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First Discussion

Chairman: Professor W. Melville Arnott

Abstract

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Dr. Walter Sommerville (Middlesex Hospital)

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Dr. W. A. Alexander: I do not think it inappropriate at this time to recall that I met Sir Thomas Lauder Brunton in London in the Spring of 1914 at a dinner of the London University of Edinburgh Club, in my capacity as a Senior President of the Royal Medical Society at that time. During the evening I had the pleasure of sitting beside him and my recollection of him, is of a man of small stature with grey-white hair and a trim beard, he was venerable in my eyes but actually he was only 70 years of age. I remember his keen interest in what was happening in Edinburgh, especially in the Royal Medical Society. The occasion and the man remain vivid in my memory.

Dr. Walter Sommerville (Middlesex Hospital): Dr. Russell Rees has presented in a very impressive and easy to understand fashion, what happens when a ligature is placed around the artery of a dog. He has also referred to what happens when a human individual has an occlusion in an artery. When he had operated on his animals, what became of them? Did they lie gently? Did they move around in cages? I ask this because in very carefully controlled observations on animals Epstein and his group found that if one applied ligature to a coronary artery and then divided the group of animals into two, one of them being kept at enforced rest and the other at enforced exercise, subsequently examination of the latter group showed a profuse collateral circulation in relation to the group that was kept at rest. The implication of this being that if a ligature is tied round a dog's coronary artery the animal should be allowed to run around in order to increase its collateral circulation. The counterpart of this has very often been cited in man and is one of the main supports of the doctrine that after he has had acute cardiac infarction he should get up out of bed and walk.

Dr. Rees: Our animals are neither forcibly exercised nor rested, they were allowed to walk around their cages as they wished. One third of them died but it was not possible to tell which ones were likely to die, though of course they did have the lower flow rates. I don't think the amount of exercise they took affected their outlook, though I quite agree that it is possible to protect animals by making them anaemic, by pre-exercising them, and by pre-treating them with vasodilator drugs. The basic collateral vasculature of man and the dog is similar from that in these animals, though of course the situation will be more complex from one to another.

Dr. Oliver (Edinburgh): I think that the most interesting aspect of the excellent communication was his account of the single dog who was found at thoracetomy to have an infarct. He showed that after he had ligated the coronary artery the collateral flow was appreciably higher in this dog than it had been in other dogs who did not have an infarct. My first question, therefore, is: Has he tried to produce the same situation by ligating coronary arteries in dogs previously made hypoxic or dogs in whom he thinks he may have in some way produced a rather better than normal collateral circulation, and if so, how did they respond? The second question is: To what extent did this dog, in fact have coronary artery disease and what was the nature of the disease? I think this is relevant in terms of the suggestion that glyceryl trinitrate and dipyndamate both had a dilating effect. It has been suggested that it would be inappropriate to use vasodilator drugs in such a situation, and what is more one would not expect to see much dilatation or improved flow if there were very advanced coronary disease. You did describe that there was coronary disease of some nature in the anterior descending artery. I would think that before we jump to the conclusion that these drugs can improve collateral flow in such a situation, we have to be careful, perhaps in relationship to Dr. Gorlin's lecture yesterday that we should know exactly to what extent there is disease of the coronary arteries. Therefore, my

third question is: If this dog had extensive coronary disease and therefore extrapolating to the human would he expect that there might be an improved collateral flow when such drugs are used?

Dr. Rees: We have carried out a similar experiment in this type of situation, we ligated arteries 3 months before performing flow measurements and then measured collateral flow within the territory that we had rendered ischaemic and we also produced fresh infarcts adjacent to it and measured collateral flow in those regions. In both types of experiments collateral flow was greater than in those dogs who had previously had normal hearts, and I am quite sure that previous coronary disease does produce an increase in the collateral vessel and does protect the animal against subsequent coronary arterial obstruction. I think there is some evidence in this which also applies to man. As to the use of vasodilator drugs, I believe it can be shown that even in severe coronary disease a vasodilatation will occur, and there is good evidence that these drugs might work, even in acute myocardial infarction.

Dr. Gorlin: From our experience with coronary arteriography study of metabolism of the heart in patients with coronary heart disease, we have been struck by two points and in seeking help, I might address these to both of the speakers. The first is that we have seen no necessary association between having a severe obstruction and the development of an appropriate collateral circulation, and I would like to ask Dr. Fulton why he thinks this patient can develop a profuse collateral response and another one does not. I would be specific and ask him if he finds any variation in the size of the normal collateral channels, that are potentially present in the absence of disease, that may influence what happens when a patient subsequently develops atherosclerosis. My second comment is, that we have never seen the collateral pathways completely compensate metabolically under conditions of stress. Almost invariably we have seen the production of lactic acid by the myocardium even in the presence of profuse collaterals supplying the post obstructive region and we would wonder whether the patency of collaterals in a sense depends on function of metabolic demands: in other words, the bombardment of this area by some form of by-product of ischaemia and this may be essential in keeping these areas open. Perhaps Dr. Rees might want to comment because of the variations he showed in the different responses in different dogs, whether the activity is different on given days or whether the by-products of the myocardium differed on different days.

Dr. Fulton: The first point about variations in collateral circulation in the normal: there is a certain variation but it is very hard to know what factors may be involved in this, I have noticed that in some instances there has been decreased collateral circulation in the presence of anaemia in the history, and this has previously been shown to be the case in experimental work as well as in observation. In regard to inadequacy of collateral circulation, it may well be that in some instances, this is based on an inherent tendency for collaterals to develop in one individual to a greater extent than another. I would make the point that in man, I think, that the rate of development of collaterals is very much slower than under the experimental conditions in the dog as Dr. Rees has so elegantly described. I think one would probably have to increase that period very considerably, I would also make the point in regard to the collaterals of dog and man, that in man it is deeper vessels rather than superficial and one does not see on the surface of the heart a development of collaterals such as he described within a short time of coronary occlusions, in fact, after years there may still be no comparable degree of superficial network although in all instances I did see deep network development of very considerable extent, I cannot answer why it should be in one instance the collaterals seem more adequate than another, I certainly would go along the whole way with your statement that you never found full compensation on the basis of my pathological studies because I do believe that the collateral circulation always follows the stimulus as I have said and I think that if it came to within an approach probably never exceeding or equalling the normal adequate circulation, this would make sense.

Dr. Rees: I would like to answer Dr. Gorlin's question about stressing these animals, I would agree that their response is inadequate, you can show after 3 months that the collateral supply at rest is the same as in the adjacent normal muscle. You cannot exercise these animals because they are anaesthetized if you give them dipyridanole you may get a three or four fold increase in the

normal adjacent muscle but only 50 to 100 per cent increase in the ischaemic tissue, so the capacity is certainly restricted.

Dr. P. Turner (St. Bartholomew's Hospital): We are very interested in the role of adrenergic blockade on cardivascular function and I would like to ask Dr. Russell Rees a question on his experiment with bretylium, there is I think a misapprehension to feel that pre-treatment with bretylium necessarily reduces the effects of the heart to sympathetic stimulation as far as circulating catecholamine are concerned it may increase the sensitivity of adrenergic receptors and I would like to ask him whether he feels that perhaps under the circumstances of his experiments with his animals there may be an increased circulating level of catecholamine and that it might be better to look at the effects of alpha and beta adrenergic receptor blockade rather than simple bretylium pre-treatment and if so whether he has done these experiments.

Dr. Rees: I was under the impression that bretylium and bethanidine would deplete an animal if given in sufficient dosage, but I don't know about that. We also performed a sympathectomy, and infiltrated with protein and I agree there may still be circulating adrenaline in those situations. As regards beta blockade, we have not done any intensive studies along the lines of procaine blocks but looking at one or two animals from day to day, up to 10 days there is a reduction of myocardial blood flow of a minor degree.

Chairman: Does reactive hyperaemia such as occurs in skeletal muscle occur in myocardium, with its blood supply reduced or occluded for a time insufficient to cause necrosis?

Dr. Rees: We have seen this on some occasions when the myocardium has been unexpectedly and dangerously atoxic for a while, but it does not seem to be a very common occurrence and we have not studied it specifically.

Dr. Friesinger (Johns Hopkins Hospital): It is now relatively easy to put a flow probe electromagnetic tie around dog's circumflex artery beyond which you can put a snare which will stop flow completely and the dog is very sensitive insofar as the reactive hyperaemia is concerned. Occluding for a short time for one or two systoles, will show a reactive hyperaemia and with occlusions say for up to 30 seconds, since these unconscious dogs are not responding insofar as any reaction of pain or any systemic haemodynamic change is concerned, very dramatic reactive hyperaemia occurs, overshoots three or four times, the resting flow, which persists for several minutes, are common.