8, THE GLEBE
STANDLAKE
WITNEY
OXON
OX8 7SS

6/1/90

Dear Krishnaja,

Thank you very much for your letter sent just before Christmas. First let me deal with work Matters. Dr. (Mrs) Bhatt wrote to me asking for a copy of the memorandum describing POLYFIT and I told her you had a copy of the program itself. I hope now the program is on your computer at Bombay. If you or she have any problems with its implementation please write and I am sure I can help.

Of course you can send your chromosomal data to me. Could you please include the distribution data as this is useful in the analysis. I will fit it as best I can and we shall see what it looks like. It may be worth publishing.

I am afraid I did not get to Brazil. The IAEA did not have sufficient money to support me as well as David. The course lasted three weeks with the middle week taken up with a meeting of the IAEA chromosome aberration group. They have decided to do some collaborative work on the adaptive response of chromosome aberration yield.

However to compensate I have had trips to The Hague and to Leiden to Nat's laboratory. Toward the end of the year David and I went to Madrid. It was my first trip to Spain and one I enjoyed very much. We were treated like royalty by the conference organizers and we spent two days being shown some of the sights of Spain.

I cannot remember what I told you about the Edwards family in my last letter so that if I repeat myself I am sure you will understand. Brenda, my wife, started a new part-time job last January. The year before

she was working for the Red Cross Society teaching first aid to school children and to other people in work because by law it is required that companies have some first aid expertise. The Red Cross then decided to reduce her wages by a factor of two and she resigned. She then took on a job at the local playgroup to help them out because the then supervisor had resigned. She is now working as an occupational therapist helper in Oxford. This involves visiting mainly elderly and infirm people in their own homes to assess whether they need any physical aids to help them to stay

in their own home rather than go into an institution. She is employed by the local authority who are essentially funded from the community charge or poll tax which was one of the issues which led to Mrs Thatcher's downfall. My wife in now in the position of being employed to do a job for which there is no money to provide the aids which she thinks are necessary.

I think I told you that Catherine is training to be a nurse at Winchester, which is about 60 miles south of Oxford. She bought a car just before last Christmas but in the gales which occurred about this time last year a tree fell and

completely demolished it. Fortunately Katherine was not in the car at the time. She is in fact enjoying her course very much and seems to be coping very well with the course work. She has spent some time in various hospital wards and also home visiting of sick patients. She particularly enjoys this aspect of the course. She had her 21st birthday this year. We hired the local village hall so she could have a disco/dance. She invited about 140 guests but it all went very well. In September she went with two friends to the Canary Islands for a holiday and so she is enjoying life to the full

Richard is in his second year at Nottingham University. He is taking a degree in Mathematics with Engineering and I think he is doing reasonably well. He has joined the Rambling Society and spends a few weekends walking in the Peak District, in the Yorkshire Dales and in the Lake District. These places are in the middle to north of England. Last summer he went climbing in Scotland which contains the highest mountains in Great Britain. He just returned back to Nottingham from a visit to Scotland in which he hoped to use ice equipment to walk in snow. There was snow certainly, but there were also avalanches and landslides

and so what he could do was a bit limited. The snow was too soft to use the ice equipment properly.

Last May, Brenda and I went to the western end of Crete. It was a nature ramble type of holiday with a botanist and an ornithologist included in the party. It was good to have indiginous plants pointed out and the multitude of birds identified. I must admit that the large number of latin names saturated my mind after a while. However we both enjoyed the holiday and would consider a similar holiday again. This time we would take a bird and a plant reference book with us.

During the year, Brenda became very involved with restoration of our

village church. Rain was coming through the roof and the windows were seriously knowed. A large sum of money was needed for repair and Brenda was part of the small village committee which set itself the task of raising it. Overall about £100,000 was raised most of it from members of what is a small village of about 1500 people. A commendable effort!

We spent Christmas at home as we usually do. Brenda's mother stayed with us but unfortunately developed a nasty cold and was in bed for two days. We took her back today which was about a week longer than she had intended to stay. My mother was due to come for Christmas but developed a cold beforehand and so did not come. She lives in a warden controlled flat

very close to us so we were able to visit her on Christmas Day.

I enjoyed reading about your holiday and particularly liked the photograph you sent. When you write about your family it is good to have a mental picture of them. I was sorry to read about your depressed feeling but I hope that 1991 will be a better year for you.

Wishing all the best for 1991 to you and your family

with kind regards

Alan


By air mail
Par avion
OXFORD
7 JAN
1991
20P
33P
Dr. Krishnaja A.P.
B-8 Vindhya,
Anushakti Nagar,
Bombay 400094,
India


23-1-91

National Radiological Protection Board, Chilton, Didcot, Oxon OX11 0RQ. Tel: (0235) 831600
Telex: 837124 RADPRO G · Fax: (0235) 833891

Dr. [redacted] Krishnaja, A. P
Molecular Biology and Agriculture Division,
Bhabha Atomic Research Centre,
Bombay 400085,
India.

Your ref:

Our ref:

Date: 13th February 1990

Dear Dr. Krishnaja,

Thank you for your letter asking for the method of estimation of the coefficients α and β in the dose response curve. It is a big subject and more than I can put into one letter, but I will try.

Mathematically you have a set of data of dose (D), cells scored (C) and aberrations scored (A) and as yield equation:-

$$Y = \gamma + \alpha D + \beta D^2$$

The observed yield for each dose is A/C. The problem is to find values for γ, α and β which give the "best" fit to the data points. Statistically there are several possible criteria for deciding the "best" fit. They are different and give different answers but they are all based on the concept of "weighted least squares". Thus a computer program which finds a weighted least squares solution is essential. We have such a program at NRPB called POLYFIT and you are welcome to a copy.

The concept of weighted least squares as applied to the above problem is to calculate the function

$$\sum_{\text{all points}} (Y_o - Y_f)^2 / \sigma^2$$

and find the values of γ, α and β which make it a minimum.
Y_o is the observed yield ($= A/C$). Y_f is the fitted yield which is altered as γ, α and β are altered. σ^2 is an estimate of the variance at each point and it is this value which distinguishes the different criteria for "best" fit.

In chromsome aberration work with human blood, particularly dicentric scoring, we know that the aberrations are distributed among the cells in accordance with the Poisson distribution although it is something that should be checked. Therefore the standard error (σ) can be estimated from the square root of the aberrations scored ($\sqrt{A/C}$).

/contd....

Received 20-2-90
20-2-90

Example

Dose(D)	Cells scored(C)	Dicentrics seen(A)	Yield(Y_o)	SE ($\sigma = \frac{\sqrt{A}}{C}$)
0	2000	1	.0005	.0005
0.2	2000	18	.009	.00212
0.5	1000	40	.040	.00632
1.0	1000	92	.092	.00959
1.5	600	123	.205	.0185
2.0	500	171	.342	.0262
3.0	300	186	.62	.0455
4.0	200	216	1.08	.0735

Putting the dose, D, yield Y_o and SE (σ) into the computer program POLYFIT gives the output 1. The column 'FITTED Y' contains the best fit values of yield and these are better estimates of the yields than Y_o. We can therefore derive better estimates of σ as follows:

$$\sigma = \sqrt{Y_f \times C}/C$$

These new estimates of σ are put into the program POLYFIT with the dose D and the yield Y_o. This produces output 2. This produces an even better estimate of Y_f which produce a third estimate of σ. Putting this into POLYFIT gives output 3. Outputs 2 and 3 are so close together that further iterations are pointless. The output 3 is identical to the maximum likelihood fit and produces maximum likelihood estimates of the coefficients γ, α and β.

I think this is enough for one letter. When you have understood this I will then tell you what I do when the Poisson distribution does not apply.

With kind regards,

Alan

Alan A. Edwards

If you want a copy of POLYFIT written in FORTRAN I can put it onto floppy disc. Alternatively I can write it to magnetic tape or as a last resort give you a listing

A.

Dr (Mrs) Krishnaja A. M.

13-8 Vindhya,

Annshakti Nagar

Bombay 400094

India

12-3-90.

Dear Dr. Edwards,

Thank you very much for your letter dated 13-2-90, explaining the method of estimation of the coefficients α & β in the dose response curve. I understood it in parts - ie to find out whether distribution is Poisson or not, and once you have the filled field and SE (σ) to derive the weighing factors for output & etc. certain points are still not clear to me - how to arrive at the best fit values of yield (Y_F). How do you calculate it. for the chi-squared value how is it that the no. of Degrees of freedom is given as 5. Would you be kind enough to explain these points.

Meanwhile I would welcome a copy of POLYFIT or magnetic tape of a dosing which one is convenient to you for sending. Please write to my home address.

Before coming to cases where poisson distribution does not apply I still have not understood clearly what you had tried to explain about cases where poisson distribution does apply

I hope you will again spare some time for me in this regard.

Thanking you and with kind regards

Yours Sincerely,

National Radiological Protection Board, Chilton, Didcot, Oxon OX11 0RQ. Tel: (0235) 831600
Telex: 837124 RADPRO G · Fax: (0235) 833891

Dr. Krishnaja A.P.,
B-8 Vindhya,
Anushakti Nagar,
Bombay 400094,
India.

Your ref:

Our ref:

Date: 27th March 1990

Dear Krishnaja,

Thank you for your letter of 12th March. I enclose a listing of the program 'POLYFIT'. It is written in Fortran and it has comment statements to tell you how to run it and to say what it does. There are a few computer specific instructions and you may have to alter these. Good luck with getting it onto your computer.

You had two other questions.

The "best fit" values of yield are given by the maximum likelihood solution. The iterative method described in my last letter gives the maximum likelihood solution when further iterations no longer alter the solution. Thus output 3 gives a close approximation to the "best fit". The program POLYFIT does the algebra to produce each of outputs 1 to 3.

In the example I sent you there are 8 data points. There are 3 fitted parameters in the polynomial $\gamma + \alpha D + \beta D^2$. Hence the degree of freedom is 8-3 = 5. The total sum of squares should be distributed as the chi-squared distribution on 5 degrees of freedom and this forms a test of how good the fit is.

I hope that has answered your questions. If it hasn't do write again.

Yours sincerely,

Alan

Alan A. Edwards

Recieved 4-4-90

4-4-90

Dear Krishnaja,

I was pleased to read that you had passed your driving test. I am gradually persuading Brenda to be more adventurous on holidays. We are going to Crete for 10 days in early May. Maybe one day I shall persuade her to go to India!

kind regards

Alan

National Radiological Protection Board, Chilton, Didcot, Oxon OX11 0RQ. Tel: (0235) 831600
Telex: 837124 RADPRO G · Fax: (0235) 833891

Dr. Krishnaja AP,
B-8 Vindhya,
Annshakti Nagar,
Bombay 400094,
India.

Your ref:

Our ref:

Date: 13th June 1991

Dear Krishnaja,

Thank you for your letter enclosing your data. I have analysed it as I usually do - testing for overdispersion and then fitting by maximum likelihood techniques. I assume you have used gamma-rays, eg. cobalt-60 or caesium-137. If so the results are very good indeed, bearing a marked similarity to our own. I enclose all the relevant printouts.

I checked all the distributions you sent. Some I agree with your analysis, others I do not. I enclose a copy of your analyses marking the discrepancies. I think you must have calculated u and σ^2/y by hand and so I enclose my computer code written in Fortran. I hope this will be useful to you. For dicentrics and dicentrics + rings the distributions are very close to Poisson. For total aberrations there is some sign of overdispersion ($\sigma^2/y > 1$) but it is not sufficient to take into account for curve fitting purposes. (There is a mistake in the 5 Gy data and if that turns out to be overdispersed I could change my mind). Acentrics are definitely overdispersed and I have assumed a factor of 1.2 for all dose points.

For fitting I find it necessary to have a point at zero dose. I assumed that 2000 cells were scored with 1 dicentric and 6 acentrics. You should really provide one and 5000 cells would be nice but 2000 would suffice. The dicentrics and dicentrics + rings fit very well indeed. The value of χ^2 is just less than the degrees of freedom and therefore the printed errors need to be adjusted as shown. This is because the computer is programmed to give estimates of errors based essentially on the value of χ^2 and I judge that Poisson errors are more appropriate. The acentric and total aberration fits are very poor and there is strong evidence for lack of fit. This supports very nicely our contention that the scoring of dicentrics are more reliable than the scoring for acentrics. There is just one further point I would like to make which might help for future work. At some doses I feel you have too much scoring because the extra accuracy gained is not really worth the effort. This is particularly true at 4 and 5 Gy. As a general guide I would aim at about 100 dicentrics at any one dose and at about 2000 cells if that is reached first.

/contd.....

Now to your other question about comparing means. This is best answered by example. For dicentrics we know that the Poisson distribution applies. Suppose the two yields are 300 dicentrics in 1000 cells and 200 dicentrics in 800 cells.

The yields are 0.300 ± .0173 and 0.25 ± .0177 dicentrics per cell

The difference is 0.050 ± .0247

The numbers after ± are standard errors and are derived as follows:

1. $\sqrt{300}/1000 = .0173$

2. $\sqrt{200}/800 = .0177$

3. $\sqrt{(.0173)^2+(.0177)^2} = .0247$

The first two assume the Poisson distribution ie. the standard error is the square root of the mean. The third is the statistical adding of variances of two independent quantities. The question, "Are the two yields the same?" is converted to "Is the difference of the two yields zero?" In this case the difference is just over two standard errors away from zero (2.02 in fact) which would be just significant at the 95% level.

For G2 irradiation where chromatid damage is seen, you need to check whether the Poisson distribution applies or not using the Papworth u-test. If it does apply you use the above test. If the aberrations are overdispersed (like acentrics in your data) then the standard errors in 1 and 2 above would have to be adjusted. If, for example, the values for σ^2/y were 1.2 then the standard errors in 1, 2 and 3 above would be:-

1. $\sqrt{300 \times 1.2}/1000 = .0190$

2. $\sqrt{200 \times 1.2}/800 = .0194$

3. $\sqrt{.0190^2 + .0194^2} = .0271$

In this case the difference in yield would be not quite significantly different from zero (1.85 standard errors).

I hope I have explained this clearly.

With kind regards,

Alan

Alan A. Edwards

13/6/91

Dear Krishnaja,

Just a very brief note to let you know that I did receive your letter in February and that I will write to you sometime. At the moment I am very, very busy. I am going to Germany tomorrow to irradiate blood on a particle accelerator. In early July, Brenda and I will be on holiday to Hungary. In early September I am going to a meeting in Padua in Northern Italy. In between all of this we are having a visitor from Russia who is going to bring with him data of chromosome aberrations in Chernobyl survivors. But, I will write sometime.

Let me very belatedly send my condolences on the death of your Uncle. I do know what it feels like to lose a loved one - my own father died about seven years ago. I hope you are now reasonably recovered from your second operation and that all your family are well.

With my kind regards

Alan

National Radiological Protection Board, Chilton, Didcot, Oxon OX11 0RQ. Tel: (0235) 831600
Telex: 837124 RADPRO G · Fax: (0235) 833891

Dr. Krishnaja AP,
B-8 Vindhya,
Annshakti Nagar,
Bombay 400094,
India.

Your ref:

Our ref:

Date: 7th August 1991

Dear Dr. Krishnaja,

Thank you for your letter and the micronuclei data. I note the error on total aberrations in 5 Gy. I have run the u-test and the distribution is close to Poisson and I enclose the printout.

I have tested and fitted the micronuclei data, outputs enclosed. Yes, the micronuclei are overdispersed. The average factor is about 1.2 but whether there really is a trend of σ^2/y with dose is marginal. I have assumed not and used 1.2 for all doses. From the printout, the fit is not good but as you say the 2 and 3 Gy points are the suspect ones. The observed yield at 2 Gy is too low and that at 3 Gy is too high. But remember that there is a lot of scoring at these two points and expected uncertainties are based purely on counting statistics. In both cases the difference between the observed and fitted yields are only about 10% which is really very good.

Compared with total aberrations, micronuclei have a higher control level, have a higher value for α (although significance is doubtful) and a much lower value for ß. As far as I can see your conclusions using gamma-rays agree very well with ours using x-rays.

With regard to publication, I do not think that the chromosome aberration and micronuclei curves would be accepted alone. They need to be published along with some other data. One of the trends these days is to try to measure heterogeneity in the response of different donors. In this respect your observation of differences in the spontaneous frequency of MN between "Thal. traits" and normals when you do not see a difference for CA is interesting. Is the sensitivity to radiation different between the two groups? I am afraid I do not know what "Thal. traits" are, but assuming they are a disease or a syndrome, are they related to cellular repair or do they have a mutational cause? If so, there is a chance that differences could exist and I would be pleased to look at the data for you.

With regard to your differences in MN yield, the yields with standard errors are:

1. 775/5000 = 0.155 ± .0063
2. 1550/5000 = 0.310 ± .0090
3. 791/4000 = 0.198 ± .0080

The standard errors include a factor for $\sigma^2/y = 1.3$. The difference between 2 and 1 is 0.155 ± .011 which is clearly significant.

The difference between 3 and 1 is 0.043 ± .010 which is significant.

/contd.....

Dr. Krishnaja AP

However, the tests are done based on slightly enhanced Poisson errors. If the above are based on the means of different people and there is heterogeneity within the groups the standard errors above should be changed and significance might be altered. Again I am happy to look at this for you but I need the scoring for each individual and not just the totals you have given me already.

With regard to your control levels for aberrations, I do not regard them as low because they lie well within the range of measurements I have seen. You have obviously selected a very good donor. I have not re-run the fits with these control levels but will do so when they are required for publication.

With kind regards,

Alan

Alan A. Edwards

England.
8/8/91

Dear Krishnaja,

Again this is just a quick personal note to enclose a photograph of Brenda and myself. It was taken very recently. We are in our "Sunday best" because we attended the wedding of friend's daughter. We do not have any recent photographs of all of us together. I shall have to take some of Catherine and Richard and I will send these sometime in the future.

The trip to Germany went well and the cells cultured. Preliminary results give a very low yield of dicentrics (RBE with respect to gamma rays about 0.1). We enjoyed our holiday in Hungary and saw quite a number of birds we have never seen before. More of my impressions later. My next trip is to Padua near Venice at the beginning of October. When you next write please explain what "coronatic music" is. You have mentioned that Rohini has had coaching but I don't know what it is.

I will write at greater length soon. In the meanwhile, kind regards to you and your family.

Alan

National Radiological Protection Board, Chilton, Didcot, Oxon OX11 0RQ. Tel: (0235) 831600
Telex: 837124 RADPRO G · Fax: (0235) 833891

Dr Krishnaja AP
B-8 Vindhya
Annshakti Nagar
Bombay 400094
India

Your ref:

Our ref:

Date: 16 September 1991

Dear Krishnaja

Thank you for the additional data on MN for normals and thalassaemia heterozygotes. My analysis is now as follows.

Normal subjects - zero dose

All 15 subjects are from the same population χ^2 = 13.4 on 14DF assuming Poisson estimates of errors. Therefore I have combined these and used the overall distribution. The ratio σ^2_y is 1.17 and this is used to enhance the Poisson estimate of SE based on 188 MN.

The mean is 0.0125 ± .0010.

Thalassaemia heterozygotes - zero dose

Here the 15 subjects are not the same χ^2 = 60.9 on 14DF and even the overall σ^2_y of 1.27 cannot account for this. The standard error is therefore based on the heterogeneity of the population.

The mean is 0.0231 ± .0026.

The difference between heterozygotes and normals is therefore significant

Difference = 0.0106 ± .0028.

This I think you have already deduced.

Normal subjects - 2 Gy

The 5 subjects are not significantly different on a χ^2 test (χ^2 = 6.9 on 4DF, p = .14). If one includes the over dispersion of aberrations ($\frac{\sigma^2}{y}$ = 1.28) then the test (χ^2 = 5.4 on 4DF, p = .25) suggests even better agreement. The data have been combined and the SE is based on the person to person variation.

Mean = .155 ± .007.

From the fit of the data to a dose response curve for the same 5 persons an estimate of the mean is

Mean = .173 ± .010.

These two estimates are not significantly different.

Thalassaemia heterozygotes - 2 Gy

The 9 subjects are different (χ^2 = 116 on 8DF). Even the inclusion of a variance to mean ratio of 1.31 makes no difference to the conclusion. The standard error is therefore based on the person to person variation.

Mean = .260 ± .020.

The difference between the means of irradiated heterozygotes and normals (even taking the higher estimate) is:

Difference = .083 ± .022.

which is significant.

The conclusion is, as you have already deduced, is that both the control level and the radiation induced micronuclei in the thalassaemia heterozygotes are higher than in normal controls.

You asked about the Mann-Whitney 'U' test. I have never used it but I have read about it. It is a test to judge whether samples taken from two different populations differ. In that sense it does the same job as the 't-test' but the 't-test' assumes that the populations from which samples are taken are normally distributed. If the normal distribution does not apply then the Mann-Whitney test can be used. It works as follows:

The observations are placed in order of size. Denoting N for the 15 normal and T for the 15 thal traits the result for the spontaneous level would be.

5	8	11	12	13	14	15	18	19	20-24	25-29	30+
N	N	N	N	N	N	N	T	T	T	T	T
	N		N	N	N	N	T	N	T	T	T
	T				N	N			T	T	T
	T					T					

For all values of N, you then add up how many of the T's are lower. Eg, for the N's at 11 there are 2 T's which are lower. For cases where N and T are equal you must average, so that there will on average be one lower for each of the two N's at an observation 8.

The sum is

$$1\ (0) + 2\ (1) + 8\ (2) + 3\ (2.5) + 1\ (5.5) = 31$$

You then compare this number with numbers in a special table (copy enclosed) to give a guide to probability of fit. In this case for $n_1 = n_2 = 15$ the critical number is 40 at a probability of 0.002 on two tailed criterion and so the two distributions are significantly different as shown previously.

I think for the samples you have given me the numbers are generally quite large so that the 't-test' which in essence I have used applies reasonably well. There is only one thing that worries me a little, (and it is something you have picked up). The That traits 2 Gy data seem to fall into two distinct categories (180-211 and 290-341). There is a big gap and it is surprising there is nothing in between. Apart from the micronuclei data is there anything which distinguishes the first 4 from the remaining 5? Or is it just another of those unsolved statistical quirks that occur from time to time?

I have enclosed computer print-outs on dispersion that I have used.

With kind regards

Alan

Alan A Edwards

Encl

	CB	CG.
20°	−·0055 ± ·001	·0141 ± ·003
15°	·008 ± ·002	·012 ± ·002

8, The Glebe,
Standlake
Witney
Oxon OX8 7SS
17 Sept 1991

Dear Krishnaja,

Again another brief personal note. I am still very busy. Very soon after receiving your last letter I went to Padua in Italy for a small conference on radiation models and had to wait until I returned before replying to you. Padua is a delightful little town with many monuments. The inside walls of these monument are covered in frescos depicting Bible stories and incidents but the size and number of these are the lasting impression. They are certainly worth a visit if ever you have the opportunity.

Thank you for your description of carnatic music. It has given me at least some idea of its nature and purpose. I guess I shall have to hear it to get a better impression. I enclose a photograph of Richard taken by his girlfriend. He hates having his photograph taken and this is one taken just before he realised it was being taken. So it is a smuggled photograph. I will have to find one of Catherine and send that to you perhaps next time.

I will write a longer letter telling the 1991 version of the Edwards news later in the year.

With kind regards

Alan

National Radiological Protection Board, Chilton, Didcot, Oxon OX11 0RQ. Tel: (0235) 831600
Telex: 837124 RADPRO G · Fax: (0235) 833891

Dr. Krishnaja A.P
Bombay

Your ref:

Our ref:

Date: 4 Oct 1991

Dear Krishnaja,

This is just a short note to enclose the omitted print-outs. I also enclose a copy of an explanation of the Mann-Whitney test with tables.

I think this data may well be worth publishing. I think the emphasis should be on the medical aspects with the micronuclei techniques used as a tool to detect the heterozygous population. You also show micronuclei seem to work whereas chromosome aberrations do not. Good luck.

I am off on my travels again, this time a holiday. Brenda and I are going on a long weekend to Paris in the middle of October and then for a week to Madeira in the middle of November. I'll give you my impressions next time I write.

With kind regards

Alan

Alan A. Edwards

RJ 23-10-91

8, THE GLEBE
STANDLAKE,
WITNEY
OXON
OX8 7SS
9 JAN 1992

Dear Krishnaja,

I have at long last found some time to write to you again and give you our 1991 news. It has been a mixed year with a few highlights and some disappointments.

On the work front I have had four trips abroad, twice to Germany, to Padua in Italy near Venice and to Brussels. Of these, I liked Padua the best and I actually had time to wander around the town which is unusual. Being a very strong Catholic area, the churches and their outbuilding were covered with murals. Every square inch (sorry it's the old British unit which shows my age) was covered with paintings - walls ceilings really quite breathtaking. Brussels is not a place I would choose to go for a holiday. I only found one square with buildings of architectural interest

2/ and that was it. I did not have any chance to look round Bonn or Cologne on one of the German trips but on the other we took a day off looking at towns on the River Rhine while we were waiting for the lymphocytes to culture. On this occasion I was with Jayne and Paula who work setting up cultures and do most of our scoring. We visited Niersteiner which is the place which produces a well known German white wine but I was not too impressed. I prefer the smaller villages on the Mosel which Brenda and I visited about three years previously.

At work we now have greater ties with the Soviet Union (or at least that was what it was). David has been to Russia a couple of times to advise on applications of chromosomal studies following the Chernobyl fire in 1986. We had a Soviet scientist with us

And now to family matters. Brenda is still working as an occupational therapist assistant and still providing aids to infirm and incapacitated people still living in their own homes. She enjoys the home visits, meeting and helping people but the job is more and more involved with producing bits of paper to demonstrate you are really working to 100% capacity. Brenda of course would prefer to spend the 20% of time taken up with this paper work actually helping their clients and so she is a little fed up with the job.

In May, Catherine became engaged. She was only half-way through her nursing but plans to finish it before marrying. In June she failed an examination but passed this on a resit. This was the first failure she had had having passed all essays and projects up to that date. Fortunately she has had good reports for the time

for six weeks. In essence he completed his project in about a week but we found other things for him to do. We found out a lot about life in Russia, first hand, and the enormous differences in the societies. It is non-sensical to compare prices on official exchange rates. Accommodation is very cheap by British standards but with much poorer facilities. He told us that his wife and daughter aged 6, lived in two rooms and shared a kitchen and bathroom with five other couples. By British standards this is poor accommodation. The real problem is that there is little prospect of him being able to rent or live in anything better because 90% of his income is spent on food. Also the food he can buy is very limited and according to news reports received here since his return prospects and food availability have become worse. The Russian states have an enormous problem and now we have of a revolution in Georgia.

5/ she has spent on the hospital wards and in other nursing departments. However in November she failed another written paper and has just retaken it just after Christmas. We have not had the results yet but Katherine does not think she has done very well. As far as I can make out if she fails the resit she will be out. Katherine's fiancé is due to start a similar course in October although it is possible he could start in April. This means that when they plan to marry in July 1993, he will be about one year through his course and if Katherine fails what sort of job she will have, I just don't know. Where they plan to live and what they plan to live on is a mystery to me but these mere trifles do not seem to be important to Katherine.

At about the time we heard that Katherine had failed her first examination, we heard that Richard had failed his second year at Nottingham. However by the time he came home he had sorted

himself out and is in fact repeating the second year of the same course. His punishment is that he had to fund it himself which he is doing. He has had two holidays this year - one walking in the Pyrenees in the summer and the other skiing in Roumania. In fact he came back from his skiing with a suspected broken wrist. The x rays showed a small fracture in the wrist end of the radius and there is some doubt about how serious this is. His arm is in plaster and it is too painful to write. I think the crack will heal quickly and the pain is caused by a severe sprain.

The good news is that we have had two excellent holidays this year. One was to Hungary, mainly birdwatching which is something that Brenda is interested in. With the official exchange rate eating out was extremely cheap. We had a good guide

7/ who told us about Hungarian life and attitudes. We stayed in East Hungary for five days on the great plain and then into mountain and forest area near the Czechoslovakia border. Our last night was in Budapest although we did not visit the town itself because it was much too hot. We did see many birds that we had never seen before and we thoroughly enjoyed it. We also went to Madeira which is an island in the Atlantic Ocean off the coast of Africa for a late holiday. Here we did a lot of walking mainly along irrigation channels called levadas. Here we saw bananas growing and many other plants we grow in pots indoors and find hard to keep were just growing in the wild. The week we spent there was not really enough and it is certainly a place I would like to visit again. Before that we went on a weekend to Paris with some friends who live in Standlake. There were four couples altogether and we visited all the famous landmarks, Eiffel Tower, Arc de Triomphe, Sacre Coeur etc.

8/ We also visited the Palace of Versailles although I would not recommend going into the palace itself. It was devoid of any furniture and very crowded with visitors. Instead the gardens were beautifully laid out and two outer palaces called the Petit Trianon and the Grand Trianon had a lot of character and were well furnished. They at least gave a lived in appearance. We both felt we could go back to Paris and cover more of the sights we did not see.

Thank you for your description of carnatic music - it is quite clearly something I shall have to listen to on some occasion. You are quite right I have put on some weight since we met in Tokyo. It is called "middle age spread". It may interest you to know that I am developing a few grey hairs as well.

9/ Do write and tell me what has been happening in India. One the news it is only the disasters that are reported although nothing was said about the heavy rains in Bombay during the summer. So do tell what you can of ordinary life in India. I hope that last year was a good one for you and that you have now recovered from the operation on your foot. I think you said in one of your more recent letters that you were driving again and so it seems to have improved. It is good to hear news of you and your family and so do write when you have some time.

With my kind regards to you and your family for good health in 1992.

Alan

By air mail
Par avion

Be properly addressed
POSTCODE

Dr. Krishnaja A.P.

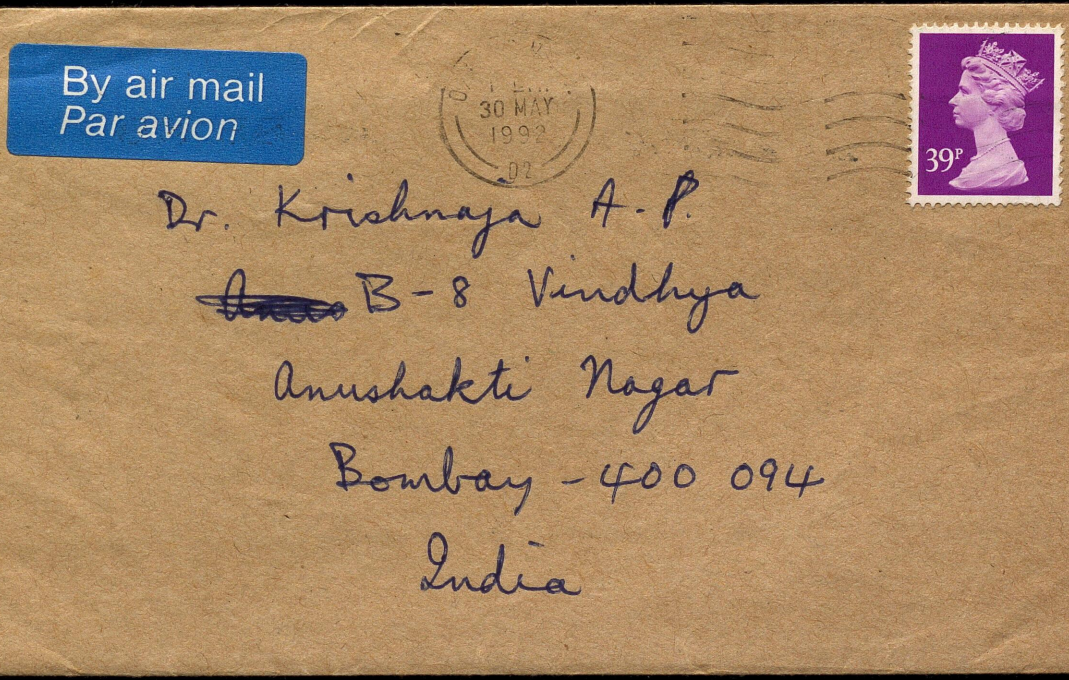
B-8 Vindhya,

Amshakti Nagar,

Bombay 400094

India

replied on 26-1-92


By air mail
Par avion
30 MAY
1992
39P
Dr. Krishnaja A.P.
B-8 Vindhya
Anushakti Nagar
Bombay - 400 094
India

8, THE GLEBE,
STANDLAKE,
WITNEY
OXON
OX8 7SS

May 29th 1992

Dear Krishnaja,

I did receive your letter of January this year and your reminder in May. I am very sorry, I should have replied earlier. Unfortunately the first letter arrived at a bad time. We had just heard that Katherine had failed an examination and was requested to leave her nursing course. She was heartbroken and she needed our help. We are still arguing with the nursing school and the English Nursing Board about this case but I do not hold out much hope of any success.

As to advice on where to send the paper, the only journal I can think of is Mutation Research but I am a little

surprised that Dr. Natarajan did not suggest that.

I am sure that by now you have given birth. Congratulations and I hope all went well. I am sure you will have your hands full for at least the next three months.

Not long after your first letter arrived I went to a meeting at Caen in France and it looks as if we shall be using an accelerator there to irradiate blood. Immediately following the receipt of your second letter Brenda and I went on holiday to Venice and Florence for a week. Venice I enjoyed very much but Florence I found overpowering. To enjoy Florence you need to be an art enthusiast and three days was too much for me. However I am still pleased to have visited because I did find a few

items of interest. One was a collection of very well preserved books from the 15th and 16th centuries. They were painstakingly written by monks and were passages from the Bible and there were recorded chants in use at the time. We spent about 2 to 3 hours marvelling at these. I am not sure we came back from the holiday very rested because we were walking around all day in fairly warm conditions.

In England we are in the middle of a heatwave. Temperatures of 25°C plus are very unusual for May but I guess these are quite cool temperatures for India.

I am sure you have heard that we have had a General Election here. The Conservative Party under Mr. Major were re-elected but with a reduced majority. In my view they succeeded with a very negative campaign. Their main argument was that the Labour Party proposals would cost a lot of money

ad that would mean higher taxes. Clearly they were believed and thus re-elected.

To answer your last question, I don't think I have met I. Hansman but I think I have seen his name on one or two papers in conjunction with Prof. Harder who I do know.

To repeat, I hope all is well with you. Do let me know more about your baby.

With kind regards

Alan

By air mail
Par avion

Dr. Krishnaja A. P.
B-8 Vindhya
Annshakti Nagar
Bombay 400094
India

8, THE GLEBE,
STANDLAKE
WITNEY
OXON
OX8 7SS
3 Jan 1993

Dear Krishnaja,

It seem quite a long time since I last wrote to you. I did receive your last letter telling me of the birth of your baby and the sad news about your brother. I offer congratulations and commiserations at the same time.

I cannot remember precisely what I told you in my last letter and so if I repeat myself I am sure you will understand. Richard has now completed his second year of his degree course. He had to do some work during the summer holidays in order

to pass into the final year. He takes some more examinations at the end of January and I hope he is able to pass them. The job situation in Britain is very bad and many of his contemporaries are still unemployed after graduating. At work we usually have more than 100 applicants for each scientific post many of them well overqualified for the job.

Catherine has not been able to train as a nurse. Nowadays in Britain the primary requirement of a nurse is to be academic and at the moment even trained academic nurses are having great difficulty finding a job. This is because, by government decree, accountants must control

the Health Service. Doctors now have to buy hospital services on behalf of their patients and only have a limited amount of money to do this. When the money runs out - hard luck. Those in work can pay themselves, even though they have, in effect, paid for it in their taxes, or continue to be ill and hope they cure themselves. Catherine has been working part-time through a nursing agency often, paradoxically, in National Health Service hospitals. So essentially she has been doing a job, for which she officially is not qualified all because the hospitals cannot afford to employ a qualified person on a permanent basis. The system defies any attempts on my part to explain it logically. The unfortunate part of all

this is that the general stress on Katherine has contributed to a skin condition which the medical call eczema and in which the skin all over her body seems to shed about twice a week. She is extremely itchy most of the time. Our wonderful medical profession are on a temporary basis able to allay irritation but have done nothing to find out the cause of the problem. In the middle of all of this Katherine has found herself a job operating a cardiac machine in a hospital provided she passes a medical test. What will happen, I don't know.

Brenda still has her job as a part-time occupational therapist assistant but lack of local government funds are making the job very difficult.

My life is rather brighter - I still have a job. David Lloyd and I are still in the chromosome aberration field and are now becoming involved in the relationships between specific chromosome exchanges/ deletions and specific cancers. I can see some great advances in the next five to ten years. I think I told you about our holiday in Venice and Florence but later in the year, Brenda and I went to the United States for three weeks. It included a conference at Gatlenburg and so it was not all holiday. Before the conference we toured in Tennessee and afterwards we took a coach trip in New England to see the wonderful autumn colours of the trees. We in fact were about a week early but nevertheless had

some idea of the full glory of the colours. It was certainly a holiday to remember. I have also had two trips to France and used an accelerator there to irradiate blood. I took some time off to see the Bayeux tapestry which was woven by Monks who told the story of the Norman invasion of England in 1066. It is a very famous tapestry but I had never seen it before.

I think that must be all for now. Do send me a photograph of your baby and all the family. I hope you had a very happy Christmas and somewhat belatedly I wish your and your family a very Happy New Year.

with kind regards

Alan

8, The Glebe,
Standlake
Witney
Oxon
OX8 7SS
23/4/93

Dear Krishnaja,

You have sent me a lot of data and asked what is superficially a simple question. The answer is in my views not very clear cut and the whole problem is an excellent example of using statistical methods as a tool to help thinking but the final conclusion is a question of scientific judgement which you will have to apply.

I think it best to explain the statistical methods I have employed and the assumptions made. But first I would like to say that general quality of the data looks very good indeed. The number of centric rings scored is small compared with dicentrics, just as it should be. You score about half as many excess acentrics as you do dicentrics which is very much in line with our experience. This of course means that an analysis of total aberrations would give similar results to an analysis of just dicentrics + centric rings. I have therefore performed the analysis for dicentrics + rings and for excess acentrics only.

The 200 R data

The first thing to do is to test whether it is reasonable to combine the 6 samples of Group I and the 10 samples of group II From the distributions of aberrations amongst the cells we can test whether it is reasonable to use the Poisson distribution or not.

For dicentrics + rings the variance appears slightly greater than the mean but it is still probably reasonable to use the Poisson distribution. For excess acentrics the variance was on average about a factor 1·3 higher than the mean and it is clearly not reasonable to use the Poisson distribution.

(a) Dicentrics + centric rings

To test whether is 6 observations in group I are homogeneous we proceed as follows. The mean yield is 338 in 1324 cells = ·255 and using this mean an expected number of dicentrics+ring can be calculated. This leads to the following table.

cells scored	observed cc+rings O	expected cc+rings E	$\frac{(O-E)^2}{E}$
100	25	25·5	·01
130	33	33·2	·00
175	53	44·7	1·54
210	52	53·6	·05
300	67	76·6	1·20
409	108	104·4	·12
Totals 1324	338		2·9

For a homogeneous population, the total in the last column should be distributed as χ^2 on 5 degrees of freedom. A value of 2·9 is reasonable and so the population can be combined.

A similar table can be constructed for the 10 samples in group II. Here the mean is 388 in 1219 cells = ·318 and the sum of the final column is 8·5 which on 9 degrees of freedom is perfectly reasonable. It is now justifiable to calculated the means of groups I and II and to estimate uncertainties using

the Poisson distribution. The means are

Group II mean = .318 standard error = $\sqrt{388}/1219 = .016$

Group I mean = .255 standard error = $\sqrt{338}/1324 = .014$

The difference is .063 and the standard error = $\sqrt{.016^2 + .014^2} = .021$

The mean of group II is therefore significantly greater than group I.

(b) Excess acentrics.

Similar calculations can be done for excess acentrics except that the last column is calculated from $(O-E)^2/1.3E$. This is an attempt to take into account the overdispersion of excess acentrics among the cells. For group II a value for χ^2 of 4.9 is obtained on 9 degrees of freedom which is acceptable. For group I the value of χ^2 is 21.7 which on 5 degrees of freedom not acceptable. Inspection of the group I data shows that observation 2 (43 excess acentrics in 130 cells) is completely out of line with all other observations. If this observation is ignored then groups I and II are identical. If the observation is included the means of groups I and II are $.161 \pm .026$ and $.149 \pm .013$ which are not significantly different. The standard errors are computed assuming the factor 1.3 to allow for overdispersion and in the case of group I the extra variation because the population is not homogeneous. (Note in group II, observation 1, the excess acentrics should be 55 in 300 cells and not 35)

It is now that you need to apply scientific judgement. The dicentric + ring analysis says that group I has a yield about 20% higher than group II. Against this, it is possible to fit an overall mean of .285 to all 16 observations and obtain a value for $\chi^2 = 20.9$ on 5 degrees of freedom. This does not

indicate significant heterogeneity. It is just that most of group II give a yield higher then most of group I. For excess acentrics there is no discernable difference between the two group and if anything the yield in group I is higher than in group II.

I think that before concluding that Groups I and II are different in dicentric yield you need to satisfy yourself that the two groups are expected to be different. You should also be satisfied that the difference is in the expected directions and that there is a good reason for the effect to be seen in dicentrics and not acentrics.

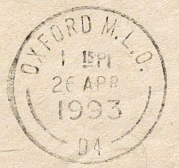
The 100R data

A similar analysis could be done with the two groups at 100R but they do not look significantly different to me. The dicentric + ring yields are 57/700 compared with 106/1500.

I hope this helps and you can make something of it.

With kind regards

Alan.



Dr. Krishnaja A.P.

B-8 Vindhya

Anashakti Nagar

Bombay 400094

India

8, THE GLEBE,
STANDLAKE,
WITNEY
OXON
24/4/93

Dear Krishnaja,

This will be just a short note to enclose my thoughts on your recent data. I hope it helps.

The riots and bombings in Bombay were reported in England and Brenda and I both thought of you and hoped you were not involved. The cause of the riots however was not well covered and the various reports I found confusing. Do you know what lies behind the disturbances. I guess, just as we have with Northern Ireland there is a mixture of religious and social groups who consider themselves disadvantaged and the refusal of authorities to try to improve or accomodate the underprivileged

eventually causes a riot. Unfortunately everybody loses because the element of fear and distrust enters everybody's life.

Brenda and I went away for a few days to the New Forest which is an area of woodland and open moor in the south of England. It was very restful. We have booked a holiday for September and we are going to Egypt with a few days in Cairo and then a boat trip along the Nile. We still have to obtain our visas and have a few innoculations against various nasty diseases.

Richard is home for Easter but returns next Tuesday to Nottingham. This should be his last term and we both hope that he will receive his degree.

With the present job market, I really do not know what he will do then. He is aiming at the sporting/recreation industry looking for a job at an outward bound centre. With his climbing and walking experience this is where his interests really lie.

Catherine is a little better I think. She has abandoned conventional drug type medicine and is trying homeopathic treatment. This so far is related to diet and she now does not eat beef or pork or milk products. The overall effect has been gradual but she generally appears calmer but she is still very itchy all over her body. Her skin however does look better.

Her job as a cardiographer is going well but she doesn't really find it stimulating enough. We received

some information recently which suggests that she might be able to take a short course to become an enrolled nurse and at least start on the nursing ladder. The paradox is that enrolled nurses are being phased out but the hope is that she can then convert to a registered nurse which is what she should be. What would happen then I don't know because registered nurses are being phased out. It is obviously going to be a long and complicated story.

I hope all your family are well. Children really do grow up very rapidly and their needs change just as rapidly.

With kind regards

Alan

By air mail
Par avion

Dr. (Mrs) Krishnaja A.P.,

B 8 Vindhya,

Amrshakti Nagar

Bombay 400094

India

OXFORD 18/DEC/93
RLG

8, THE GLEBE
STANDLAKE
WITNEY
OXON
OX8 7SS

18 December 1993

Dear Krishnaja,

Thank you very much for your last letter in May and particularly for your thoughts about Katherine. I have not replied earlier because there have been further developments here.

Not very long after I received your letter, Katherine received a telephone call from her former tutor at Winchester. She told Katherine that Winchester were applying to run a course which would lead to an enrolled nurse status and having completed that she would be able to convert to a registered general nurse possibly elsewhere.

If all went well this would give Katherine the qualifications she should have been aiming for in the first place. So in October she gave up her job in Oxford and is now doing nursing at Winchester. There is now only one cloud on the horizon. I cannot remember whether I told you in a previous letter but during the period between her finishing nursing and about July and August last year, she developed a peculiar skin condition for which her skin peeled completely every few days. She had suffered with patchy eczema before but it was reasonably under control. Now this was all over the body and seemed out of control.

Under the local hospital, she was in hospital for two separate weeks and improved on both occasions. However they decided that a week in hospital every month could not form the basis of a permanent cure and tried steroid injections which Catherine was not all all keen on and psoriin based ultra violet treatment. In fact this just did not work. They burnt Catherine twice with this treatment and the whole thing made her worse. We went back to her doctor and asked for a second opinion. He sympathasised but said that the Oxford hospital were the experts and did not know wher to send her for such an opinion. We had purely by chance heard of an alternative medicine centre in

Southampton which claimed to treat diseases like eczema. Out of desperation more than anything else we took Katherine there to try. The doctor there put her on a strict diet - no beef, no pork, no dairy products, no potatoes or tomatoes. The basis of this was the result of some wierd test based on skin conductivity as far as could work it out. I must admit I was very skeptical and so was Katherine's doctor but to be fair we both have to admit that Katherine's skin has improved considerably. She still has bouts of itchiness but I she has now returned to the condition she was before this all started. Now Katherine has a medical at Winchester in a few days

and if she fails that she will be off the course on medical grounds. We shall just have to hope.

Richard finally received a degree this year. He is still looking for a job. It appears in England nobody wants to employ somebody without "experience" and you can't get "experience" without a job. He has a degree in mathematics and the government are saying we want more people with degrees in science and mathematics. He is keen on outdoor pursuits, walking climbing and camping and he very nearly got a job at a centre. He was short listed but just failed to get the job.

On a more cheerful note, Brenda and I went to Egypt this year for our

holiday. We stayed three nights in Cairo and then flew to Aswan for a ten day cruise along the Nile to Cairo. We went to all the ancient Egyptian sights that were open and it was surprising how much temples and pyramids had survived to the present day. The pyramids date back four or five thousand years and the temples two to three thousand years. The wall carvings which describe life and beliefs in ancient Egypt really have to be seen to be believed. We took photographs of course but they don't do it justice. The pictures mean much more to us because we have seen the actual sights. Brenda said it was the best holiday she had ever had.

At work we are now looking at specific DNA changes in cells in relation to cancer. The new in situ hybridisation techniques are being used and we are beginning to discover just how complicated chromosomal changes can be. The emphasis is much more in elucidating the mechanisms that eventually lead to cancer particularly in humans. In the past we have known that the process is very complicated and even now we only have a vague idea of the various stages of development. This has meant that that we have not known where to look to find that part of the process which has most bearing on dose rate and quality effects which is what I am interested in.

In the past year of two it has suddenly become obvious that ~~the~~ one of the areas to study is the way the cells handles DNA breaks. So it is repair processes in cells that is one of the major factors in producing radiation quality and dose rate effects. Of course we ~~were~~ are using the lymphocyte for this study.

I hope to hear from you soon. I wish you and all your family a very happy Christmas and all good wishes for the New Year.

With my kind regards

Alan