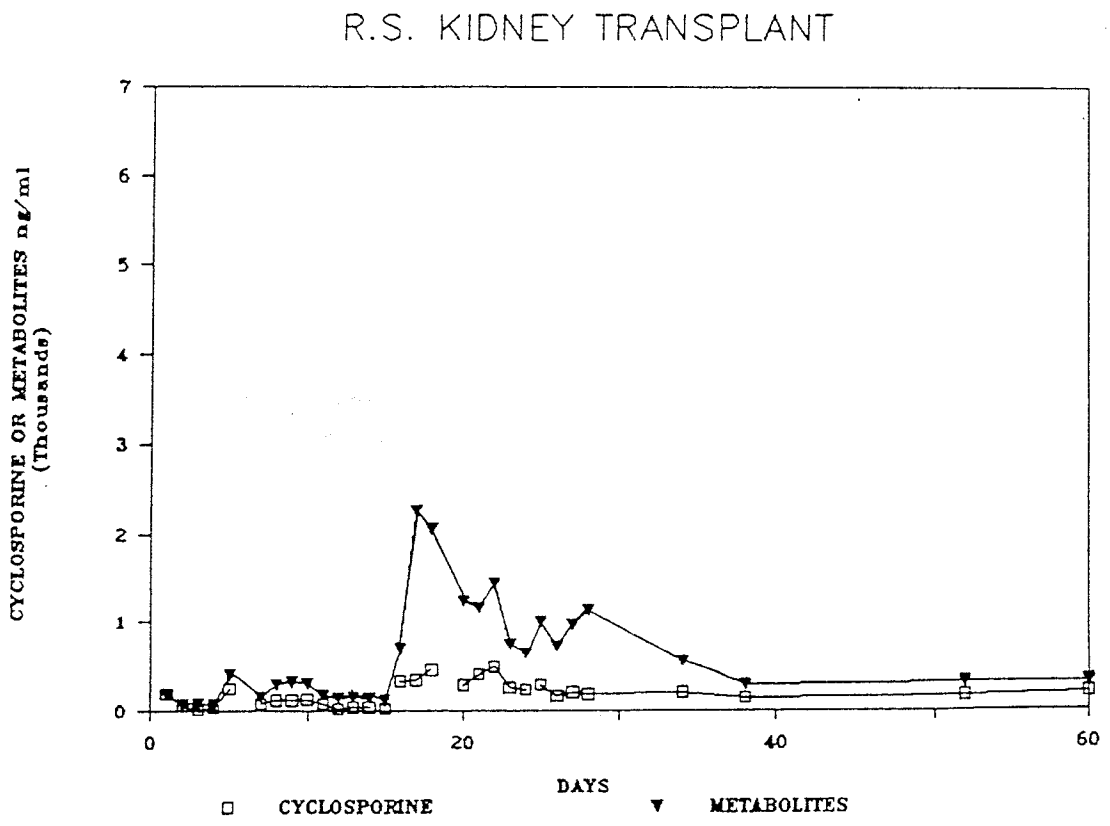


Figure 3



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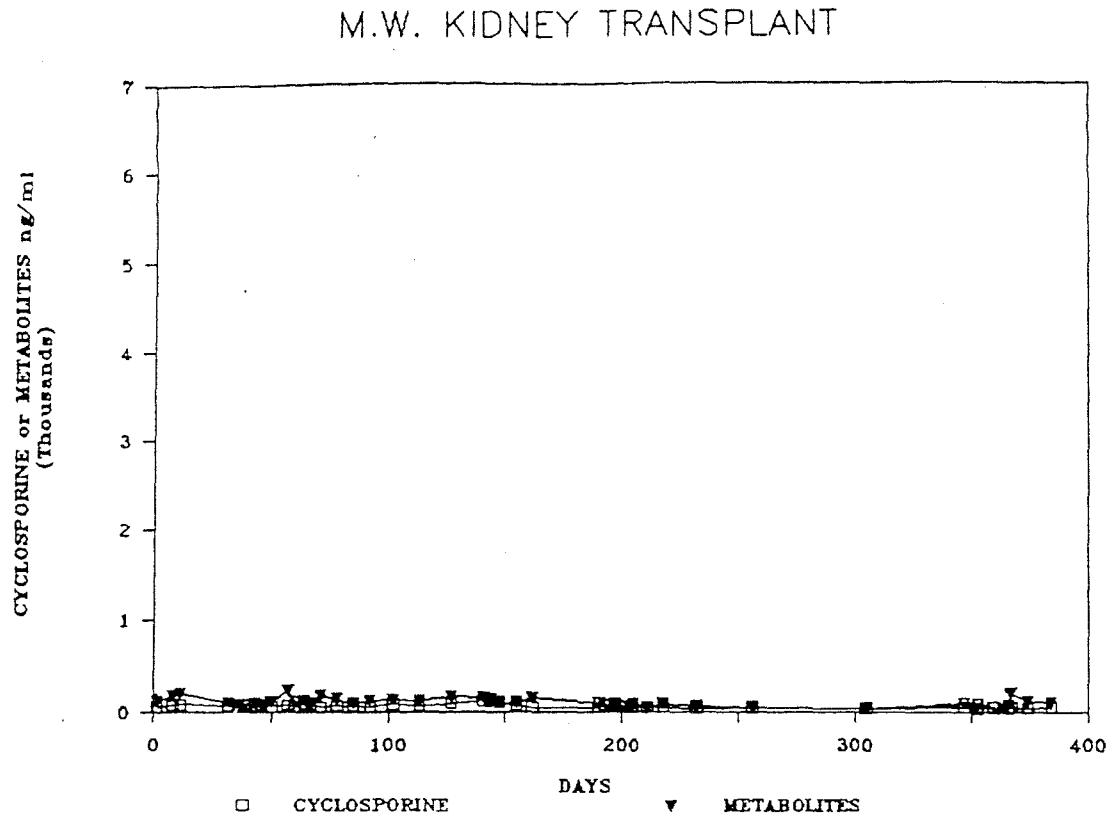

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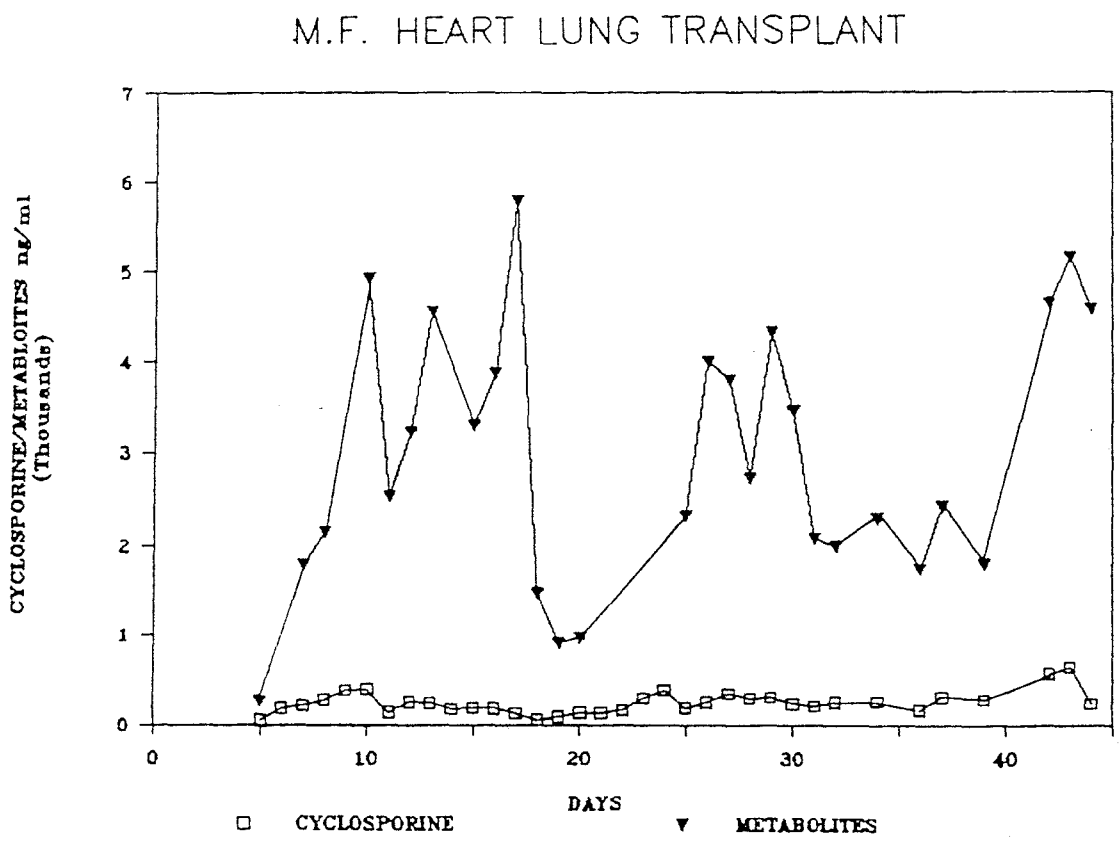

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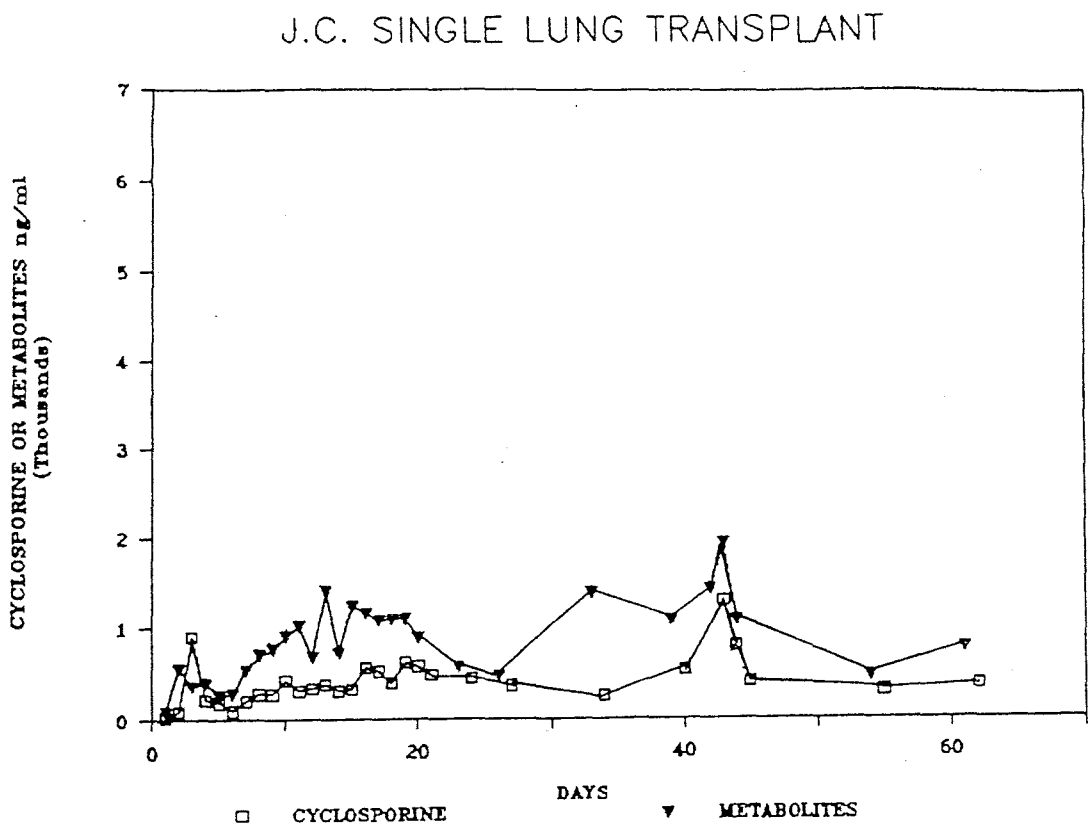

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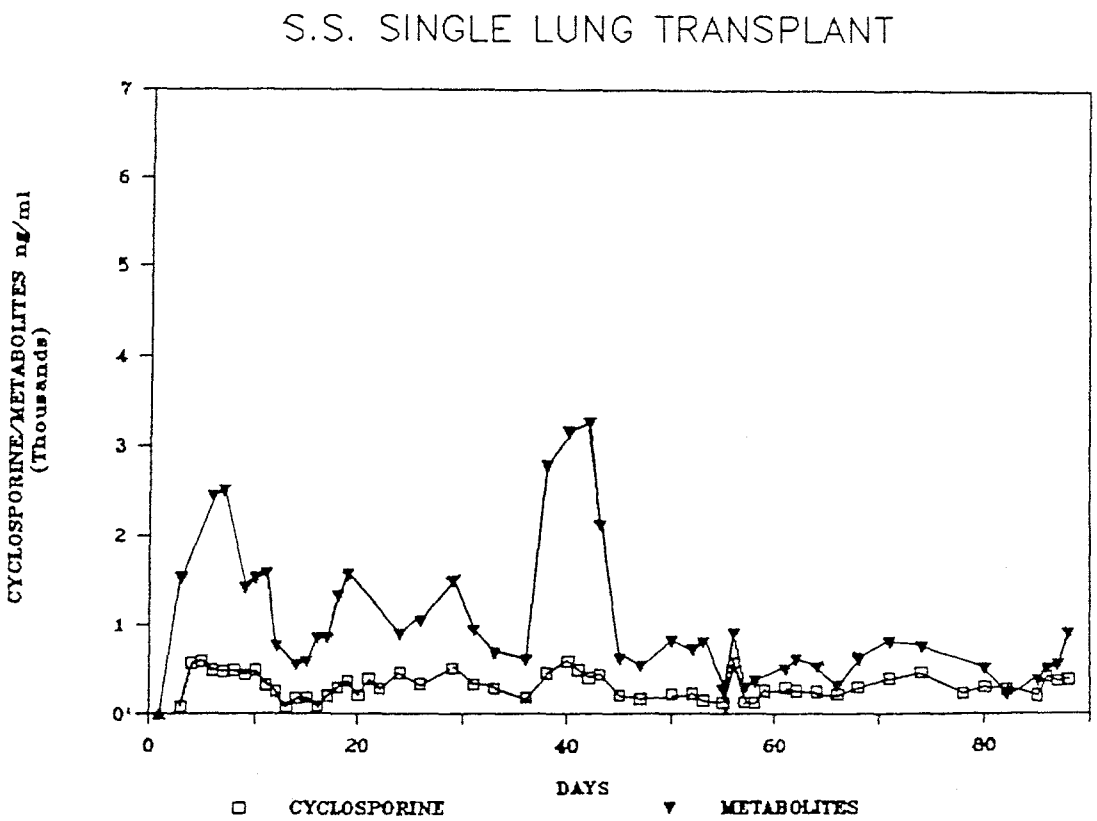

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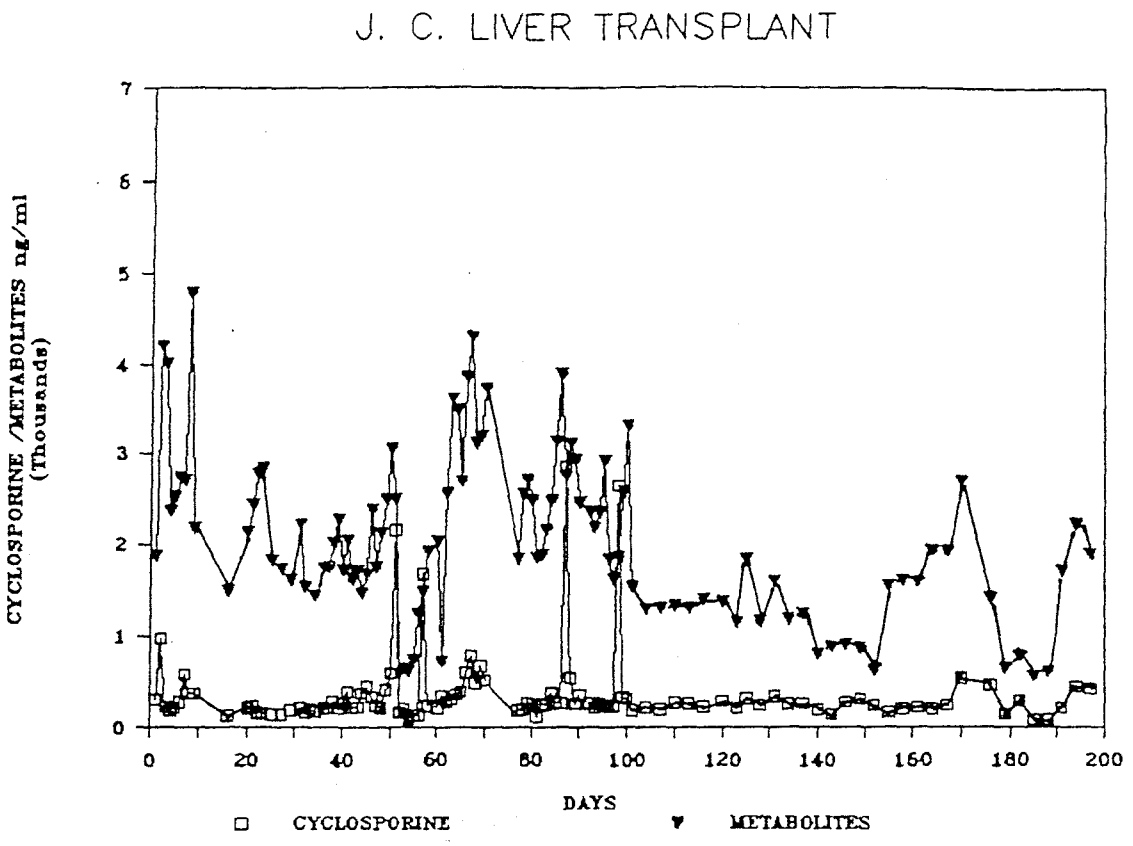

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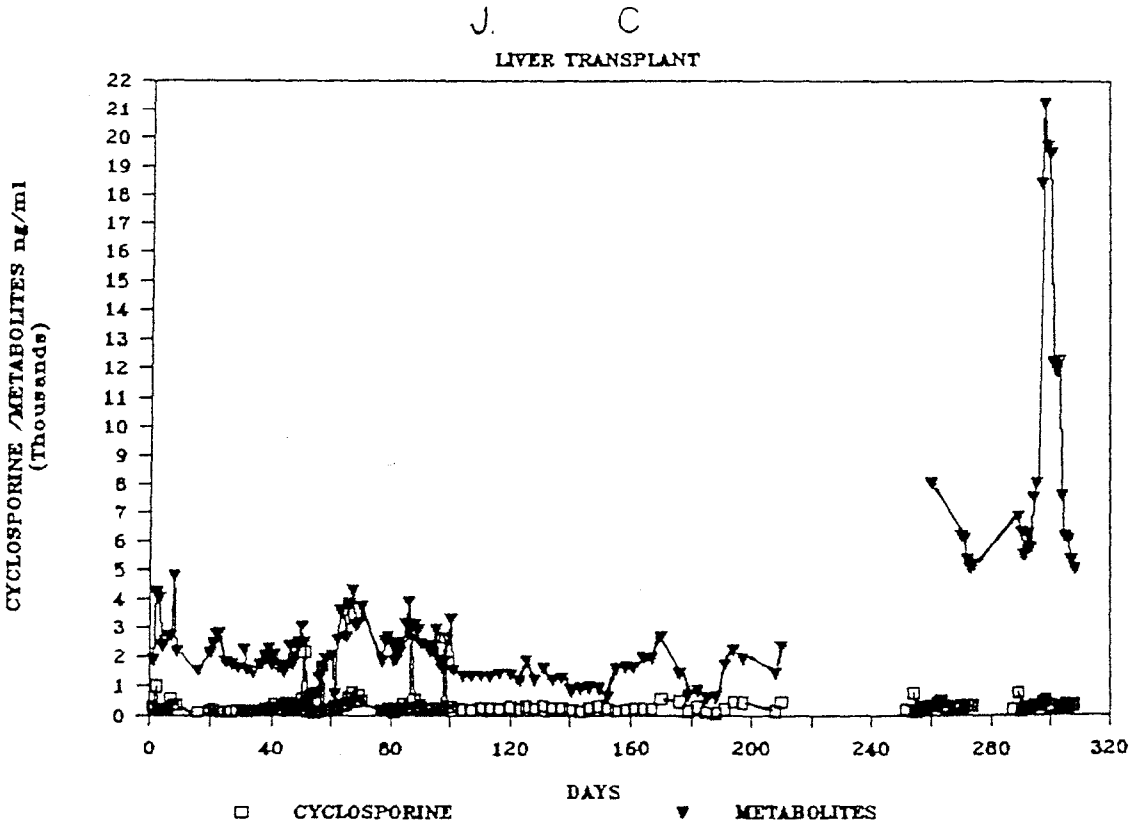

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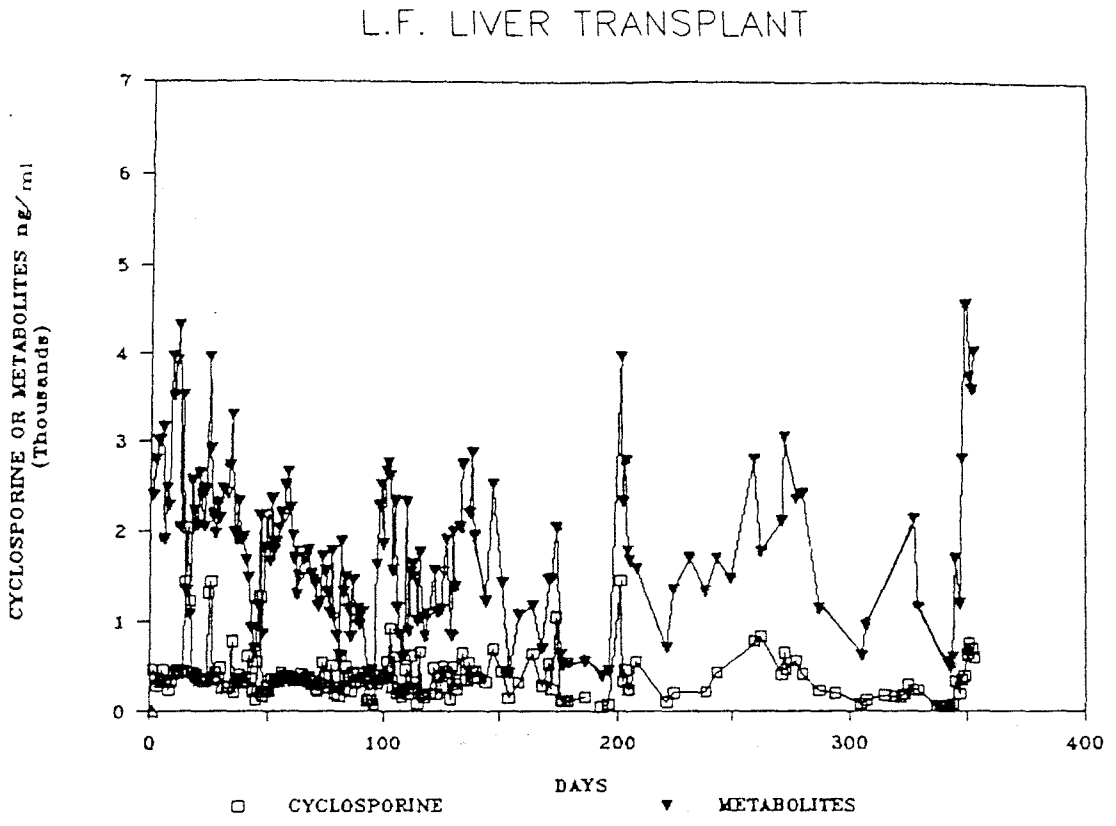

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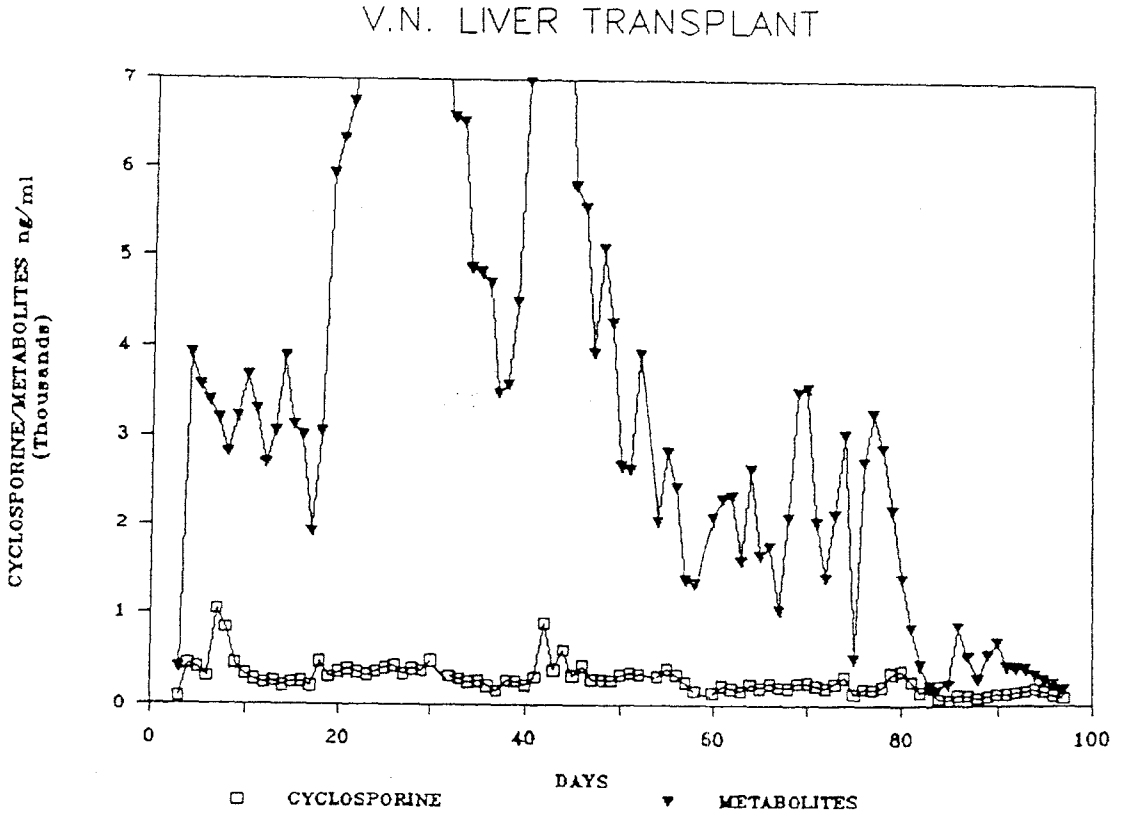

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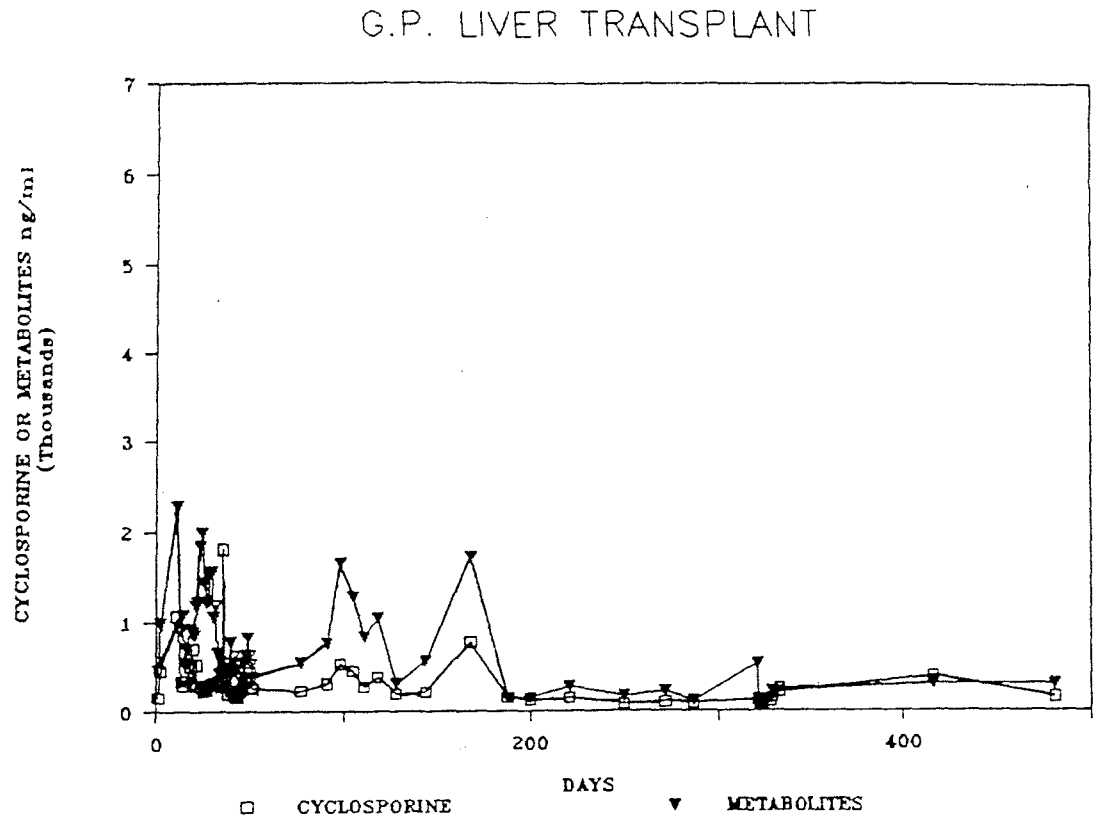

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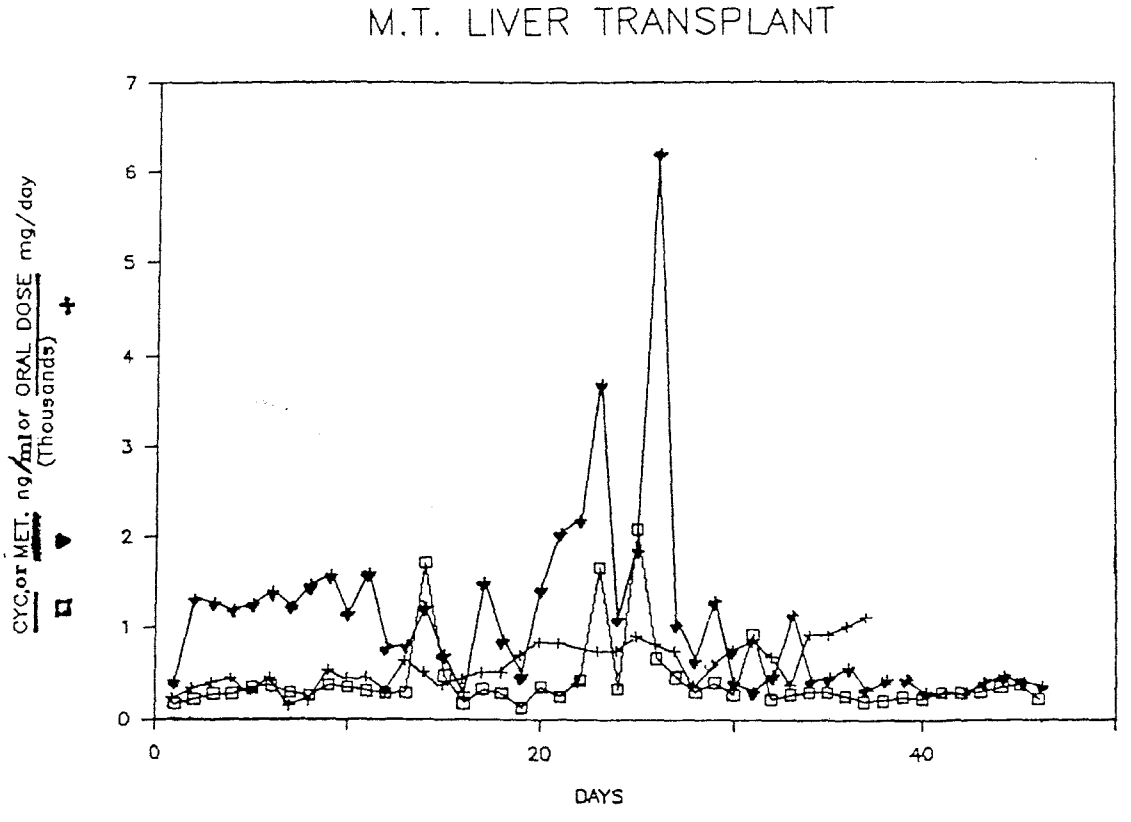

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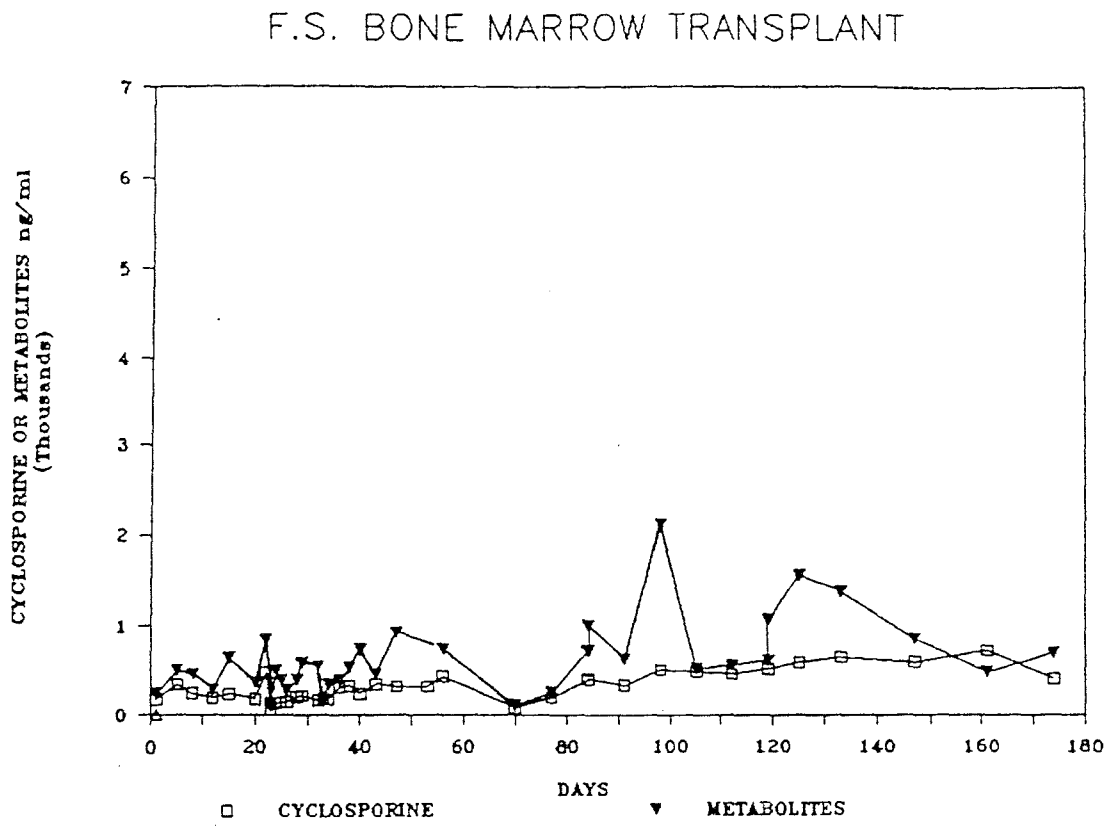

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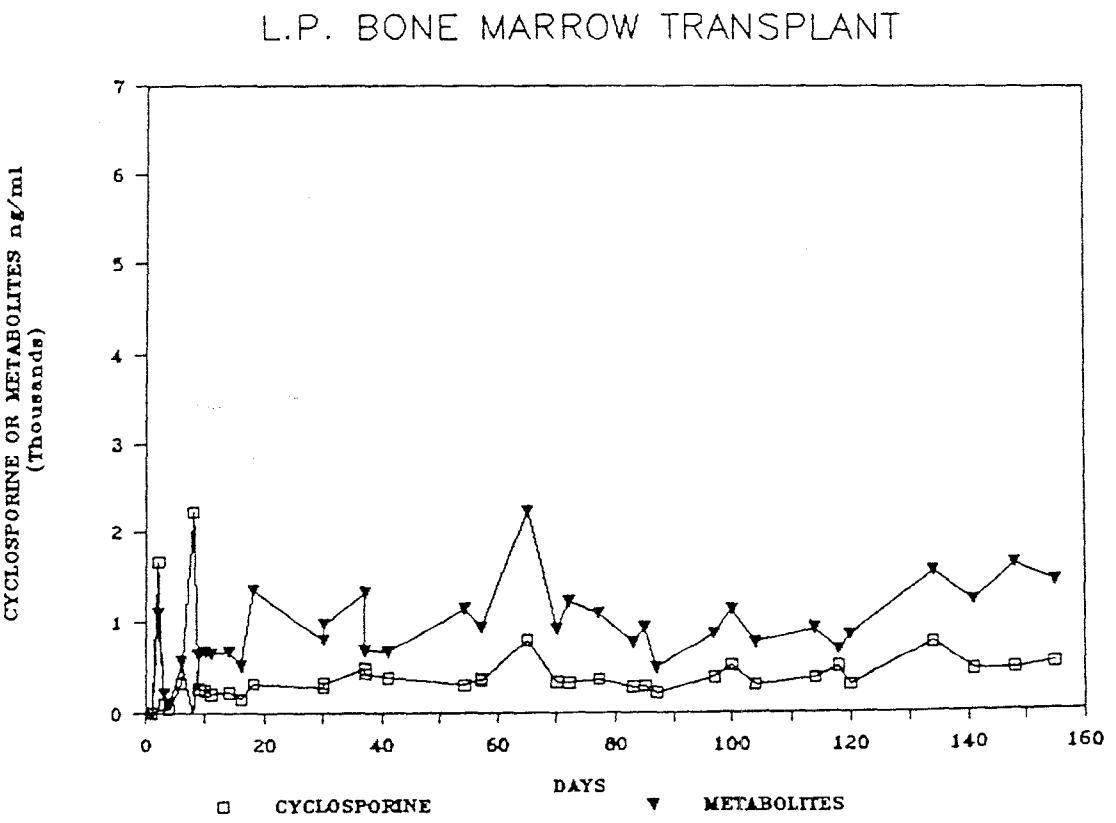

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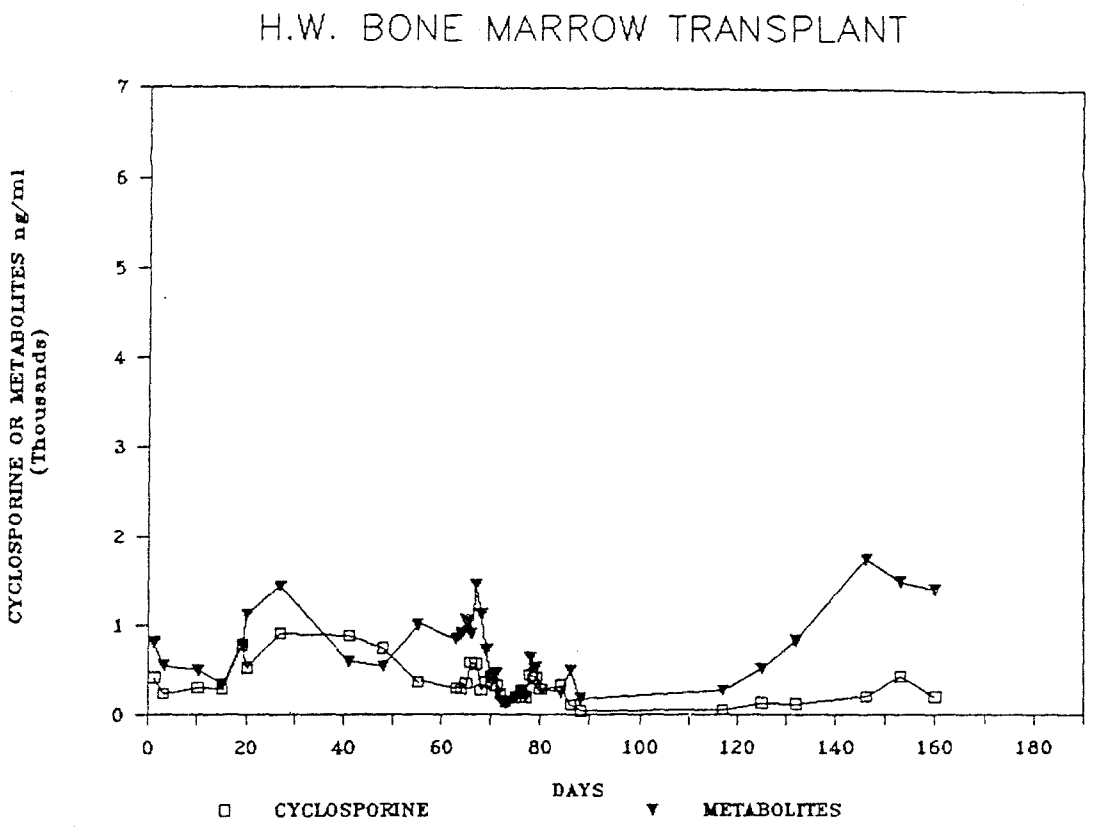
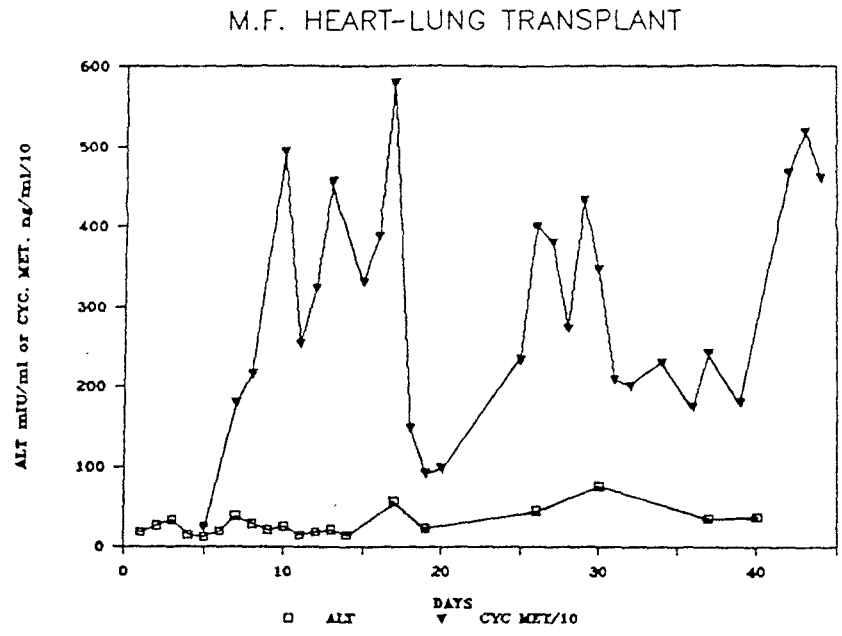
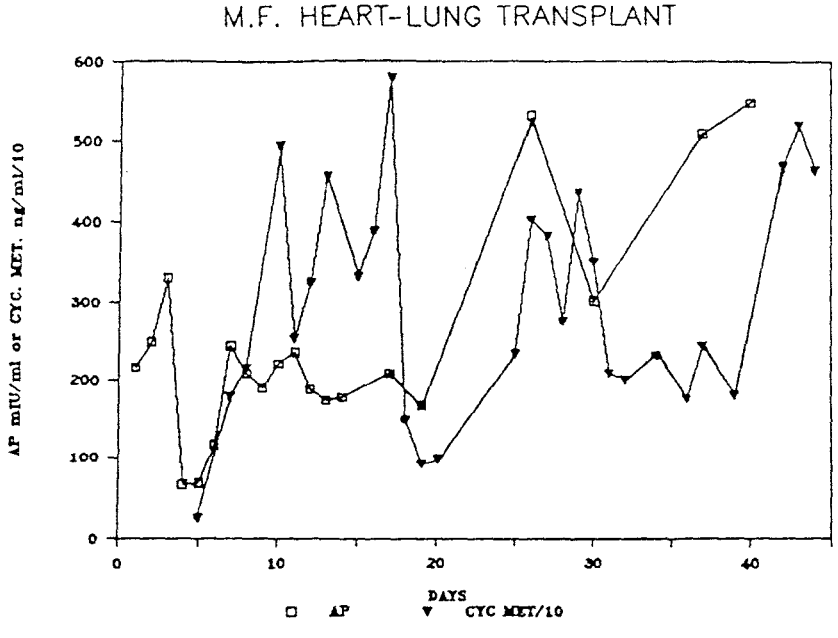

H.W. BONE MARROW TRANSPLANT
CYCLOSPORINE OR METABOLITES ng/ml
(Thousands)
7
6
5
4
3
2
1
0
0
20
40
60
80
100
120
140
160
180
DAYS
CYCLOSPORINE
METABOLITES

Figure 17


M.F. HEART-LUNG TRANSPLANT
ALT mIU/ml or CYC. MET. ng/ml/10
600
500
400
300
200
100
0
0
10
20
30
40
DAYS
ALT
CYC MET/10


M.F. HEART-LUNG TRANSPLANT
AP mIU/ml or CYC. MET. ng/ml/10
600
500
400
300
200
100
0
0
10
20
30
40
DAYS
AP
CYC MET/10

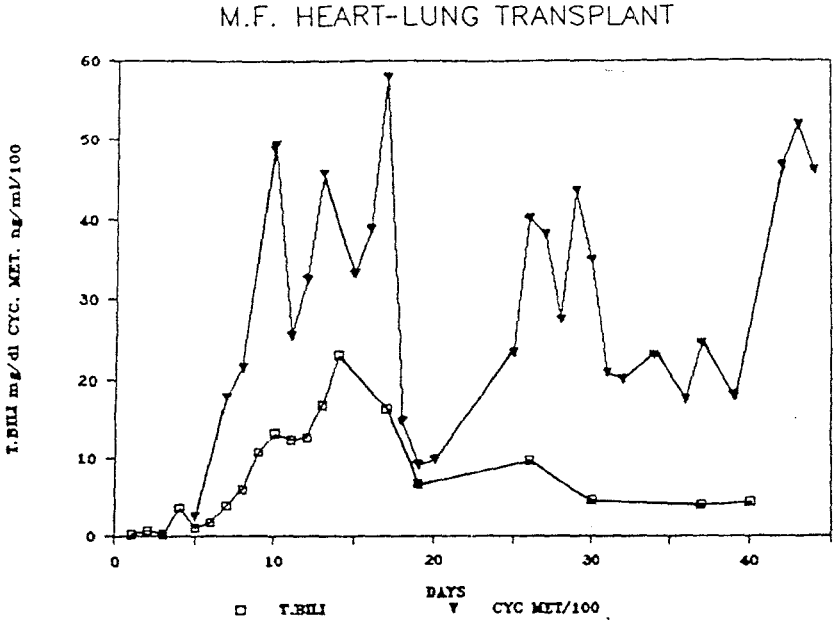
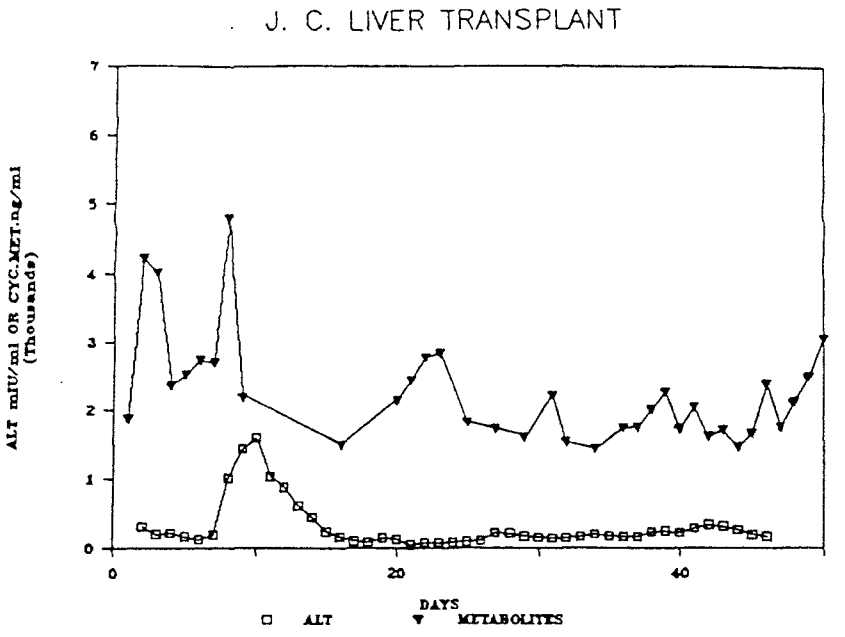
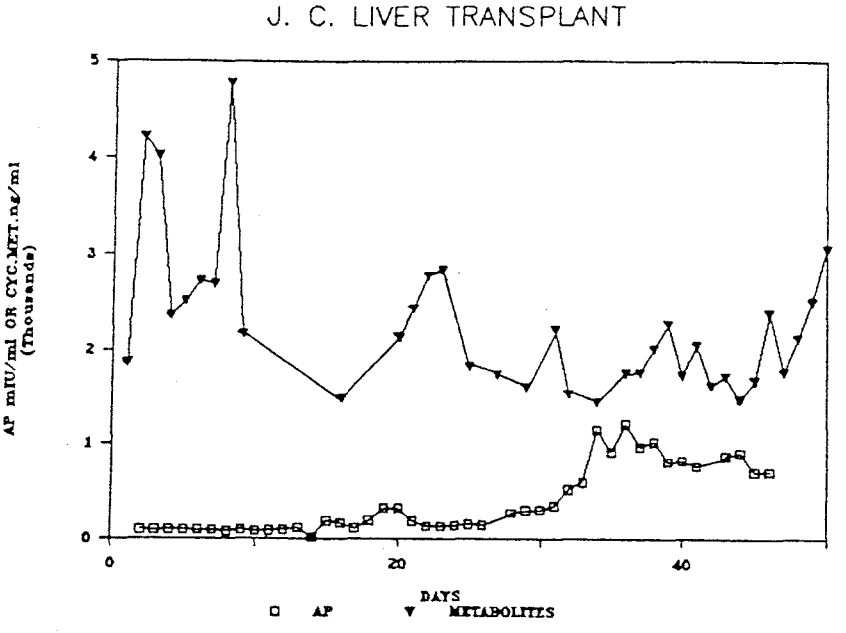

M.F. HEART-LUNG TRANSPLANT
T.BILI mg/dl CYC. MET. ng/ml/100
60
50
40
30
20
10
0
0
10
20
30
40
DAYS
T.BILI
CYC MET/100

Figure 18


J. C. LIVER TRANSPLANT
ALT mIU/ml OR CYC.MET.ng/ml (Thousands)
DAYS
ALT
METABOLITES


J. C. LIVER TRANSPLANT
AP mIU/ml OR CYC.MET.ng/ml (Thousands)
DAYS
AP
METABOLITES

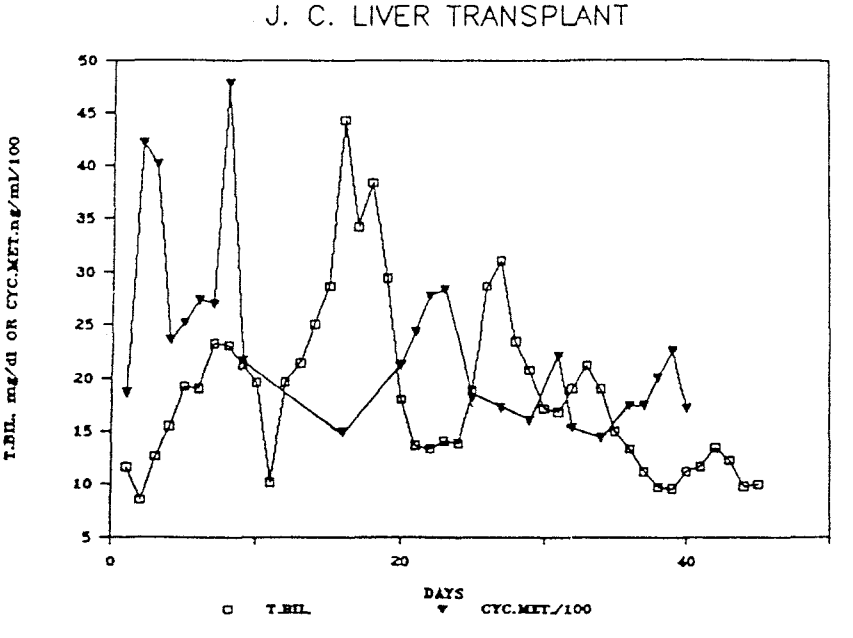
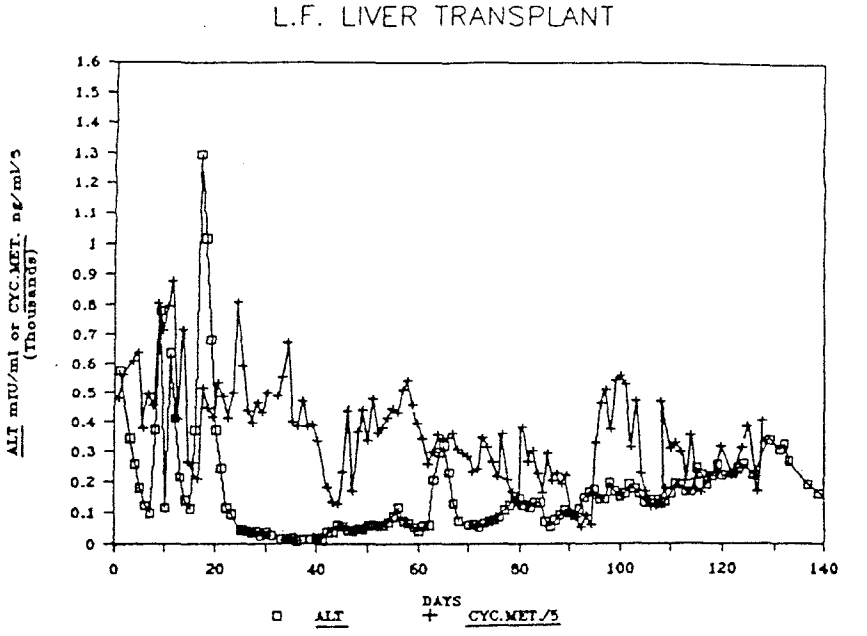
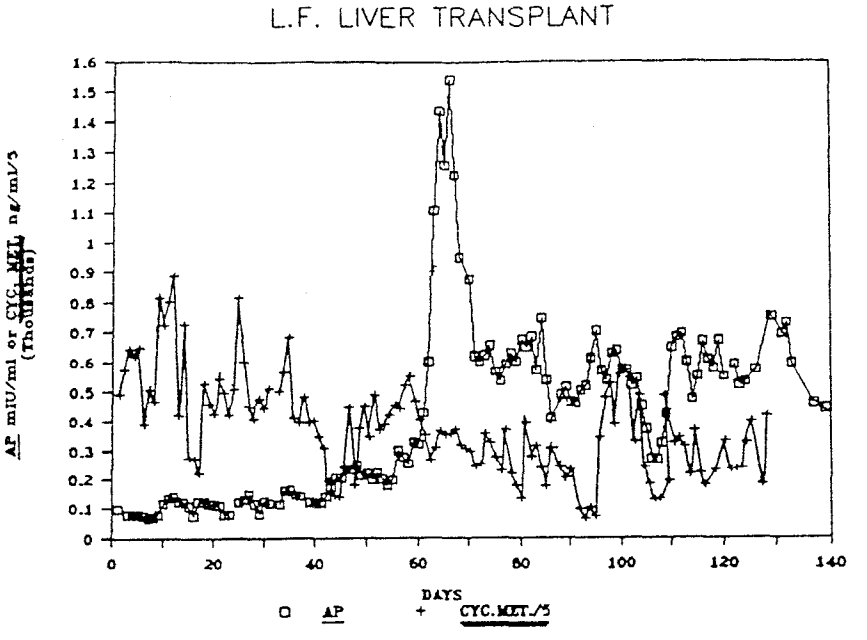

J. C. LIVER TRANSPLANT
T.BIL. mg/dl OR CYC.MET.ng/mL/100
DAYS
T.BIL.
CYC.MET./100

Figure 19


L.F. LIVER TRANSPLANT
ALT mIU/ml or CYC.MET. ng/ml/5 (Thousands)
DAYS
ALT
CYC.MET./5


L.F. LIVER TRANSPLANT
AP mIU/ml or CYC. MET. ng/ml/5 (Thousands)
DAYS
AP
CYC.MET./5

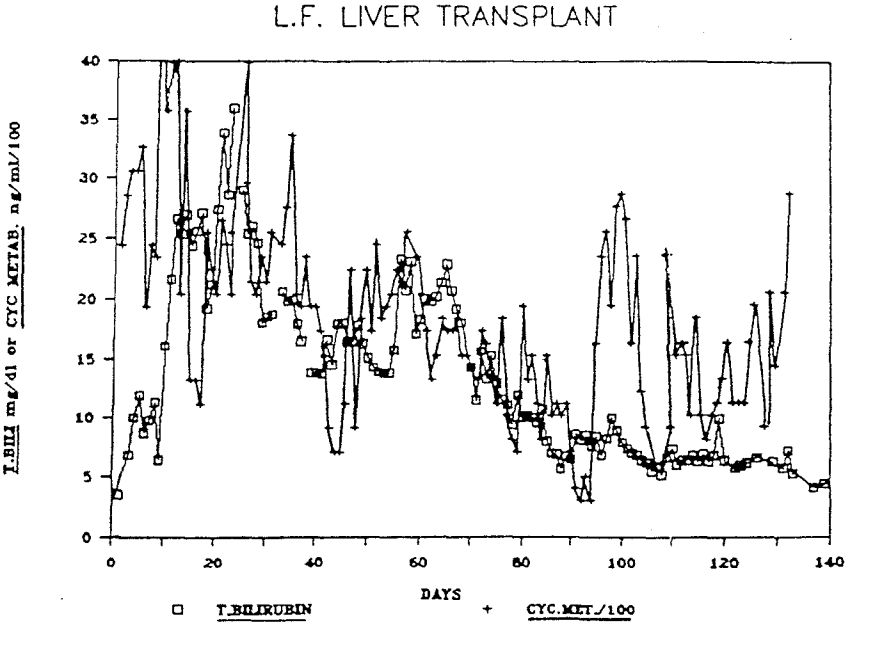
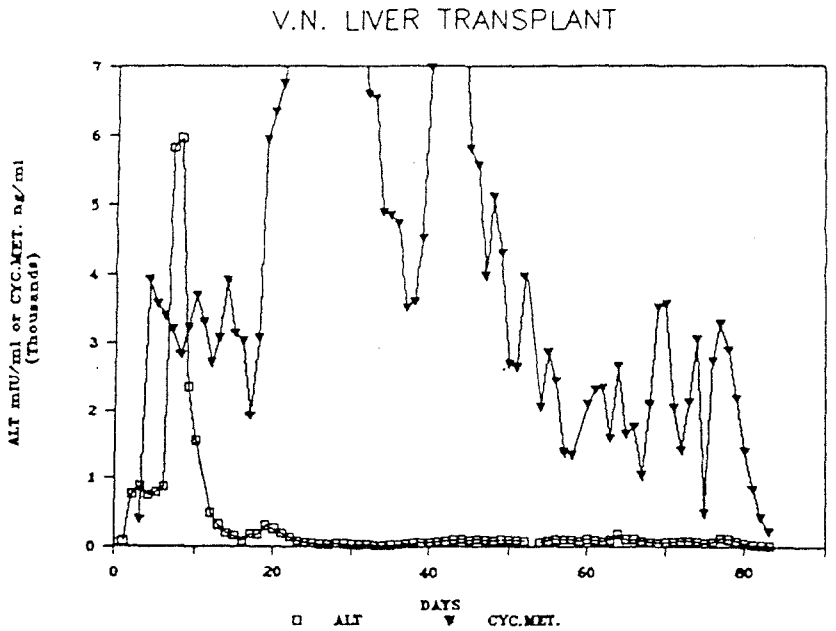
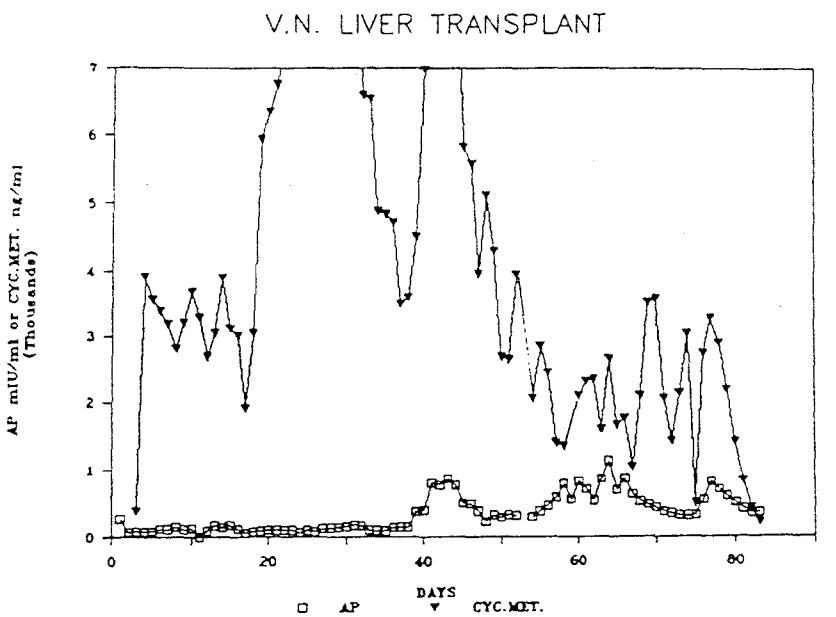

L.F. LIVER TRANSPLANT
T.BILI mg/dl or CYC METAB. ng/ml/100
DAYS
T.BILIRUBIN
CYC.MET./100

Figure 20


V.N. LIVER TRANSPLANT
ALT mIU/ml or CYC.MET. ng/ml (Thousands)
DAYS
ALT
CYC.MET.


V.N. LIVER TRANSPLANT
AP mIU/ml or CYC.MET. ng/ml (Thousands)
DAYS
AP
CYC.MET.

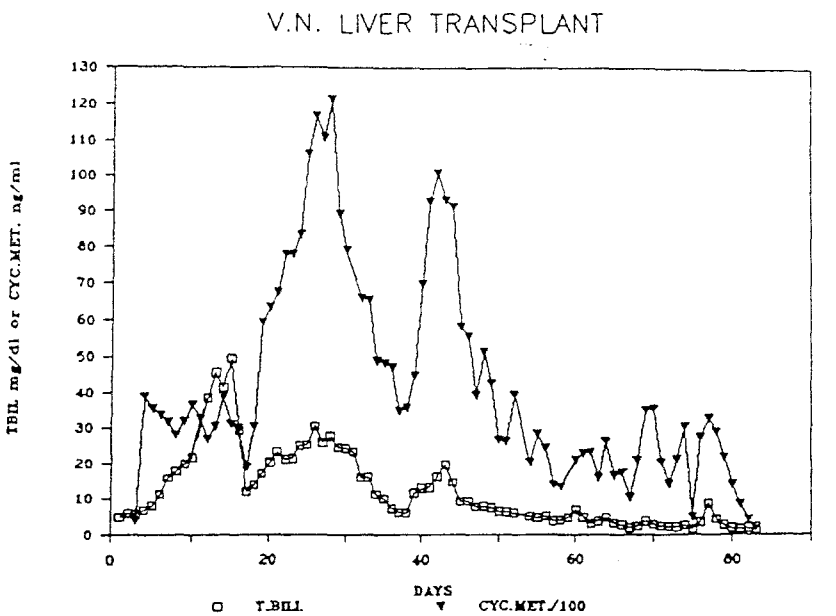
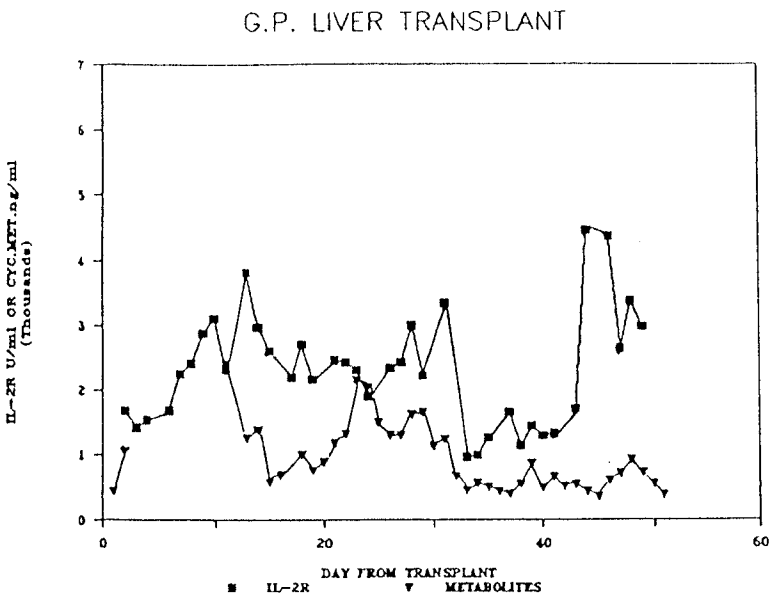
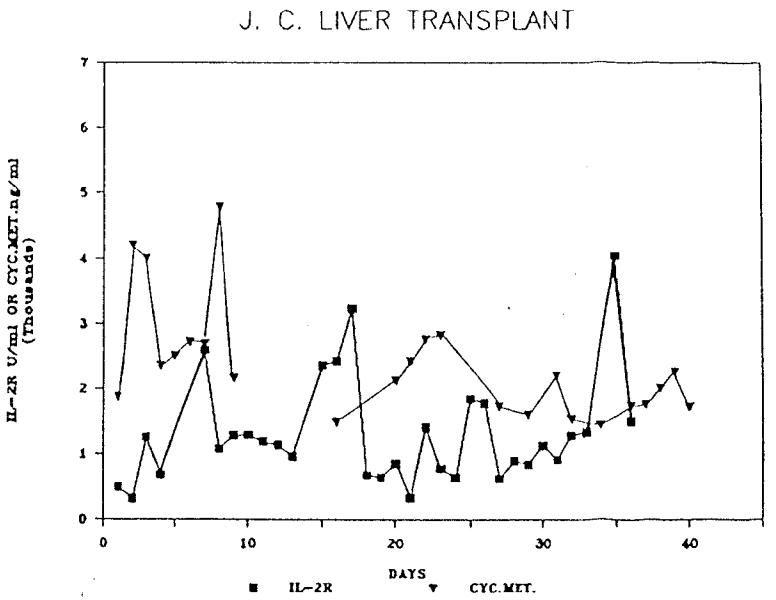
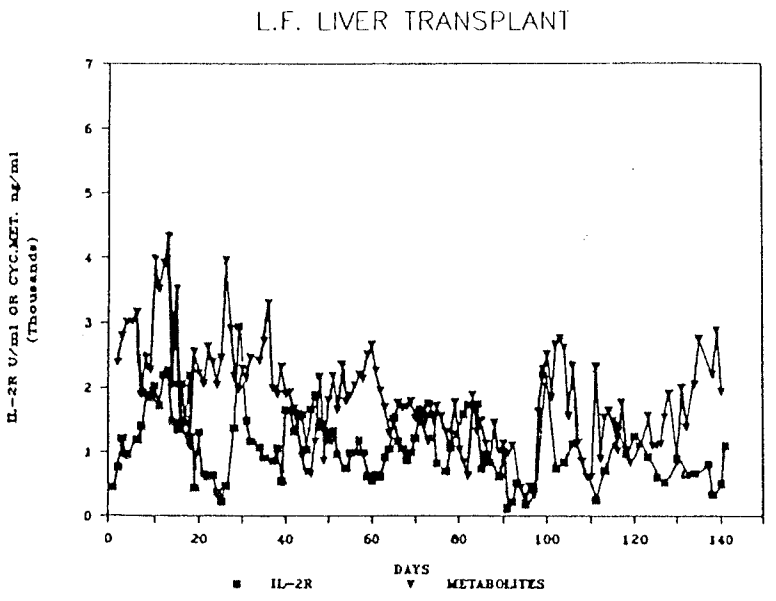

V.N. LIVER TRANSPLANT
TBIL mg/dl or CYC.MET. ng/ml
DAYS
T.BILL
CYC.MET./100

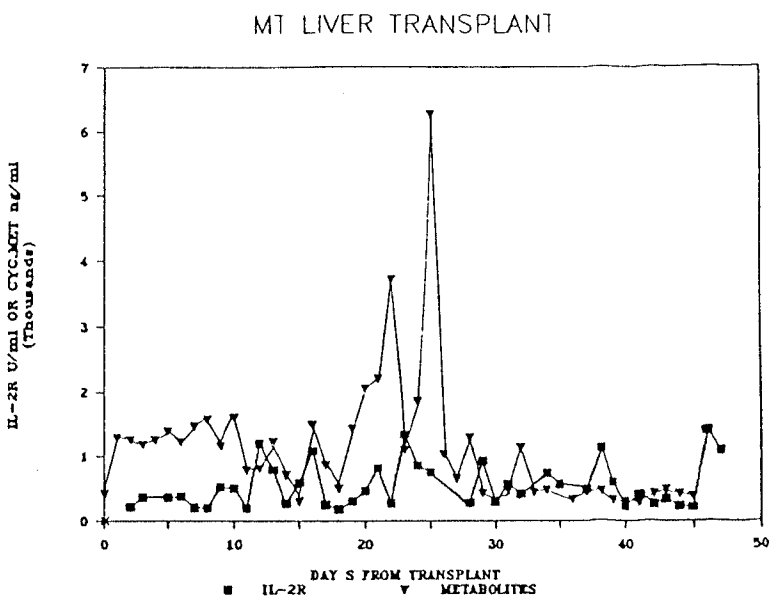
Figure 21

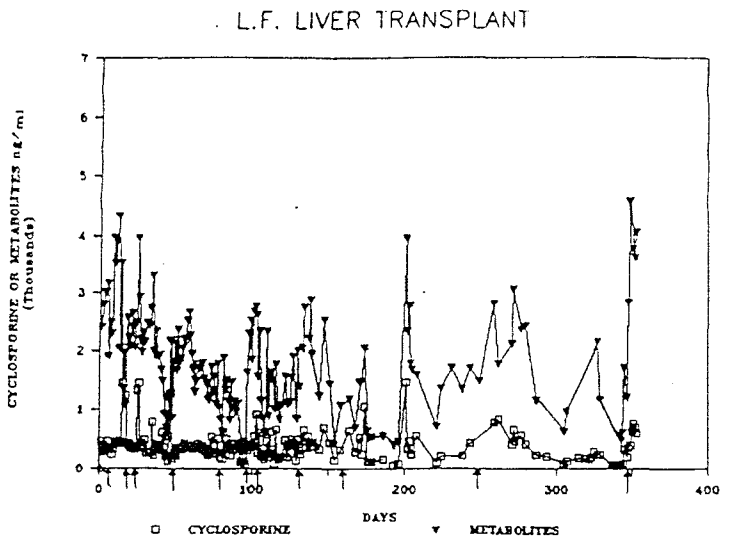
Figure 22

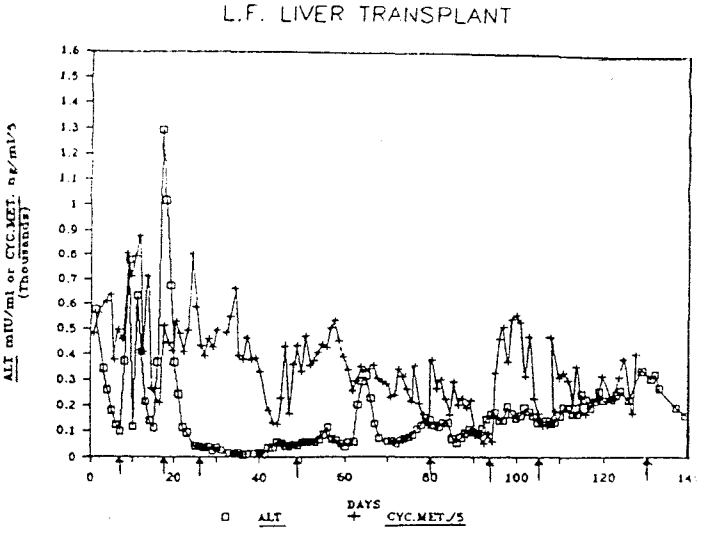

G.P. LIVER TRANSPLANT
IL-2R U/ml OR CYC.MET.ng/ml (Thousands)
DAY FROM TRANSPLANT
IL-2R
METABOLITES

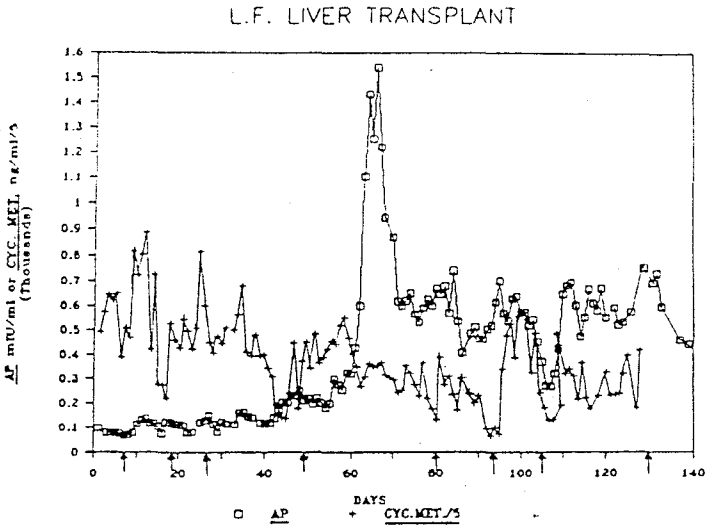

J. C. LIVER TRANSPLANT
IL-2R U/ml OR CYC.MET.ng/ml (Thousands)
DAYS
IL-2R
CYC.MET.

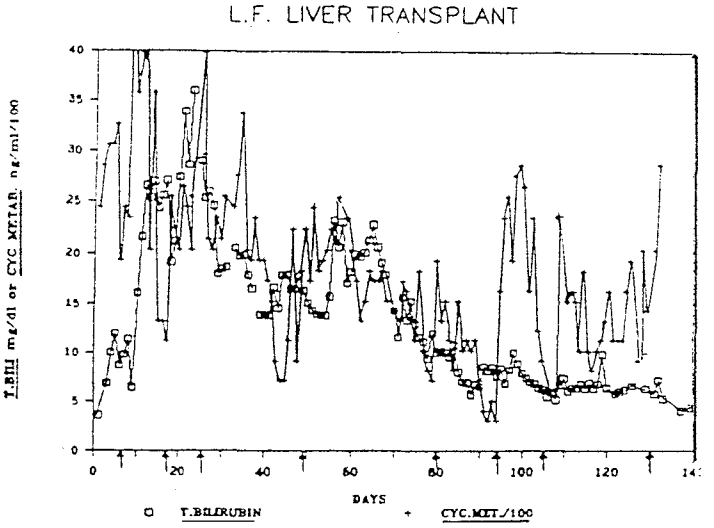

L.F. LIVER TRANSPLANT
IL-2R U/ml OR CYC.MET. ng/ml (Thousands)
DAYS
IL-2R
METABOLITES

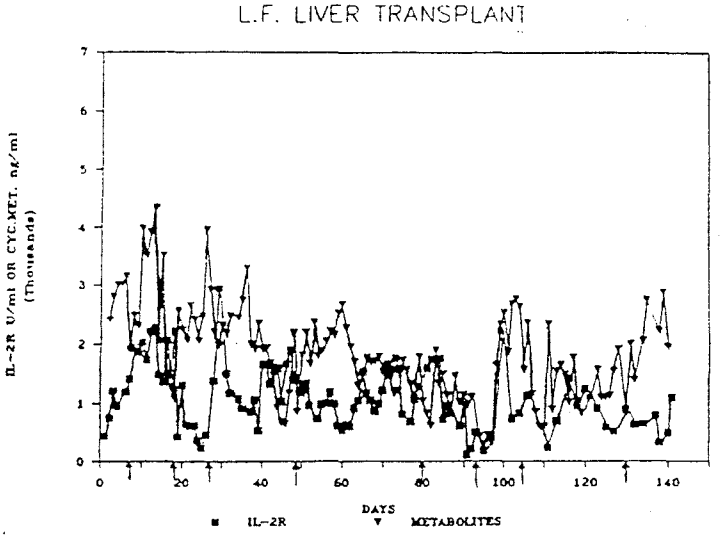

MT LIVER TRANSPLANT
IL-2R U/ml OR CYC.MET ng/ml (Thousands)
DAY S FROM TRANSPLANT
IL-2R
METABOLITES


L.F. LIVER TRANSPLANT
CYCLOSPORINE OR METABOLITES ng/ml (Thousands)
DAYS
CYCLOSPORINE
METABOLITES


L.F. LIVER TRANSPLANT
ALT mIU/ml or CYC.MET. ng/ml/5 (Thousands)
DAYS
ALT
CYC.MET./5


L.F. LIVER TRANSPLANT
AP mIU/ml or CYC.MET. ng/ml/5 (Thousands)
DAYS
AP
CYC.MET./5


L.F. LIVER TRANSPLANT
T.BILI mg/dl or CYC.METAB. ng/ml/100
DAYS
T.BILIRUBIN
CYC.MET./100


L.F. LIVER TRANSPLANT
IL-2R U/ml OR CYC.MET. ng/ml (Thousands)
DAYS
IL-2R
METABOLITES