

File Renaud

FILE MEMORANDUM

September 12, 1980

RESTRICTED

Meeting with Professor Serge Renaud (CTMC Grantee)

On September 10 Drs. Bilimoria and Smith attended a meeting with Professor Serge Renaud at the Department of Nutrition, Université de Montréal. Also attending the meeting were:-

Chris Seymour - CTMC
Peter Brown - Carreras/Rothmans U.K.
Keith West^{As} - Carreras/Rothmans U.K.
Norman Cohen - Rothmans
Roland Leger - Benson & Hedges

No representatives from Macdonalds was able to attend.

The purpose of the meeting was to update the group on Professor Renaud's latest work and to discuss proposed future work. The meeting also took advantage of the visit of the Carreras representatives who are very interested in this work.

Professor Renaud first reviewed his earlier work which shows clearly the effect of differences in diet, particularly the intake levels of saturated fats, on the functioning of platelets in blood, which are important in clotting and in the predisposition of subjects to coronary heart disease (CHD). (He has seen parallel effects in animal studies). He attributes the success of his team in this work largely to two factors: (a) the identification of groups of subjects with consistent lifestyles and stable but markedly different diets, and the use of a convenient mobile laboratory for rapid testing of the blood platelets, which are inherently unstable after sampling. (For example, by 2 hours after sampling, the blood clotting time has decreased by about 70%). To date most of his subjects have been farmers in distinct regions of either France or Scotland, although a further study is about to start in Belgium.

A change in diet from high to low use of saturated fats (dairy products, and visible fat) to unsaturated fats (vegetable/cereal oils) has been shown to be effective in significantly improving the platelet function of blood within about one year.

Because of the implication of smoking in contributing to CHD, Professor Renaud has included comparisons of non-smokers and smokers in some of his work. He had found very little difference in platelet functions between non-smokers and moderate and heavy smokers of matched diet. However at our meeting Peter Brown pointed out that, because subjects were tested in the morning without having smoked since the previous day, Renaud's smokers were in fact 'deprived' smokers, and any transitory effect of smoking on platelet function would have been missed.

109874934

More Recent Work

In 1979 a study was conducted in which smokers' blood was sampled before smoking and again 10 minutes after completion of smoking 1 cigarette. Smoking produced a dramatic change in some of the platelet function tests for subjects with both higher and lower saturated fat intakes, although the response change was lower for those using less saturated fats.

Subjects were asked to come to the mobile laboratory on 3 occasions at weekly intervals. Comparisons were made between subjects not smoking, and smoking a low nicotine cigarette (0.6 mg/cigt.) and a high nicotine cigarette (1.5 mg/cigt.). With both cigarettes, subjects were asked to inhale deeply. No differences were found in platelet function effects between the low and high nicotine cigarettes.

When Professor Renaud discussed this with Geoff Felton, Geoff pointed out that the nicotine yields actually inhaled from the two cigarettes could have been much closer than these 'standard' yields, and may in fact have been the same, because of compensation in many ways (size and number of puffs, butt length, and inability to deeply inhale the stronger cigarette smoke). Hence these findings do not prove that nicotine is not the important agent in smoke concerning the change in platelet functions.

In fact Professor Renaud is fairly convinced that nicotine does have an important effect. He did an in-vitro study by adding nicotine to blood platelets in plasma, and observed a sizeable increase in response in some of the aggregation tests.

Proposed Study

Evidently a further study is required, with the objective of finding what smoke component is the cause of the effect on platelet function. For example, what is the relative importance of nicotine and carbon monoxide? Is there no relationship between COHb levels and platelets? (It is possible that since CO is rapidly taken out of the blood by the red cells, it may have no effect on the platelets. Professor Renaud believes that condemnation of CO was on the basis of very little data). It is also important to find out how transitory the effect of smoking is, and how significant is the effect compared to other activities, for example a jog up the road.

Peter Brown has suggested the attached protocol (Appendix) for a new study. At our meeting Peter pointed out that in the 1979 study, the residual nicotine in the blood at the time of sampling (10 minutes after cessation) would already have been very low, hence the suggested new timing of blood sampling. He offered that Carreras would do the analyses of blood-and cigarette butt-nicotines if the study is carried out in Europe.

109874935

Peter Brown's suggested cigarettes (Auslese and the 2 Gauloise versions) assume that the study would be done in France. However the location for the study has still to be decided. For the very low delivery cigarette, one without a carbon filter was suggested because of his concern as to whether irritants in smoke (eg acrolein) play a part in smoke's effect on platelet function and hence on CHD. (Renaud has made a brief test with Viscount Number 1 -- "less than 0.1 mg nicotine" from Canada, and found no effect on platelet function).

Keith Wesmas has had considerable experience with tests using nicotine tablets. He suggested that a useful study could be made by simulating different levels of nicotine and carbon monoxide intake in smoking either by administering nicotine tablets or breathing CO/air mixtures. However it was recognized that results of such a study would not satisfy governments to anything like the extent of direct smoking experiments. At the meeting, in vitro experiments with CO, acrolein and HCN were suggested.

Recommendation

It was recommended to check the degree of interest of the full Technical Committee of CTMC in the proposed new study, and hence in its further financial support by CTMC. Both Dr. Bilimoria and the author feel this to be a very worthwhile project. Preparations for the study could then commence, concerning for example location and detailed discussion of the protocol, and hence the costs/duration of the project. Professor Renaud's summary of the recent work will be prepared as soon as possible (target - October). Chris Seymour will be in the U.K. in the second week of October and will be seeing Peter Brown then.

Miscellaneous

Professor Renaud told us of other aspects of his work on factors affecting platelet functions.

- cholesterol has a very weak effect.
- lanosterol (a precursor of cholesterol) has a very pronounced effect on platelet function even in minute amounts.
- contraceptive pills give a very pronounced effect on platelet function (to be published soon in "Science").

109874936

Detailed information (computer output) on diet component effects from previous studies (250 male subjects) have shown that magnesium, calcium and alcohol intake tend to counteract the effects of saturated fats. They have also shown up effects on blood pressure; for example, alcohol's positive effect and magnesium's negative effect (the latter being particularly relevant to the effects of "hard" water).

A good description of the functioning of blood platelets is given in "Scientific American", June 1980, pages 86-103.



TAS/kb

cc: Messrs. R.M. Gibb
S.M. Candlish
R.S. Wade
M.P. Scherbak
R.L. Rice
Ms. J. Johnson
Dr. M.H. Bilimoria
Dr. P.J. Dunn
Dr. T.A. Smith
Dr. A. Porter
Circulation
Central File (P)

109874937

APPENDIX

SUGGESTED PROTOCOL TO EXAMINE THE EFFECT OF A RANGE OF CIGARETTE TIPS
ON PLATELET FUNCTION AND IDENTIFY A NO-EFFECT LEVEL

- Cigarettes : very low delivery (Auslese Extrem Leicht)
(not carbon filter) ((German) 0.1 mg Nicotine/cig)
- low-medium delivery (Gauloise Caporal Doux)
(0.5-0.6 mg Nicotine/cig)
- medium-high delivery (Gauloise Caporal)
(1.1-1.5 mg Nicotine/cig)
- Smoking Regime : 6 replicates with each cigarette, subjects should
be asked to inhale smoke moderately on 3 occasions
and deeply on 3 occasions. If possible some measure
of the individual's smoking regime should be recorded.
- Blood Sampling : Before smoking; when stopping; 5, 10, 15, 20, 30
and 60 minutes after smoking.
- Alveolar CO : Measured when sampling blood.
- Platelet Function : On all blood samples.
- Carboxyhaemoglobin : On all blood samples.
- Blood Nicotine : On all blood samples (if possible)
- Butt Nicotine : On all cigarette butts; filtration efficiency
of filter must be known.
- Smoke Chemistry : A smoke chemistry profile should be obtained on
cigarettes actually used for study.

109374938