

SRG meeting

**Minutes of the SRG Meeting, Viking Inn, Montreal, Canada,  
5th-7th May, 1992.**

Attendance: Dr C J P de Siqueira      Dr P Madsen  
                  Dr S R Massey                Dr D Pangritz  
                  Mr T G Mitchell                Dr S Appleton  
                  Dr L J Rudge (secretary)      Dr R E Thornton (chairman)

Dr A Springall (consultant)    Mr P N Lee (consultant)

**Tuesday 5th May**

**Budget (LJR/RET).**

The 1992 expenditure is forecast as £288,354, allocated to 8 projects. The estimated budget for 1993 is £360,000. This allows for continuing grants as well as an allowance for new projects, which was felt necessary when considering the large number of proposals received this year.

**Review of Molecular Biology Projects (LJR).**

1. **Dr G Currie & Dr J Jenkins, Marie Curie Institute, U.K.  
The Role of p53 in Cell Growth and Malignant Transformation.**

This project investigates the normal function of a cellular protein, p53, the mutation of which is thought to be an important step in tumourigenesis. The progress in the work funded specifically by the SRG was briefly reviewed. Using yeast cells, three proteins have been detected which interact in cell cycle control along with p53. These have been sequenced and human homologues will be identified. Dr Jenkins is confident that the yeast program will answer the question of where p53 fits into the complex control system within the next few years. This may have implications in understanding the effect of p53 mutations and possible ways to restore cell control in p53 mutated cells.

**Comments;**

Current funding expires in September 1992 but it was felt that the importance and scientific standard of this work merited continuation of support. Also, the advice of Dr Jenkins was considered helpful in interpreting the vast literature.

2. **Dr J Field, Liverpool University, U.K.  
p53 Overexpression and Mutation in Head and Neck Cancer.**

The work at the Marie Curie Institute was compared to the SRG-funded work of Dr Field (who recently succeeded Prof P Stell). Dr Field has identified p53 overexpression and sequenced p53 mutations from various head and neck tumours.

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Comments;

It was felt that the expertise of Dr Field was not comparable to that of Dr Jenkins and that the high frequency of p53 mutations in tumours was now well established. Funding for Dr Field is due to finish at the end of 1992 and is unlikely to be continued.

Other;

An important area identified with regard to p53 was that of identifiable mutation spectra being attributed to specific environmental and endogenous factors. A specific base transversion has been claimed to be caused by benz(a)pyrene, but this mutation has also been associated with many other chemicals.

3. **Prof J Idle & Dr A Daly, Newcastle University, U.K.**  
**The Association between Metabolising Enzyme Polymorphisms and Lung Cancer Susceptibility.**

Since Prof Idle is reluctant to attribute SRG funding to a specific project, an overview of his research was given. A new technique, called Single Stranded Conformational Polymorphism, will speed up the detection of rare CYP2D6 mutations which, at present, are undetected by the routine assays. Racial variations in polymorphisms will be studied in a Turkish population and in black and white Americans.

The association between the CYP2D6 extensive metaboliser genotype and lung cancer will be investigated in two case-control epidemiological studies, in Norway and America. The American study is to be funded by the C.T.R. Prof Idle is also to investigate any association between genotype and bladder cancer and the recently reported protection against Parkinson's disease seen in extensive metabolisers.

Prof Idle intends to produce assays for polymorphisms in the gene CYP1A1 and also the gene coding for glutathione-S-transferase  $\mu$ .

Comments;

Concerns were expressed about apparent poor financial management and about the increasing diversity of the project. Considering the large range of metabolising enzymes, their overlap in substrate specificity, particularly with relation to tobacco smoke constituents, and the likelihood of them all harbouring polymorphisms, then it appears unlikely that a specific relative risk for individuals can be calculated.

**Other SRG Projects (RET).**

4. **Prof J Clausen, Roskilde University, Denmark.**  
**The Formation and Repair of DNA Adducts.**

Prof Clausen compares smokers and non-smokers susceptibility to the formation of adducts, by incubating lymphocytes with polycyclic aromatic hydrocarbons. He has found the adduct levels of smokers and non-smokers to

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be comparable. Some other workers have shown a significant difference in adduct levels between smokers and non-smokers but with a large degree of overlap between the two groups. It may be that adducts are of little importance in carcinogenesis and that irritation plays a bigger role.

Comments;

Prof Clausen's progress report was assessed by our consultant, Prof J Parry, who questioned the relevance of the model to the human. Prof Clausen is to present his work at a conference in Rome which will be attended by RET. This will allow some assessment of the standing of Prof Clausen's work within the scientific community.

5. **Dr D Cooper, Thrombosis Research Institute, London, U.K.  
Mutations in Thrombotic Disease.**

Dr Cooper presented his work to the SRG in Berlin, describing inherited mutations associated with thrombotic disorders. He is considered a scientist of high calibre who holds the view that endogenous compounds are important in the cellular changes leading to carcinogenesis. His SRG funded work will commence in 1 months time, when he has secured a suitable research assistant.

6. **Dr A Springall & Mr P N Lee, U.K.  
Segregation Analysis. (presented by AS/PNL).**

PNL presented the epidemiology of lung cancer. Out of 12 case-control studies, all showed a positive familial grouping of lung cancer, with an approximate doubling of the risk associated with having relatives with lung cancer. Segregation analysis is a new statistical tool which looks at genetic inheritance patterns in disease incidence while allowing environmental factors to be considered. The objective of this project was to review the methodology of segregation analysis, its potential uses and problems. The technique involves applying models to find which is most likely to have produced the dataset. Complex equations take into account the assumed probability of the genotype arising in offspring, the probability of the genotype producing the related phenotype (penetrance), and the possible involvement of an environmental factor.

The method was used in the study of 337 probands from S. Louisiana by Sellers *et al.* which concluded that lung cancer incidence in families fits a model of codominant gene inheritance. The 3 genotypes had the same susceptibility to lung cancer but different ages of onset. Dr Springall and Mr Lee have purchased the dataset and are re-analysing it but have been unable to reproduce Sellers' results so far and are concerned that his model may be the wrong one. This project will also include a review of another statistical technique called linkage analysis which uses marker genes to identify the location of the gene of interest. The higher the probability of a marker gene being inherited along with the gene for a certain disease, then the closer these two genes are likely to be on the chromosome.

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### ETS Studies (AS/PNL)

Three studies are being considered by the SRG. The objective of each is to assess whether the claimed relative risk of lung cancer for non-smoking women with smoking husbands can be explained by confounding factors.

i. **Wynder (American Health Foundation).**

This case-control study will include populations from both USA and Japan, and focus mainly on differences in diet. It looks at both active and passive smoking which is unlikely to be the best way to address the ETS issue. This study will probably be funded by the German Forschungsrat.

ii. **Sterling.**

This study addresses the hypothesis that the increased risk in women married to smokers is due to chemical exposure within the home, from cleaning products and from chemicals brought home by the husband from his workplace. It incorporates two studies; a survey incorporating a house chemical audit, and a costly case-control study. This is a high risk study since it focuses on a very specific hypothesis and, even if proved right, may still be regarded sceptically among the scientific community.

iii. **Gori/Proctor (Covington and Burling).**

This is a survey comparing risk factors in non-smokers either exposed or not exposed to ETS. It looks at a large number of factors but is also very expensive. The study is to be conducted in the U.S.A. and does not address the issue in Japan, where the greatest risk due to ETS has been claimed.

iv. **PNL proposes to design a study of passive smoking and confounders, incorporating populations in U.K., another European country, U.S.A. and Japan. This will use market research and will therefore be cheaper.**

v. **Misclassification is another important source of bias and has been assessed in a population of 400 Japanese women in a recent study by Proctor *et al.* The preliminary results suggest that misclassification is higher in Japan than in the West and that the rate of smoker denial is higher in smokers married to non-smokers. This bias in misclassification appears to negate the overall bias, but more data are needed to confirm this. The study also showed cotinine levels to be slightly lower in non-smokers married to smokers compared with non-smokers married to non-smokers, indicating that cotinine is unlikely to be a useful indicator of exposure.**

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Wednesday 6th May

7. **Dr V Knott, Royal Ottawa Hospital, Canada.**  
**Nicotine -Induced Changes in Frontal-Lobe Function.**

Members of the SRG visited Dr V Knott for a presentation of his research. Dr Knott stated that his work stems from the hypothesis that smoking enables subjects to modulate their coping ability through changes in central nervous system activity. Dr Knott's current project investigates the effects of smoking on "executive function" of the frontal-lobe, which governs information ordering and selection.

Changes in brain activity are measured by EEG, with advanced on-line computation enabling the alpha, beta, theta and delta wave forms to be discriminated. Fast alpha waves are seen in the aroused state while slow delta waves are seen during sleep. Scans of the brain enabled levels of each wave form to be visually compared in each area. Computation of various expectancy waves eg. p300 and mismatchnegative (MMN) was also possible.

In the first task, in which subjects had to discriminate and respond to a rare tone, smoking did not produce any improvement in performance. The conclusion was that the task was too easy and did not involve the executive function. As a result, a further task was devised, requiring the detection of 3 even or odd digits in sequence, against two kinds of distraction - white noise and occasional digits being read out in a female voice. Work is now in progress using this paradigm.

Dr Knott also referred to work carried out on other projects (not supported by the SRG). In one study, an increase in alpha activity for own cigarette versus sham smoking was noted in contrast to a decrease in alpha activity for experimental cigarette versus sham. In other studies, mecamylamine, a nicotine antagonist, was shown to have no effect on the response to smoking. Both results to some extent question the importance of nicotine. The former, if confirmed by further studies, would appear to have relevance in product discrimination.

**Comments;**

Members of the SRG agreed that progress on this project was reasonable, the work being conducted to high professional standards, and accordingly agreed to fund the work through to December 1993. The members also agreed that site visits were a useful aid to assessing a project.

Thursday 7th May

**Alzheimer's disease and nicotine (PNL/LJR).**

PNL reviewed the epidemiology of Alzheimer's disease and smoking. Of 17 case-control studies published to date, 14 showed a negative association between Alzheimer's disease and smoking. Meta-analysis of the 4 studies without any obvious sources of bias gave a significantly reduced risk of 0.64. PNL concluded that, despite the poor quality of the studies, the data was

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strongly suggestive of a negative association and there was also evidence for a dose-response relationship. The results published by Van Duijn and Hofman, suggesting that the negative association only holds for familial Alzheimer's disease, are not conclusive and have not been confirmed in any other studies.

Evidence exists to suggest that nicotine slows the degeneration of nerves following nerve lesion or exposure to the neurotoxin MPTP (which produces Parkinson's disease). Nicotine also increases the number of nicotine receptors in the brain in smokers, which may counteract the loss of nicotine receptors seen in Alzheimer's patients. Nicotine has been shown to produce an acute improvement in attention in Alzheimer patients but produces severe mood changes at higher doses.

The pathological changes in the brain occurring in Alzheimer patients and consequent possibilities for treatment were reviewed. Pharmaceutical companies have tried a number of treatments, none of which have been very successful so far. These include replacement of choline, and use of acetylcholinesterase inhibitors and muscarinic receptor agonists. Cycloserine is undergoing clinical trials in Dr Knott's laboratories. It is an antibiotic which potentiates the effect of glutamate, another neurotransmitter depleted in Alzheimer's patients. Our consultant, Dr S Wonnacott, believes that a combination of cycloserine and nicotine will provide the best treatment for Alzheimer's disease.

The possible role for nicotine transdermal patches was discussed. These appear to be of low efficacy in smoking cessation and unlikely to provide satisfaction to the smoker, due to the slow rise in plasma nicotine. However, the nicotine profile may be comparable to that achieved by other methods of tobacco usage. The ability of transdermal nicotine to enhance cognitive function is being addressed in a study by Prof D Warburton. Nicotine patches are under trial for the relief of ulcerative colitis (Prof Rhodes) and an attempt will be made to find trials being conducted using nicotine patches with Alzheimer patients.

Stowic Resources are a small pharmaceutical company who approached Sir Patrick Sheehy asking for support for a novel design of transdermal patch. It is claimed to be superior to other products available in a number of aspects, particularly because it has controlled zero-order release, making it independent of concentration and interindividual variation in skin absorption rate.

**Comment;**

It was concluded that Alzheimer's disease and the possible protective effects of nicotine is an area of importance but that the question of BAT's involvement with the production of nicotine patches is outside the scope of the SRG.

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**Proposed Studies (RET).**

8. **Prof J Gray, Institute of Psychiatry, London, U.K.**  
**The Protective Effect of Smoking Against Neurodegenerative Disease.**

This proposal encompasses a multidisciplinary investigation into the mechanisms of Alzheimer's and Parkinson's disease and the apparent protective effect of nicotine, using both clinical trials and animal models. The proposal will be circulated to SRG members for assessment. It was noted that Prof Gray has already discussed this proposal with Sir Patrick Sheehy and was well received.

9. **Dr P E Brown, Newcastle University, U.K.**  
**The Synthesis of Novel Nicotinic Ligands.**

This project proposed to design and synthesise novel compounds to bind with brain nicotinic receptors. It was considered that such work had already been addressed within the tobacco industry, and that, if a chemical was produced, it would take at least 10-20 years before it could be of clinical use. This project will not receive SRG funding.

**Other BATCo Funded Projects (RET).**

10. **Prof K Syrjanen, University of Kuopio, Finland.**  
**Human Papilloma Virus in Cervical Cancer.**

This project is studying the association between human papilloma virus and cervical cancer. 16 viruses have been sequenced so far. Present funding expires in December 1992 but is likely to be continued for a further two years.

11. **Dr H Rothschild, New Orleans, U.S.A.**

Money was provided by BATCo to purchase a dataset from Dr Rothschild, the segregation analysis of which was published in the paper by Sellers *et al.* This data is now being analysed by Dr Springall and Mr Lee (see point 6).

12. **Prof M A Smith, Leeds General Infirmary, U.K.**  
**Bone Mineralisation as a Predictive Marker for the Onset of Osteoporosis.**

Different measurements of bone and mineral loss during osteoporosis are to be compared between osteoporotic patients, controls, and women who have just reached menopause, to see if any changes are predictive of the future development of osteoporosis. Some studies have indicated a positive association between smoking and osteoporosis although the evidence is inconclusive. Smoking history is routinely asked of all subjects and no association with smoking has been shown.

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13. **Mr P N Lee, Sutton, U.K.**  
**Differences Between Active Smokers, Those Exposed to ETS, and Those not Exposed to Tobacco Smoke.**

£2,000 has been used to buy data from The Health Promotion Research Trust. It contains 1100 pieces of information on each of 9000 people, covering lifestyle factors, physiological measurements and personality type. The data will be analysed to assess the magnitude of confounding by these factors in risk calculations for diseases said to be associated with smoking or ETS exposure.

#### **Association between Bird Keeping and Lung Cancer (PNL).**

Holst first reported a relative risk of 6.7 for lung cancer in people who had kept birds between 5 and 14 years. PNL, together with Dr F J C Roe and Dr A Gardener, has conducted a further case-control study in Lanarkshire, Scotland and calculated a lung cancer relative risk of 1.29 for keeping any bird. This was significantly higher for keeping a pigeon (3.53), and greatest for subjects who worked in a greenhouse with chicken manure (10.01).

In conclusion, this latest study partly supports the idea of bird-keeping as a risk factor for lung cancer but Holst's work may have overestimated the effect.

#### **Clinical Misdiagnosis (PNL)**

PNL is analysing data from a study in Budapest, comparing clinical diagnosis with postmortem diagnosis. Preliminary data indicates that 40% of lung cancers diagnosed as the underlying cause clinically, were not found to be the cause at post-mortem. Also, 70% of lung cancers diagnosed as the cause at post-mortem were not detected clinically.

With further funding from Philip Morris, PNL may look at clinician bias in diagnosis when a patient's smoking status is known.

#### **Future SRG Meetings.**

It was felt that annual SRG meetings were too infrequent to allow proper discussion of projects. Permission would be sought to hold a meeting in London in November 1992 and again in Denmark in June 1993.

Dr L J Rudge  
Dr R E Thornton

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