1. (a) The following SAS code was used. Note that x1 is transformed to be 1 for the active drug and zero for the placebo. Glimmix estimates the log odds of an abnormal electrocardiogram because Y is coded 1 for abnormal and zero for a normal electrocardiogram.

```sas
/* Analyze the data from a crossover trial on cerebrovascular deficiency from example 8.1 in DHLZ */

/* THE VARIABLES WERE CODED AS FOLLOWS: */

ID = CLUSTER VARIABLE
CLASS = 1, NEEDED TO RUN GEE2
Y = 1 abnormal electrocardiogram
    0 normal electrocardiogram
Int = 1 (INTERCEPT)
X1 = 1 placebo (treatment B)
    0 active drug A
X2 = 1 if period 2
    0 if period 1
X12 = X1*X2
order = 1 if B before A
        0 if A before B

REFERENCE: JONES AND KENWARD(1989)
            CHAPMAN AND HALL, P.9 */

data set1;
  infile "c:\st565\dhlz.example8_1.dat";
  input patient class y int x1 x2 x12 order ;
  /* Recode the variables */
  x1=abs(1-x1);
  x12=x1*x2;
  run;

  /* Fit a model use GLMMIX to include a random location effect */
```
%inc 'c:\mydocuments\courses\st557\sas\glmm800.sas' / nosource;
run;

/***************************************************************************/

%glimmix(data=set1,
stmts=%str(
   class patient ;
   model y = x1 x2 x12 / covb
       solution ddfm=kr;
   random intercept / subject=patient g
gcorr solution;),
   error=binomial, link=logit,
   converge=1e-8, maxit=20, out=setp
 )
run;

proc print data=setp (obs=5); run;

Estimates for fixed effects parameters are given below:

| Effect | Estimate | Standard Error | DF  | t Value | Pr > |t| |
|--------|----------|----------------|-----|---------|-------|---|
| Intercept | 0.8109 | 0.8703 | 65 | 0.93 | 0.3549 |
| x1    | 4.4901  | 1.3409  | 65 | 3.35 | 0.0014 |
| x2    | -0.1688 | 1.2320  | 65 | -0.14 | 0.8915 |
| x12   | -3.2772 | 2.4097  | 65 | -1.36 | 0.1785 |

$\beta_1$ is the logarithm of the ratio of conditional odds obtained by dividing the odds of having an abnormal electrocardiogram when the active drug is given in the first period by the odds of having an abnormal electrocardiogram when the placebo is given in the first period. The estimate of the corresponding conditional odds ratio is $\exp(\hat{\beta}_1) = \exp(4.4901) = 89.13$, and an approximate 95% confidence interval for this conditional odds ratio is $(6.436, 1234.3)$. This conditional odds ratio is not well estimated, but there is evidence that the active drug increases the risk of an abnormal electrocardiogram.

$\beta_2$ is the logarithm of the ratio of conditional odds obtained by dividing the odds of having an abnormal electrocardiogram in period 1 when the placebo is given by the odds of having an abnormal electrocardiogram in the second period when the placebo is given. The estimate of the corresponding conditional odds ratio is $\exp(-.1688) = 0.84$ and an approximate 95% confidence interval for this conditional odds ratio is $(.076, 9.45)$. There is no significant period effect for the placebo treatment.
\[ \beta_3 = [(\beta_0 + \beta_1 + \text{beta}_2 + \text{beta}_3) - \beta_0] - [(\beta_0 + \beta_1) - \beta_0] \] is a difference in two log-odds ratios. The logarithm of the ratio of conditional odds obtained by dividing the odds of having an abnormal electrocardiogram when the active drug is given in the second period divided by the odds of having an abnormal electrocardiogram when the placebo is given in the second period minus the logarithm of the ratio of conditional odds obtained by dividing the odds of having an abnormal electrocardiogram when the active drug is given in the first period divided by the odds of having an abnormal electrocardiogram when the placebo is given in the first period. The estimate of the corresponding ratio of conditional odds ratios is \( \exp(\hat{\beta}_3) = \exp(-3.2772) = .038 \), and an approximate 95% confidence interval for this ratio of conditional odds ratios is (.000335, 4.25). The estimate of this ratio of conditional odds ratios is not significantly different from one.

Including the insignificant interaction between drug effects and period in the model seems to distort the estimation of the effect of the active drug. It is worthwhile in this case to fit a logistic regression model with conditionally additive period and treatment effects, i.e., fit the model

\[
\log\left(\frac{\pi_{ij}}{1 - \pi_{ij}}\right) = \beta_0 + \beta_1 X_{1ij} + \beta_2 X_{2ij} + \eta_i
\]

The estimated parameters for this model are shown below:

| Effect | Estimate | Error | DF  | t Value | Pr > |t| |
|--------|----------|-------|-----|---------|-------|
| Intercept | 1.6141   | 0.6388 | 72  | 2.53    | 0.0137 |
| x1      | 2.7607   | 0.4559 | 68.9| 6.06    | <.0001 |
| x2      | -1.7089  | 0.4548 | 69.2| -3.76   | 0.0004 |

These results indicate that in either period the odds of an abnormal electrocardiogram with the active drug are about \( \exp(2.7607) = 15.8 \) times greater than the the odds of an abnormal electrocardiogram with the placebo, with approximate 95% confidence interval (6.5, 38.6). These results also indicate a significant period effect. Within either treatment group, the odds of an abnormal electrocardiogram in the second period are about 18% of the odds of an abnormal electrocardiogram in the first period.

Take a look at the data. When the placebo is given the observed proportions of abnormal electrocardiograms are .606 and .647 in the first and second periods, respectively. When the active drug is given the observed proportions of abnormal electrocardiograms are .824 and .667 in the first and second periods, respectively. Is there an overall increase in the incidence of abnormal electrocardiograms when the active drug is used or does the increase only occur in the first period? Do the results from either of the models fit about accurately reflect the pattern in the data?

(b) Given the value of the random effect for the \( i \)-th patient, the conditional distribution for the binary responses is

\[ y_{ij} | \eta_i \sim Bin(1, \pi_{ij}) \]
It follows that the conditional variance is
\[ \text{var}(y_{ij} | \eta_i) = \pi_{ij}(1 - \pi_{ij}) \]

(c) The GLIMMIX macro used to fit the models in part (a) assumes that the random patient effects are independent and identically distributed according to a normal distribution with mean zero and unknown variance \( \sigma^2_{\eta} \). Define
\[ f(\eta_i; \sigma^2_{\eta}) = \frac{1}{\sqrt{2\pi}\sigma_{\eta}} e^{-\eta_i^2/(2\sigma_{\eta})} \]

Then
\[ E(Y_{ij}) = Pr(Y_{ij} = 1) = \int Pr(Y_{ij} = 1 | \eta_i) f(\eta_i; \sigma^2_{\eta}) d\eta_i = \int \pi_{ij} f(\eta_i; \sigma^2_{\eta}) d\eta_i \]

where
\[ \pi_{ij} = \frac{\exp(\beta_0 + \beta_1 X_{ij1} + \beta_2 X_{ij2} + \beta_3 X_{ij1} X_{ij2} + \eta_i)}{1 + \exp(\beta_0 + \beta_1 X_{ij1} + \beta_2 X_{ij2} + \beta_3 X_{ij1} X_{ij2} + \eta_i)} \]

Then,
\[ \text{var}(y_{ij}) = E(y_{ij}^2) - (E(y_{ij}))^2 = p(y_{ij} = 1) - p(y_{ij} = 1)^2 = \int \pi_{ij} f(\eta_i; \sigma^2_{\eta}) d\eta_i - \left( \int \pi_{ij} f(\eta_i; \sigma^2_{\eta}) d\eta_i \right)^2 \]

(d) For the first model fit in part (a), the approximate REML estimate of \( \sigma^2_{\eta} \) is 19.16. For the second model fit in part (a), the approximate REML estimate of the variance of the patient effects is 18.91, almost the same estimate.

(e) The results for fitting marginal logistic models on pages 820 and 823 of the notes seem to better reflect the effects of the active drug on incidence of abnormal electrocardiograms. The GLIMMIX results for the first model fit in part (a) seem to overstate drug and period effects. GLIMMIX estimates a very large variance for the random patient effects. This may occur because random patient effects cannot be distinguished from drug and period effects in this case. For each of the four distinct sets of values for \((X_1, X_2)\) there are only two types of patients, those with abnormal electrocardiograms \((Y=1)\) and those with normal electrocardiograms \((Y=0)\). When the response is binary and there are only a few repeated measures on each subject, the estimation procedure used by GLIMMIX can produce biased results (see Breslow and Clayton, 1993, JASA, 9-25). It was not a good idea to use GLIMMIX for this analysis.

(f) In this case, \(X_{ij1} = 1, X_{ij2} = 1, X_{ij1}X_{ij2} = 1\). Since you do not know the value of the random effect for any subject, the best thing to do is set it equal to its mean, which is zero. Then
\[ \hat{\pi}_{ij} = \frac{\exp(\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 + \hat{\beta}_3)}{1 + \exp(\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 + \hat{\beta}_3)} = \frac{\exp(1.855)}{1 + \exp(1.855)} = 0.865 \]

To obtain a standard error, first obtain the standard error of the logit. Do not ignore the correlations among the parameter estimates or the variation in the random patient effect. The reported REML estimate of the covariance matrix of the parameter estimates is

4
Covariance Matrix for Fixed Effects

<table>
<thead>
<tr>
<th>Row</th>
<th>Effect</th>
<th>Col1</th>
<th>Col2</th>
<th>Col3</th>
<th>Col4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intercept</td>
<td>0.7588</td>
<td>-0.7588</td>
<td>-0.7588</td>
<td>1.4234</td>
</tr>
<tr>
<td>2</td>
<td>x1</td>
<td>-0.7588</td>
<td>1.8125</td>
<td>1.3295</td>
<td>-3.0478</td>
</tr>
<tr>
<td>3</td>
<td>x2</td>
<td>-0.7588</td>
<td>1.3295</td>
<td>1.5199</td>
<td>-2.7552</td>
</tr>
<tr>
<td>4</td>
<td>x12</td>
<td>1.4234</td>
<td>-3.0478</td>
<td>-2.7552</td>
<td>5.8267</td>
</tr>
</tbody>
</table>

The sum of the variances and covariances in the table shown above provides an estimate of the variance of $\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 + \hat{\beta}_3$. This value is 0.7825. Since the variance of the random patient effect is estimated as 19.16, an estimate of

$$\text{Var}(\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 + \hat{\beta}_3 + \eta_{36})$$

is $0.7825+19.16=19.9425$ and the estimated standard error is 4.466. Applying the delta method, the standard error the conditional probability of success is estimated as $\hat{\pi}_{ij}(1 - \hat{\pi}_{ij}) \ast 4.466 = 0.52$. This is a large standard error for a predicted probability.

(g) When the active drug is given in the first period, we estimated $\beta_0 + \beta_1 + \beta_2 + \beta_3 + \eta_i$ as

$$\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 + \hat{\beta}_3 + 0 = 1.855$$

The REML estimate of the variance of the random patient effects is 19.16. If the random patient effects have a normal distribution, then values of the random patient effects have probability .95 of being within two standard deviations of zero, the mean of the random patient effects. Consequently, random patient effects are likely to be between -8.579 and 8.579 and

$$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \eta_i$$

is likely to be between 1.855-8.579=-6.724 and 1.855+8.579=10.434. Probabilities are likely to be between .0012 and .9997, which is a result of no practical value. Using a random effects model was not a good idea for this cross-over study, at least when the interaction between period and treatment is included in the model. DHLZ were able to get reasonable results using a random effects model, on pages 176-177, when they considered a model with just a drug effect or a model where the logits were linked to additive drug and period effects. They did not consider a model that also included a drug*period interaction like they did in Chapter 8.
2. (a) Fit independent poisson counts at the each time point. SAS code for plotting mean counts across time for the six treatments and fitting a separate log-linear model at each time point is shown below.

/* Enter the papalloma data */

data set1;
  infile 'c:\mydocuments\mpap.dat';
  input mouse trt diet surgery y week;
run;

proc format; value trt
  1 = 'adlib/no surgery'
  2 = 'adlib/ADX'
  3 = 'DER/no surgery'
  4 = 'DER/ADX'
  5 = 'adlib/ADX-GCH'
  6 = 'DER/ADX-GCH';
run;

proc sort data=set1; by trt week; run;

proc means data=set1 noprint;
  by trt week;
  var y;
  output out=means mean=y;
run;

proc print data=means;
run;

axis1 label=(f=swiss h=1.8 a=90 r=0 "Papalloma Rate")
  order = 0 to 15 by 5
  value=(f=swiss h=1.8) w=3.0
  length= 4.0in;

axis2 label=(f=swiss h=2.0 "Time(weeks)")
  order = 10 to 30 by 4
  value=(f=swiss h=1.8) w= 3.0
  length = 6.5 in;

SYMBOL1 V=CIRCLE H=1.7 w=3 l=1 i=join ;
SYMBOL2 V=DIAMOND H=1.7 w=3 l=3 i=join ;
SYMBOL3 V=square H=1.7 w=3 l=9 i=join ;
SYMBOL4 V=dot H=1.7 w=3 l=2 i=join ;
SYMBOL5 V=triangle H=1.7 w=3 l=4 i=join ;
SYMBOL6 V='=' H=1.7 w=3 l=10 i=join ;
PROC GPLOT DATA=means;  
PLOT y*week=trt /  
    vaxis=axis1 haxis=axis2;  
TITLE1 ls=0.01in H=2.0 F=swiss "Average Papalloma Counts";  
    footnote ls=0.01in;  
RUN;  
proc sort data=set1;  
by week;  
/* Fit a separate log-linear model to  
compare mean counts for the six  
treatments at each time point. */  
proc genmod data=set1;  
by week;  
class mouse trt;  
model y = trt / itprint  
    dist=poisson link=log covb;  
run;  
  
Week14 is shown as an example.  

Analysis Of Parameter Estimates  

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Confidence Limits</th>
<th>Chi-Square</th>
<th>Pr&gt;ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1</td>
<td>-2.5902</td>
<td>0.7284</td>
<td>-4.0178 -1.1627</td>
<td>12.65</td>
<td>0.0004</td>
</tr>
<tr>
<td>trt 1</td>
<td>1</td>
<td>4.9152</td>
<td>0.7386</td>
<td>3.4676 6.3627</td>
<td>44.29</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>trt 2</td>
<td>1</td>
<td>4.5550</td>
<td>0.7510</td>
<td>3.0831 6.0270</td>
<td>36.79</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>trt 3</td>
<td>1</td>
<td>2.8381</td>
<td>0.8207</td>
<td>1.2295 4.4467</td>
<td>11.96</td>
<td>0.0005</td>
</tr>
<tr>
<td>trt 4</td>
<td>1</td>
<td>3.3231</td>
<td>0.7936</td>
<td>1.7677 4.8786</td>
<td>17.53</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>trt 5</td>
<td>1</td>
<td>1.7917</td>
<td>0.8422</td>
<td>0.1411 3.4424</td>
<td>4.53</td>
<td>0.0334</td>
</tr>
<tr>
<td>trt 6</td>
<td>0</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000 0.0000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This table shows that the first five treatments are significantly different from treatment 6  
with respect to the mean number of papallomas at week 16. Treatments 6 is protective.  
Papalloma counts for treatment 6 are relatively low across all time points. You could  
examine comparisons with other treatments by re-running the analysis 5 times with each of  
the other treatments given the highest code on one of the runs.  

(b) Results from the analysis of the counts at week 14 are shown below:  

Criteria For Assessing Goodness Of Fit  

<table>
<thead>
<tr>
<th>Criterion</th>
<th>DF</th>
<th>Value</th>
<th>Value/DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deviance</td>
<td>204</td>
<td>839.0620</td>
<td>4.1130</td>
</tr>
</tbody>
</table>

7
If the expected counts are large enough for a normal distribution to be a good approximation to the Poisson distribution and the counts have independent Poisson distributions for the mice in the six treatment groups, then the Pearson goodness of fit statistic should have an approximate central chi-square distribution with 204 df. At week 14, the observed value of the Pearson statistics is five times larger than the mean of a central chi-square random variable with 204 degrees of freedom. There is more variation among papilloma counts within treatment groups than can be attributed to counts with Poisson distributions, i.e., the within treatment group variances are much larger than the corresponding mean counts.

To allow for the extra variance, you could abandon the Poisson distribution and use a model where the within treatment variance in the papilloma counts is allowed to be 5.0232 times larger than the mean count for each treatment. This can be achieved by putting the pscale option in the GENMOD as shown below:

```plaintext
proc genmod data=set1;
  by week;
    class mouse trt;
    model y = trt / itprint covb
dist=poisson link=log;
run;
```

Results for week 14 are shown below. Note that the parameter estimates are unchanged. They are still obtained by maximizing a Poisson likelihood function (which is incorrect, but it produces consistent estimates of the parameters in this case). Standard errors of the parameter estimates have been inflated by a factor of $\sqrt{5.0232} = 2.412$. This changes the p-values for the tests of significance. Diets 5 and 6 are no longer significantly different at week 14, for example.
Another alternative is to use the negative binomial distribution for the counts. The negative binomial distribution contains another parameter that allows the variance of the counts to be different from the mean. GENMOD code that specifies the negative binomial distribution is shown below:

```plaintext
proc genmod data=set1;
  by week;
    class mouse trt;
    model y = trt / itprint covb
dist=negbin link=log;
run;
```

Note that the parameter estimates are slightly changed because they are obtained from maximizing a likelihood function for independent negative binomial counts. Also note the values of the standard errors.

### Analysis Of Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Wald 95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1</td>
<td>-2.5903</td>
<td>0.6274</td>
<td>-3.8199 -1.3606</td>
</tr>
<tr>
<td>trt</td>
<td>1</td>
<td>4.9152</td>
<td>0.6889</td>
<td>3.5650 6.2654</td>
</tr>
<tr>
<td>trt</td>
<td>2</td>
<td>4.5550</td>
<td>0.6919</td>
<td>3.1990 5.9111</td>
</tr>
<tr>
<td>trt</td>
<td>3</td>
<td>2.8381</td>
<td>0.7024</td>
<td>1.4614 4.2148</td>
</tr>
<tr>
<td>trt</td>
<td>4</td>
<td>3.3232</td>
<td>0.6869</td>
<td>1.9769 4.6694</td>
</tr>
<tr>
<td>trt</td>
<td>5</td>
<td>1.7918</td>
<td>0.7138</td>
<td>0.3928 3.1907</td>
</tr>
<tr>
<td>trt</td>
<td>6</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000 0.0000</td>
</tr>
</tbody>
</table>
Dispersion 1 2.4117 0.4269 1.7047 3.4120

Analysis Of Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>17.05</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>trt 1</td>
<td>50.91</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>trt 2</td>
<td>43.34</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>trt 3</td>
<td>16.33</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>trt 4</td>
<td>23.41</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>trt 5</td>
<td>6.30</td>
<td>0.0121</td>
</tr>
<tr>
<td>trt 6</td>
<td>.</td>
<td>.</td>
</tr>
</tbody>
</table>

(c) Code for fitting some models is shown below. Note that in week 10 there were no papillomas observed for some diets. This cause numerical problems with a Poisson distribution because the variance of the counts is taken to be a multiple of the mean. With time*diet interactions in the model, we can fit a different mean for each diet at each time point, and the program tries to fit a zero mean when the sample mean is zero for any diet at any time point. The you get a zero on the diagonal of the information matrix and the program cannot proceed when it tries to invert that matrix. To avoid this we added .01 to each count, so the total number of papillomas would never be exactly zero for any diet at any time point.

```plaintext
data set2;
set set1;
y=y+0.01;
run;

proc genmod data=set2 descending;
class mouse trt week;
model y = trt|week /
dist=poisson link=log
itprint pscale
converge=1e-8 maxit=50;
repeated subject=mouse(trt) / type=un
   modelse covb corrw;
run;

proc genmod data=set2 descending;
class mouse trt week;
model y = trt|week /
dist=poisson link=log
itprint pscale
converge=1e-8 maxit=50;
```

10
repeated subject=mouse(trt) / type=ar(1)
  modelse covb corrw;
run;

proc genmod data=set2 descending;
class mouse trt week;
model y = trt|week /
  dist=poisson link=log
  itprint pscale
  converge=1e-8 maxit=50;
repeated subject=mouse(trt) / type=arh(1)
  modelse covb corrw;
run;

proc genmod data=set2 descending;
class mouse trt week;
model y = trt|week /
  dist=poisson link=log
  itprint pscale
  converge=1e-8 maxit=50;
repeated subject=mouse(trt) / type=toep
  modelse covb corrw;
run;

proc genmod data=set2 descending;
class mouse trt week;
model y = trt|week /
  dist=poisson link=log
  itprint pscale
  converge=1e-8 maxit=50;
repeated subject=mouse(trt) / type=cs
  modelse covb corrw;
run;

You do not get any statistic from GENMOD like the AIC criterion that you can use to choose between correlation structures. One thing you could do is examine the estimate of the correlation matrix for papalloma counts recorded on the same mouse across the six points in time. This matrix is shown below. The pattern does not seem to correspond to an AR(1) structure or an exchangeable structure. Robust estimation yields about the same results regardless of what correlation structure you select.

<table>
<thead>
<tr>
<th>Col1</th>
<th>Col2</th>
<th>Col3</th>
<th>Col4</th>
<th>Col5</th>
<th>Col6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Row1</td>
<td>1.0000</td>
<td>0.3780</td>
<td>0.4003</td>
<td>0.3174</td>
<td>0.2894</td>
</tr>
<tr>
<td>Row2</td>
<td>0.3780</td>
<td>1.0000</td>
<td>0.6826</td>
<td>0.6456</td>
<td>0.6715</td>
</tr>
</tbody>
</table>
(d) Given the results from part (c), this part was done assuming a general correlation structure for papilloma counts recorded on the same animal across time. We attempted to fit some time trends using polynomial curves. The following code was used.

```plaintext
proc genmod data=set2 descending;
class mouse trt;
model y = trt week trt*week week*week
     trt*week*week week*week*week / noint
dist=poisson link=log
itprint pscale
converge=1e-8 maxit=50;
repeated subject=mouse(trt) / type=un
    modelse covb corrw;
run;
```

The estimated coefficients are shown below. Obviously, this model could be simplified.

Criteria For Assessing Goodness Of Fit

<table>
<thead>
<tr>
<th>Criterion</th>
<th>DF</th>
<th>Value</th>
<th>Value/DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deviance</td>
<td>1241</td>
<td>6225.9401</td>
<td>5.0169</td>
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Working Correlation Matrix

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### Analysis Of GEE Parameter Estimates

#### Empirical Standard Error Estimates

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3. (a) Fit a marginal Cox proportional hazards model:

#### Type 3 Tests of Fixed Effects

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<th>Effect</th>
<th>Num DF</th>
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#### Solution for Fixed Effects

| Effect | trt | week | Estimate | Standard Error | DF | t Value | Pr > |t| |
|--------|-----|------|----------|----------------|----|---------|-------|
| Intercept | -2.2119 | 0.4815 | 204      | -4.59 | <.0001 |
| trt 1    | 4.0654 | 0.5631 | 1020     | 7.22  | <.0001 |
| trt 2    | 2.9173 | 0.5844 | 1020     | 4.99  | <.0001 |
| trt 3    | 2.8258 | 0.5814 | 1020     | 4.86  | <.0001 |
The overall effects of time and treatment are significant. There is also an indicate of significant interaction between time and treatments with most of the interaction occurring at the earlier time points. Standard errors are smaller than the robust standard errors provided by the GENMOD procedure in SAS. There is much to sort out here. It may be useful to fit trends across time. Otherwise, a separate analysis comparing the treatments at each time point tells you most of what you need to know about the diet effects.
(b) Code for fitting a random effect model is shown below. Predictions of the random effects for individual animals can indicate which animals are unusually high or low responders. In this case you can select the mice that appear to be most susceptible to developing papillomas by selecting the mice with the largest positive predictions of their random effects. For this study mice 518, 534, 622, 635, 676, 690, 693, 722, 769, 786, 2623, 2653, 2264, 2681 all have predictions larger than 3.0. If you were really selecting mice for susceptibility to papillomas, it is generally better to treat them all the same. Here you had to rely on a model to adjust for diet effects.

```
%inc 'C:\mydocuments\glmm800.sas' /nosource;
run;
%glimmix(data=set2,
  stmts=%str(
    class mouse trt week;
    model y = trt|week/
       solution;
    random intercept / solution type=un subject=mouse;),
  error=poisson, link=log,
     converge=1e-8, maxit=20, out=setp)
run;
```

| Effect | mouse | Estimate | Pred  | DF  | t Value | Pr > |t| |
|--------|-------|----------|-------|-----|---------|------|---|
| Intercept | 2664  | 4.0249   | 0.3898 | 1020| 10.33   | <.0001|