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Discussion

PROFESSOR L. REID: Can I ask Dr Kamburoff a question—would she go on and speculate a little more for us about what is happening on the muscle cell? Do you think all your various receptors are the same ones that have been responding to different stimuli, or do you think that you have got your vagal and sympathetic group acting one group on your muscle cell, perhaps on a ganglion cell that is away from the muscle?

DR P. L. KAMBUROFF: I am not really very qualified to answer this question, but when we went to Aspen there seemed to be this new belief that there is a receptor for everything—a separate receptor.

Dr F. J. PRIME: I had a long talk about this with a very notable pharmacologist, who first of all maintained that there were selective receptors for a lot of substances that one mentions, such as histamine, bradykinins and all these kinds of thing. But I had a recent note from him in which he gave me a most elaborate diagram, whereby most of it could be explained by interference with the metabolism of ATP, 3′,5′-AMP and all these things; interference in that cycle at various points will account for the whole thing, so it would seem as if you might have just one receptor at the end, which responds to changes in concentration of 3′,5′-AMP, the concentration of which can be altered by a host of other things from histamine to 5-HT and all the rest of it. In point of fact nobody really knows this, it is highly suppositional.

DR R. E. C. ALTOUNYAN: Could I ask you, Dr Kamburoff, I wasn't very clear about your indoramin story, nor in fact about your thymoxamine story. To start with the indoramin, it did appear to be a bronchodilator in its own right, the conductance measurements you gave seemed to show this. Now, therefore, how can you say that it was a specific antagonist if you like, or that it worked by blocking the α-receptor and, therefore, the histamine was blocked because the α-receptor was blocked?

DR KAMBUROFF: I did not say that; what I said was that our experiment, the way we set it up, we wanted to see the action of the most specific α-blocker available, which at the time was thymoxamine; we had to β-block because phenylephrine has a β-stimulant activity, and an α-stimulant activity. So we β-blocked to cut the β-stimulant activity of phenylephrine, and then after we β-blockaded first, we saw a further bronchial constriction on phenylephrine. So that must be an α activity.

DR ALTOUNYAN: Yes, I'm not disputing that . . .

DR KAMBUROFF: Then we gave thymoxamine, and the bronchial constriction disappeared. We blocked it.

DR ALTOUNYAN: I was talking about indoramin, where the actual drug itself appeared to cause the equivalent of a bronchodilatation; and I am specifically referring to the article in the B.M.J. in which you showed its effect against exercise asthma, for example, and also here against histamine: that there was an intrinsic bronchodilator effect of the α-blocking drug which could in a non-specific way be explained, its prevention of the histamine spasm or the exercise spasm, rather than a specific action by virtue of its α-blocking effect. In other words, you have got two effects, one is bronchodilator, one is α-blocker; you are not proving that α-blockers had in fact prevented histamine contraction—this is my contention.

DR PRIME: This is a perfectly valid objection to the experiment which we did on those people with exercise-induced asthma as far as it goes, but please note most carefully that neither thymoxamine nor indoramin have any specific action on denervated smooth muscle. That is a very important point in itself. Secondly, the bronchodilator effect which we did see with both these drugs is not at all comparable in magnitude with the effect we produced by exercise. I don't think that this is an adequate explanation for the changes we saw, but admittedly it is a criticism of them.

DR J. PEAK (Leicester): I am interested in the qualitative change in sputum chemistry in chronic bronchitis. Is there actually any qualitative change in the sputum, or is it just a natural increase in the quantity?

PROFESSOR REID: Inherent in your remark is [the assumption] that we would have a base line of control sputum to compare it with. I think one has got to say that in the chemical studies we have done, we have felt that normal or control sputum is a contradiction in terms, so that even if you collected it from a tracheostomy tube, it could not be regarded as normal. So we have really been more concerned to compare different diseases; and what I can say to you is that, to take the group of chronic mucoid bronchitics, we get a wide range of neurominic acid levels, of macromolecular dry weight, etc. On the other hand, if we compare it with the sputum from patients with asthma either in an attack, or the ones who may be also bronchitic, we find that on the whole the asthma group has a wider range; they tend to have some samples that will be more viscous than what we see from the bronchitics. But one of the answers I think we can give you now, we couldn't have before, and it ties up with your work with the prostaglandin $F_2\alpha$: we've recently done some experiments on ourselves for the first time ever in a path. lab. (it's common for you to do it in physiology, but we don't usually do this in morbid anatomy); seven of us took $F_2\alpha$, about seven puffs, and we must have got the sort of change in conductance that you saw, in fact we felt tight, and one person who was mildly asthmatic, wheezed. The interesting thing was that we knew that this produced secretion. Now we felt slightly poorly for about a quarter of an hour; we were able to collect from six of us, about one ml of secretion. This enabled us to do viscosity, dry weight, sialic acid, fucose and mannose tests, and the interesting thing is that fucose, for example, is only present in the mucus; mannose is not present in the acid glycoprotein of the airways, so if there was any mannose it had come from the serum. The interesting thing was that all the secretions we had were, in terms of viscosity, in terms of macromolecular dry weight and sialic acid, in the low range that we got from bronchitics. There were two of the seven who had some mannose; the others didn't. And when we said, 'why didn't you?' it turned out that they

were the two who were both recovering from colds. What I would say to you is, we can't say it was normal sputum, but one could at least say it is secretion from a stimulated normal bronchial tree, and I think that is about as close as we will get to a control. The other way to answer your question is, if you go into the histochemistry of the glands and the goblet cells, that has a very definite place in a multidisciplinary study of mucus, because you can look at the secretion within the cell—you show that there is a wide range of cell types: you have got several types of sialic acid, several types of sulphate, and in the mucous cells of the glands, some cells have only sialic acid, some have sulphate, and you can therefore sort out the population of cells according to the distribution of acid glycoprotein. In no disease, including cystic fibrosis, or mucoviscidosis as it used to be called, in no disease is there any abnormal type of acid glycoprotein we have identified. What does happen is, you get a shift in the proportion of cells making heavily sialated acid glycoprotein, making it in its resistant form, and making it with sulphate added. So that you don't get an abnormal type of acid glycoprotein but you do probably change the total output of the factory, as it were, by changing the proportion of the different production lines. Sorry, it's a bit of a mix but I did want to get in the prostaglandins.

CHAIRMAN: Is sputum the same thing as bronchial secretion?

PROFESSOR REID: Well, you have got to accept that it does contain saliva; but in the studies we have done both of viscosity and chemistry where we have compared bronchial aspirate with sputum as produced, the results are very similar. What I think our defence or our safeguard is, is that saliva is very dilute—it does have acid glycoproteins, it does have serum, you know the liquid tissue transudate, but the macromolecular dry weight yield is extremely low; and therefore we are really not getting much trouble from that. The other thing seems to be that your ordinary bronchitic, a patient who is a regular sputum producer, seems really to add very little saliva in the process of getting the material out. Early on, we tried to do amylase studies, thinking that if we had an amylase level of the sputum, it would indicate how much saliva had been added. But one of the most extraordinary bits of work I have ever done, and it turned out when I told Sir Roy Campbell of this, this is a long time ago, he said Oh yes, he had had the same experience doing this with the first bit of research he had ever done, but he had never actually published it because he was so ashamed of his results—they were all over the place! But it is extraordinary how inconsistent the given individual is in the amylase content of those salivas. We tried it before breakfast, after breakfast, after a cigarette, when we had had something to drink, and it is just all over the place: so that it is no help at all. But one does know that saliva is very powerful, it is the cause of breakdown, even more usually than the bacteria of pus, and you saw that in mucoid sputum, we could leave it on the bench for 4 hr with hardly any change, but if you spat a small amount of saliva into that it would have liquefied within about 20 min. So I think all of those bits of evidence just mean that the presence of saliva, although we accept there must be some there, isn't effectively much of a disadvantage for the sort of studies we have been doing.