Postgraduate Medical Journal (January 1971) **47**, 44–45.

Discussion

Chairman: DR R. P. K. COE

DR LAWLER. I would like to ask Dr Fitzgerald, is there any evidence that clofibrate lowers the total body cholesterol?

DR FITZGERALD. Yes, this has been shown by Holland and his co-workers. They have measured this and shown that there is a diminution in the cholesterol pool. In addition Ahrens in the United States has shown that there is a considerable increase in neutral sterol excretion in the faeces without a concomitant increase in thyroxin excretion. So I think this is fairly clearly shown.

DR FARRANT. Could I ask Professor Pilkington whether he thinks that the clinical manifestations of the four types of lipoproteins are in such water-tight compartments as Fredrickson suggests? Because I seem to have a patient who has type IV, with a pre-beta band, who has got tuberose lesions on the elbows and knees, and these have responded to a low carbohydrate diet.

PROFESSOR PILKINGTON. When I gave the clinical expressions I should perhaps have been clearer about this particular point. What I said was that crease xanthomas were absolutely typical of Type III. Does he have that?

DR FARRANT. No.

PROFESSOR PILKINGTON. Now Dr Fitzgerald talked about an interesting North of England classification. I rather like it but it's not going to catch on unless people are going to use it, and I'm afraid I think whatever happens you're not going to win this one because Fredrickson has sown the seeds too well. I think his will be the accepted classification for some time.

DR FITZGERALD. I don't know whether you would agree or not, but in some Type II patients where you aren't getting a response to clofibrate there is evidence that the addition of vitamin E will bring about a lowering of the serum cholesterol. If anybody has got a case and is interested in that sort of thing, that is one of a series of observations that might be interesting to look at.

DR JOUHAR. Professor Macdonald, could we revert to Fabry's work which you quoted? There are two questions I would like to put, please. Is there any well-documented work other than Fabry's to support the idea that one should take meals little and often? Secondly, if I interpreted it correctly, Fabry looked at live people with ischaemic heart disease; had he looked at people who had died from ischaemic heart disease, conceivably the incidence of frequent meal-taking would have been higher rather than lower. Would you have any observations on this?

PROFESSOR MACDONALD. I think you are quite right that the subjects were those who survived. Your first point—there is a lot of evidence in man and experimental animals that the metabolism is altered if the same food is taken at different frequencies. Fabry has also done some work on obesity in children in which two groups had the same dietary intake but ate it at different frequencies, and those who had only two meals a day grew much fatter than those who had five or six meals a day. So there are quite a lot of metabolic studies being done on this point.

CHAIRMAN. I would like to ask how many of the studies which we've seen in which we get blinded by triglycerides and cholesterol levels, in how many of these studies are these fasting cholesterols and fasting triglycerides? I think that some of the research that is done on random blood lipids must not be worth what they're written on.

PROFESSOR PILKINGTON. Well, yes, if you really want to be absolutely sure you should do a fasting triglyceride. You can get away with a non-fasting cholesterol, in fact it happens to be lower than a fasting one, by and large. Now glycerides, of course, since all the fat you eat comes in as chylomicrons, will of course, go up after meals. Does that answer your question?

CHAIRMAN. Not quite. I was merely thinking of the cases where people have done surveys of coronary and arterial disease and correlated them with cholesterol levels.

PROFESSOR PILKINGTON. Well, cholesterol won't be interfered with by meals. Not really. You could do that. Cholesterol studies are perfectly valid. That's why they've been done. You see in Framingham the great study that we all base our data on, all our data on cholesterol is in fact not fasting. The staggering thing is that cholesterol should be such a good prognosticator and in fact we know that cholesterol is still a reliable risk factor for coronary heart disease.

DR DOUBY. Are there anatomical differences between the coronary arterial tree in men and women which could account for the higher instance of coronary artery disease in men?

CHAIRMAN. I think Dr Harris might have some words on this.

DR HARRIS. Based on my coronary angiography experience there is no difference between male and female coronary anatomy. There is a lot of difference among the population, but there is no distinct difference between male and female.

CHAIRMAN. Coronaries, that is! So the theory that one might have sharper turns in the coronary arteries and therefore greater atheroma does not hold.

DR HARRIS. No.

CHAIRMAN. There is a great variation though in the tree in the population, from person to person?

DR HARRIS. This makes the interpretation of coronary angiograms very difficult, because where you have lost a branch you are not sure whether it was meant to be there, or whether it was there, or whether it was never there.

CHAIRMAN. Is there any particular pattern of tree that you think is more susceptible to arrhythmias than another from the coronary angiography point of view?

DR HARRIS. No—the majority of the population have a right dominant circulation, something like 20% have left dominant, and the remaining few have an equally shared, right and left, circuit. At one stage it was thought the shared were more vulnerable to complications of infarction, but in fact this is not true.

DR MATTHEWS. Can someone say anything about the role of free fatty acids in coronary artery disease?

PROFESSOR PILKINGTON. Free fatty acids, of course, have been, as you know, now invoked as one of the things that associate with a myocardial infarct after an attack. That's all I would like to say. I don't think anybody knows the importance of this finding or its association with arrhythmias.

PROFESSOR MACDONALD. Were you asking whether the free fatty acids were raised before the attack or after the attack?

DR FITZGERALD. Dr Kurian, with Oliver, in Edinburgh, is working on dogs in which he is able to do some elegant experiments and raise the free fatty acids by non-catecholamine means. He has been producing cardiac arrhythmias in dogs. This is again experimental, but supports perhaps their thesis that free fatty acid levels above 1200 mEq/l do have an important role in the genesis of arrhythmias. Perhaps I could clarify, for people who may not be quite clear what is meant by intrinsic activity. Beta-blocking drugs are classified into various groups. The first one which I mentioned, dichloroisoprenaline, not only antagonizes the effects of catecholamines but also possesses a stimulant effect. This is a little difficult to explain. I think that you may explain it is to say that there are two steps in drug-receptor interaction. First of all, there is the affinity between the antagonist and the receptor and secondly, once it combines with the receptor some biological event occurs. These are two separate events. A beta-blocker, such as propranolol, has a high affinity for the receptor but does not cause any stimulation. Compounds like dichloroisoprenaline, alprenolol, oxprenolol, or practolol, in addition to antagonizing the effects of catecholamines on the heart or elsewhere, also have some small stimulant effect themselves. Now in the ordinary person, even in the person who has a myocardial infarction, this stimulant property in the drug is not able to express itself. The only way that you can determine if a beta-blocker has got intrinsic activity is either by depleting the animal of catecholamine stores with reserpine, when you will then demonstrate a rise in heart rate, or in rats, treated with phenobarbitone which reduces autonomic activity. But in the ordinary person, if you give them any of these compounds with intrinsic activity, you will in fact block the action of catecholamine and you won't cause any stimulation itself. And I believe, of course, that the only clinically important difference between compounds with intrinsic activity and those without is that those without permit the vagus to have complete control of the heart. You see, people say propranolol slows the heart—I'm not sure that this is so. What I believe is that the vagus slows the heart. You saw from Professor Shillingford's lovely work on coronary infarction that some of these people have got very slow hearts which were reversed by atropine or by putting their feet up. Well do you get slowing of the heart with propranolol? My basic heart rate is 52. If I take 240 mg of propranolol, my heart rate goes down from 52 beats per minute to 44. If I then take 2·4 mg of atropine, my heart rate goes up to 88. Now I don't understand how people say that propranolol slows the heart.

COLONEL J. F. WEBB. Professor Pilkington, in speaking of fat absorption, stated it takes place by chylomicrons. Is this so, or are the chylomicrons broken up into fatty acids and reformed after absorption before being passed into the body by the lymphatic pathway, rather than by the portal vein? Baker in 1942 (*Quarterly Journal of Microscopical Science*, **84**, 73, cited by Frazer (1947) *British Medical Journal*, **2**, 641) described canals in the outer membrane of the small intestinal cell along which the chylomicrons could travel and be absorbed into the lymphatic pathways without being broken up.

PROFESSOR PILKINGTON. Except for the short chain fatty acids which will undoubtedly go up into the portal vein.

CHAIRMAN. I think this should be the end of this most interesting symposium, which has been most useful from the afternoon to the evening session, and it really only leaves me to thank all the speakers for their papers and for coming and presenting them; we would also like to thank Mrs Sedgwick the recordist, and the projectionists who have done their work very effectively. I would also like to thank ICI for sponsoring the meeting, and last but not least is Dr McLean Baird for having organized it—I think he has done a remarkable job, and we do thank him very much indeed.