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Second Discussion

Chairman: Professor W. Melville Arnott

Abstract

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SECOND DISCUSSION

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Dr. Adams: I would like to ask Dr. Gorlin whether the formation of polypeptides in the area of ischaemia has actually been demonstrated. He spoke of kallikrein, but is this based on actual demonstration? One would expect some of these substances to form in an area of injury where intracellular lysozymes liberate their hydrolytic enzymes.

Dr. Gorlin: This particular demonstration has not been made in cardiac muscle, which is known to contain kallikrein, and it is also known that kallikreins are good coronary vasodilators. The particular observations have been demonstrated a number of times in peripheral skeletal muscle and the inference has been made that maybe a similar mechanism applies within the tissues of the heart.

Dr. Adams: It might be possible to arrange experiments where one can demonstrate these things. If one can take blood from the coronary sinus in an experimental animal it should be possible to pass this blood over certain pharmacological test objects, such as a guinea pig's ileum, or a rat's uterus. Dr. Bain of the Royal College of Surgeons in London has described a number of elegant techniques by which it is possible to follow the formation or release of these substances in peripheral blood in a similar manner and to make comparisons with standard to obtain some idea of the concentration which might be present.

Dr. Sommerville: Dr. Muller, in your two groups, one was with A.P. minus, meaning angina pectoris, and the other had infarcts, do you mean that they were subject to angina or that the observations were made on people during an anginal attack? I appreciate that towards the end you showed some graphs in which pressures were actually taken in the course of an anginal attack, but earlier, you quoted mean values of cardiac out-put, stroke out-put and mean PCVP (pulmonary capillary venous pressure). Later on you come to the infarcts and these patients showed much higher pressures. It was here that I found some difficulty, because your next slide demonstrated pulmonary capillary venous pressure related to heart size and as far as I could see the people with angina pectoris had smaller hearts and those with infarcts were all on the right side but in your conclusion you stated that people with cardiac infarctions had a higher pulmonary capillary venous pressure and a larger heart. Does the presence of an infarct make the heart big? Experience suggests that this is not so unless the infarct is of a very large size in which case there may be considerable replacement of cardiac muscle by fibrous and other tissues allowing the contraction of the heart to alter its behaviour and allowing the diastolic volume and pressure to increase; the result then is a large heart. Is what you are describing not so much a factor of cardiac infarction but of cardiac failure regardless of the cause?

Dr. Muller: The group called A.P. comprises patients with a typical angina pain with ECG changes on exercise, no history and no signs of previous infarction; no reference is made to anginal pain during the test except for the last slide which shows certain A.P. plus and A.P. minus lines. Of the patients with previous myocardial infarction one-fifth had heart sizes larger than 500 mm. per square metre; the rest had heart sizes within what is regarded as fairly normal limits. In my studies, I plotted the pulmonary capillary venous pressures against heart size to try and see the effects of heart size and ascertain whether the patients with previous myocardial infarction and small hearts behaved as patients without recognizable previous myocardial infarction. They did, in that they had fairly normal pulmonary capillary venous pressure but both groups rose on exercise.

Dr. Friesinger: Over the last 5 or 6 years in the course of catheterizing a number of patients with

the intention of visualizing the coronary arteries, opportunities were provided to measure left ventricular pressures. About two hundred patients who had angina pectoris or previous myocardial infarction were catheterized and some observations concerning this group are pertinent; particularly the 15 patients who showed good left ventricular systolic and diastolic pressure measurements early in the study before contrasting with other material or other manoeuvres were carried out. During the study they developed angina pectoris in these 15 patients, all of whom had a normal resting left ventricular, end-diastolic pressure was invariably elevated to a considerable degree; that is to say, more than 20 mm. Hg during the anginal episode, and this was irrespective of what the left ventricular systolic pressure was. In a number of these the left ventricular systolic pressure was considerably elevated, in excess of 180 mm. Hg, having been approximately 120 mm. Hg during the control measurements. However, in the majority of cases the systolic pressure was not appreciably elevated and there was little change in the heart rate in any of the 15 patients who were studied. These facts would fit in well with the suggestions that the left ventricular end-diastolic pressure increases where anginal pain is present. Of the remainder in this group the left ventricular end-diastolic pressure sometimes became elevated and remained elevated even in the absence of pain. In the cases where left ventricular end-diastolic and systolic pressures were elevated these may be the individuals in whom the spastic phenomenon to which Dr. Gorlin referred is primarily accounting for their anginal distress and hence resulting in such large systolic blood pressure elevations.

Sir John McMichael: May I add that many of these patients suffering from angina are also breathless and one or other symptom may predominate in their minds. They complain of pain or they complain of breathlessness or a feeling of tightness in the chest. It is often rather difficult for them to decide whether they are feeling tightness or compression or actual difficulty in breathing. Many years ago I was intrigued by Dr. Muller's observations that during these attacks of pain these patients seemed to have other manifestations of left ventricular failure, and we all know that they often develop exaggerated gallop rhythm during the actual attack.

Dr. Gorlin: I think the substrate underlying pain and conjunctive cardiac failure is myocardial ischaemia; the amount of myocardium which is afflicted by ischaemia will probably govern whether or not evidence of congestive failure occurs with a rise in left ventricular end-diastolic pressure. In our experience, as yet incompletely collated, those patients who did develop a rise in pressure, such as described by Drs. Muller and Friesinger were people who showed a remarkable output of lactic acid from the myocardium and who usually showed two or three vessel coronary involvement. Ischaemia was indeed diffuse and severe, therefore it would be no surprise if such a heart would go into failure with lack of oxygen and set off a pain mechanism. A corollary to this is the patient with aortic stenosis who, when asked to carry out the sort of work previously described, will also go into cardiac failure and his heart will show a restriction in coronary flow and an output of lactic acid from the coronary sinus. On the other hand, about twenty per cent of all our patients with angina pectoris have single vessel coronary involvement and therefore a small zone of myocardial ischaemia at only one site in the coronary vein and which is sometimes barely detectable by a lactic acid production. Such patients have had attacks of angina and such patients have not had a rise in end-diastolic pressure whilst in our hands. The final point that I would make concerns whether or not the blood pressure rises. We have seen one individual have two completely different levels of left ventricular end-diastolic pressure during two similar attacks of anginal pain; when the blood pressure was elevated the end-diastolic pressure was elevated, when the blood pressure was not elevated the end-diastolic pressure was not elevated. Thus I think we have a mixture of the diffuseness of the affliction of the myocardium; the fact that we have two unrelated but dependent symptoms or signs and then we have the final factor, that is the impedence against which the heart must contract which can of course aggravate any haemodynamic balance which may occur in this situation.

Mr Hunter: Has anyone investigated changes in the biochemistry of the cardiac muscle cells and the action of nitroglycerine?

Dr. Gorlin: In recent years I have seen only one report on work on the myocardium per se and this showed that there was uncoupling of oxidative phosphorylation in the liver and in the

myocardium. One of the problems as I understand it is the difficulty of working with a substance such as nitroglycerine which is insoluble in water in order to define its effect.

Dr. Julian: Could I ask something about the anomalies of propranalol when given to these patients who are on the edge of cardiac failure; is the drug likely to precipitate them into cardiac failure?

Dr. Gorlin: We have been very pleasantly surprised to see how infrequently clinical cardiac failure emerged with the use of propranalol. We would avoid using any adrenergic blocking agent in a patient who had massive cardiomegaly but fortunately this is rare in the patient with coronary heart disease. I don't know how it fits in with our previous conversation about the frequency of cardiac failure apparently occurring with angina attacks; maybe it's effect is to abate the hypertensive response, maybe its effect is to abate the venous return to the heart through its venodilating action which may counteract its negative actions, it is also true that this is a dose response related effect. It is well known that one may give propranalol intravenously in a dose that will actually reduce cardiac size, cardiac filling pressure, leave the cardiac output no more than 5 to 10 per cent reduced and the lower blood pressure no more than 5 per cent and will still produce effective blockade of all adrenergic stimulation of doses. Give just a little bit more than an average dose say, more than a 10th of a mg. per kg., the cardiac size, increases end-diastolic pressure goes up and of course it is a two-edged sword, but if one pays attention to dosage and if one observes the patient closely, checks his weight gain, vital capacity and so-forth, one is able to determine the right dose for a given patient.

Medical Student (Edinburgh): Are the nerve endings, which are supposed to be involved in this process of anginal pain, randomly distributed through cardiac muscle? Is there any relationship between cardiac ischaemia and the degree of anginal pain?

Dr. Fulton: I cannot give a definite numerical picture, but I can say that in the one patient an anterior infarct may be associated with intense pain, and in another with no pain at all, and this will apply equally to posterior infarcts.

Roger Smith (Edinburgh): Would Dr. Gorlin comment on a possible role of coronary vasoconstriction per se in angina?

Dr. Gorlin: To clarify my views a little bit, what I developed yesterday in part was that in the presence of organic coronary atherosclerosis there are certain pain symptoms, particularly provocative symptoms, which are associated with progressive diffuse disease, namely the triad of nocturnal, prandial and unprovoked angina. If these occur together there is a high likelihood that the entire coronary muscular tree is involved as opposed to one coronary vessel. On the other hand, in our experience and other groups who have been doing coronary arteriography for diagnostic purposes, that there is a small group of people who have severe, frequently unremitting symptoms which by all the usual criteria, are indistinguishable from classical angina pectoris, yet coronary arteriography will reveal no lesion or suggestions of a lesion. One believes that there is another category of patients who have the anginal demonstrable form of cardiac disease, I use that word advisedly because there is no way of knowing whether these people with cardiomyopathy, whether they have some small vessel disease or whether there is something wrong with the vasomotor system of the coronary bed and whether, for example, this is Raynaud's disease of the coronary tree. We have one such patient whom we suspect might well have the Raynaud's phenomena, and she has Raynaud's in her fingers, she has attacks of pain and she has a morphologically normal coronary vascular tree. I think it is important for us to realise that all that is angina may not be atherosclerosis.

Dr. Matthews (Edinburgh): Once again Dr. Gorlin has referred to pain: what weight does he place upon the incidence of pain occurring during meals. I believe that this is an unusual variance of coronary disease in Britain, this might depend I suppose on who you were having a meal with, and it might depend on the food, does Dr. Gorlin share my view?

Dr. Gorlin: We have found that pain does not increase after a meal. There are many people who, when asked to carry out a form of exercise after a meal have great difficulty in doing it, without having pain, though it is an obvious fact that when the meal was a longer meal or a heavy meal, so that after a long heavy meal where more effort is involved the patient may suffer pain, although a light meal might not affect him.

When we studied such things as the gastro-intestinal tract (with barium) we were surprised to find that the incidence of oesophagitis and the incidence of gall stones was not greater in these people who had this particular complaint than in any of the other groups.

Student – Medical School: Is it true that some people who have carried on walking when the pain comes on find relief with the continuing exercise?

Dr. Gorlin: I see many patients who are so well instructed by their physicians to stop when they develop pain, that they will not walk through their discomfort and for this reason my own personal experience with this has been very small. I have seen the usual individual who describes the pain which he felt at the first hole in the golf course, and after resting awhile he finishes his game without feeling further pain.

Dr. Friesinger: We have had the opportunity on several occasions in the course of doing exercise electrocardiography on a relatively large number of patients and often found that an individual who while walking at a constant rate informed the physician observer that he was experiencing discomfort at a time when an ischaemic change was seen on his electrocardiogram but states that this is the sort of thing that he had often walked through; the exercises would proceed and his pain would disappear and the electrocardiogram would lose its ischaemic shift. This has been unusual in our experience but in the several observations we have noted that when the pain has disappeared the heart rate was less than that when the pain was present. On several instances where a reduction in blood pressure was obtained the blood pressure was a little bit lower as the exercise proceeds and as the pain disappeared. This has been seen in published reports showing electrocardiographic tracings and blood pressure recordings in which the authors also indicated that heart rates were slower and blood pressure lower after pain and ischaemic change subsides. It seems to me possible that in addition to opening up collaterals these patients are rather good at warming up, and after they warm up they do have more peripheral vasodilation, their blood pressure is lower and their heart rate is slower, hence although the foot pounds of energy which the man is expending be the same, his heart work has been reduced and this is the mechanism by which he is relieved of his pain.

Dr. Simpson (Glasgow): Our coronary patients are encouraged to play golf and I have one or two patients who can walk through their angina very easily without stopping over the first two holes, but they will not venture out on a cold day because they cannot walk through the angina on a cold day.