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Panel discussion

DR F. J. PRIME: I have no doubt whatsoever about the value of intal, in seasonal asthmatics. Now, I am seriously in doubt about its value in people with what we call, for want of a better term, intrinsic asthma. And you seem to take issue with this, Dr Altounyan.

DR R. E. C. ALTOUNYAN: Yes. I am not suggesting that all patients with intrinsic asthma respond to intal, just as I don't agree that all extrinsic patients respond to intal. All I am saying is, that you implied in your talk, I thought, that she's got perennial symptoms, therefore it won't work; she's only a seasonal—now that again, you know there are lots of people who have perennial extrinsic symptoms because they are sensitive to house dust; but whereas that patient you said is a seasonal and, therefore, because of that, that's the only reason why you might expect her to respond to intal.

DR PRIME: Yes, certainly. If you got that message, perhaps you got a message that I didn't intend you to get, and I'm sorry for that. Nevertheless, she is very wedded to these two capsules of intal which she takes all the time, and in fact, I am not at all convinced that this is keeping her fit. However, on the other hand, one of the other patients whom I showed got a remarkable improvement in her response to a sympathomimetic drug on a couple of occasions, on which she took intal just for the hell of it because she had them around. This was the accountant lady who was very slap-dash and happy-go-lucky in the way she treated herself. I don't know what this means, if only one knew what the real pharmacology of this drug was, it would be very helpful.

DR ALTOUNYAN: Just like steroids will improve over a few days the patient's responsiveness to the β-stimulants, and to ephedrine, so does intal, in a similar way, improve the responsiveness of the right kind of patient. If the patient clinically responds, he will show this increase in response. I don't know why.

DR PRIME: Yes, I think that there are factors outside the bronchial muscle and the vasculature thereof that are concerned in this, and I have been much struck, thinking about it a good deal in the last few months, with these findings of Professor Reid and so on, about the prolonged effects of administration on bronchial secretion. Because I am quite sure that one of the reasons why you don't get any response to these powerful drugs is the fact that you have mucous impaction of one sort or another. I am sure every physician would agree with this.

DR J. MORRISON SMITH (Birmingham): Could I ask Dr Prime why the α-blocker, which seemed to be of value, was stopped—was it stopped because you ran out of tablets, or was it because it had unpleasant effects, or for some other reason?

DR PRIME: No, in the last patient whom I showed, it has not been stopped; she is still on them. I am not sure about the one before that, whether she is still having them or not. You can't buy them without a special prescription.

DR MORRISON SMITH: But there was no other specific reason?

DR PRIME: No, indeed. It is undergoing trials as an anti-hypertensive drug as well, you know, and in a way it's a sort of drug looking for a use. It's very remarkable and I think it has a place all right, somewhere along the line—perhaps not that particular one; and certainly not thymoxamine, which has a very evansecent, brief action. The main difficulty with them is the antihistaminic manifestations.

DR J. D. EDDY: Might I ask Dr Prime, is there any information as to what happens to the pulmonary artery pressure with α-blockade?

DR PRIME: No; we are looking for that now, and I can't tell you. Would you anticipate that it would have any effect?

DR EDDY: I'm just interested whether it would, because I could think that it might have other uses if it was reducing pulmonary hypertension.

DR W. G. B. CLARK (Loughborough): I would like to ask Professor Hertz, when giving orciprenaline to your patients in acute left ventricular failure with obstructive bronchial symptoms, did you have any problems at all with arrhythmias, or rapid heart rate?

PROFESSOR C. W. HERTZ: No.

DR CLARK: What dosage did you use?

PROFESSOR HERTZ: Well, these are the experiments of Hammond *et al.* I didn't do them; they commented on this problem, and they had no troubles, but I can't say now by heart, what dosage was used.

DR M. D. PEAKE (Leicester): I would like to ask Professor Hertz about some recent work done on what we hear in pulmonary oedema in the chest crepitations, whether we in fact are hearing fluid or, I believe there has been some work suggesting that it's a sudden popping open of the respiratory bronchiole due to an increased venous pressure. How are the crepitations caused?

PROFESSOR L. REID: Fluid, or popping open of airways?

PROFESSOR HERTZ: I think it is fluid.

CHAIRMAN: Dr Forgacs in London has produced evidence that it is the popping open of small airways.

DR PRIME: I would think that, first of all, it was fluid you were hearing.

PROFESSOR HERTZ: They have produced a great deal of foaming fluid when they cough in pulmonary oedema.

DR PRIME: Can you hear bubbles, then?

PROFESSOR HERTZ: I can hear bubbles, yes.

DR PRIME: I see. Now, the other, the next sort of hypothesis that came along was that it was alveoli popping open, but clearly it cannot be such small structures as alveoli, it has to be something that will open with sufficient power to make the noise. I think that if it was . . .

DR PEAKE: It's productive, isn't it?

DR PRIME: Oh, highly productive; but in the non-productive stage where you merely have pulmonary congestion, this is where you have the sign most well developed, isn't it?

PROFESSOR HERTZ: In mitral stenosis and pulmonary congestion, we have sputum and even haemosiderin or haemoglobin?

DR PRIME: Oh, yes. And I dare say air does bubble through those; but I do ask myself, Professor Hertz,

where does the air come from if it is bubbling through this fluid?

PROFESSOR HERTZ: Well, that's right. Of course this is not to say that all the passages at the same time will be filled . . . I think it's a distribution matter, isn't it? Otherwise they would be dead in a moment.

DR T. B. STRETTON: I would just like to comment that whereas Dr Forgacs has made this point that the crackling noises (crepitations) are due to small airways popping open, in pulmonary oedema and in some bronchial diseases, you hear crepitations in expiration; and that I would find very difficult to understand on his mechanism. Typically, inspiratory crepitations are at their best, I would say, in diffuse interstitial pulmonary fibrosis, where you have got extremely stiff lungs, and you hear these crackles undergo a crescendo right to the limit where they can't inspire any further. And sometimes one hears a similar situation in pulmonary oedema. But commonly, in pulmonary oedema, you hear them in expiration as well. That I would find difficult to explain on the other mechanism; and so one wonders whether there are two mechanisms.

DR D. S. ARCHER (Stockport): There has also been some work done at the London Chest Hospital on this; if you look at the timing of these crackles, in pulmonary fibrosis they classically occur very late, they are late inspiratory crackles. And they occur at the same stage of every cycle of inspiration. But in pulmonary oedema and bronchitis and so on, they occur at the beginning, they are early inspiratory crackles.

PROFESSOR REID: Can you tell us how you interpret this?

DR PRIME: I think that what this really would suggest, is that the opening snap, if it is in fact an opening snap, so to speak, that is occurring, is occurring in the patients with pulmonary fibrosis. Well, I would agree with you. It's a rather continuous thing, isn't it, and one imagines that the thing has just been torn apart. But the opening pressure of a closed bronchiole is likely to be extremely high, I think, don't you? Nobody has measured it so far as I know, but you do hear these noises all the time while pleural pressure is very low.

PROFESSOR REID: I'm still not getting a clear picture. Please make him say, at the London Chest, how does the difference between the fibrosis and the bronchitis (one would have thought they were the same) . . .

DR PRIME: No. Capel made the remark that you didn't hear them very often at the beginning of inspiration; and presumably they didn't start to open until towards the end of inspiration.

PROFESSOR REID: So that's with fibrosis; but with bronchitis it is earlier, at least I thought that was what Capel had said. Was it still thought to be airways in bronchitis, or different sized airways?

DR PRIME: Well, I've only discussed this in conversation with Capel and I think he thinks it is airways; but it might be just strong suggestion.

DR STRETTON: May I ask Dr Altounyan whether he has any other observations on the possibility that atropine blocks vagal reflexes or vagal impulses coming from the cerebrum? Has he studied this in any other patients—any patients other than himself? Because one is immediately reminded of the rare individual who responds by blocking exercise induced asthma when inhaling atropine; I have certainly tried to block neurogenic impulses by giving ganglion-blocking drugs in asthma, but it has a catastrophic effect, in my experience! But one might imagine, if there were psychogenic influences, that a ganglion-blocker would cut them off totally. There was no evidence of psychogenic impulses in these patients, but there were certainly devastating side effects—acute shock-like syndromes, and so forth.

DR ALTOUNYAN: No, I haven't deliberately set out to study this, but of course there are quite a number of instances in the literature in which atropine blocked and, therefore, they were regarded as having been psychogenic in origin, because atropine blocked and there was no other reason; people such as those two cases in whom exercise asthma was blocked. Presumably this could be psychogenic in origin. I know Godfrey, at Brompton at the time, at my suggestion was trying to induce asthma by shaking people; and he took some people up to Farnborough to shake them on an aeroplane. And one of them was completely blocked by, I think it was atropine; and he regarded this as proving that it was psychogenic. I personally, though, cannot add any more to the subject.

CHAIRMAN: It must be fear, though, Dr Altounyan.

DR ALTOUNYAN: Yes, well, fair enough—fear causing a block . . .

CHAIRMAN: Not shaking, but fear!

DR ALTOUNYAN: Yes, exactly; it was fear that caused the spasm that caused the asthma, which was blocked by atropine.

PROFESSOR REID: I wonder if I can make a brief comment on asthma and secretion because I think Dr Altounyan said something about it might even increase viscosity. One of the interesting results we found on these sort of viscosity studies on a series of patients who were given a dose of atropine (they were all mucus secretors and mucoid sputum secretors, some asthmatic, some bronchitic) was that in fact there was no increase in viscosity of secretions, and no change in the 24-hr production of sputum. Several of them complained that they were finding it difficult to get their phlegm up, but on more careful questioning it was clear that this was clearing the mouth, getting it from the pharynx or the throat, rather than from the airways; so that it doesn't seem that one is in danger of producing more viscid secretions within the airway.

DR ALTOUNYAN: And also the other important point is its effect on ciliary action, the fact that presumably they brought up the same volume, whatever that means.

PROFESSOR REID: I said in 24 hr, because in some of the ones with small volume, we had in fact a slight difference in the hour or two afterwards, but I don't think this is statistically significant.

DR EDDY: Could I ask Dr Altounyan if he has ever seen asthma worsened by atropine?

DR ALTOUNYAN: Oh yes, as I implied here, people who are in a very poor state of asthma, really going into status, atropine can really push them right into status.

DR EDDY: Why I was saying this was, because the dosage you are using is quite low and, pharmacologically, atropine in very low doses does have a vagal effect.

DR ALTOUNYAN: Oh, no, this is higher than the vagal stimulator effect . . .

DR EDDY: We have seen repeatedly, using atropine to accelerate heart rates after acute myocardial infarction, that if we give 0·6 of a mg we may get increased slowing. If we give 1·2, it breaks through and then it accelerates. This is why I was wondering if it was dose-related.

DR ALTOUNYAN: Well, I don't think that could be an explanation, because this deterioration is never immediate; you get a small kick of improvement and then a progressive deterioration, and we have really been in real trouble, on occasion. This is why, of course, the concept of using atropine in asthma is such a tricky one; because I think that unless people can be aware of this fact, that you shouldn't take it when you are getting into the worse phase, but only when you are on the up-and-up phase, whereas a bronchitic can take it all the time—this is the difficulty, you see, clinically it is a problem.

CHAIRMAN: There is in fact a paradoxical effect of atropine. At a meeting in Ireland a few months ago, a speaker there said that if you put a drop of atropine on your tongue, contrary to what you might expect, in a high percentage of people there would be intense salivation. And I must say I didn't believe this until I came back to this hospital and tried it on myself, and it certainly does work. If you take one drop of atropine and put it on your tongue, there is an intense salivation.

DR ALTOUNYAN: That had to do with SCH 1000, was it? or was it atropine?

CHAIRMAN: Atropine; the same thing.

N.B. Dr Altounyan's paper on the effect of anticholinergic drugs on bronchial obstruction has not been published, at his request. Dr Altounyan's participation in the subsequent discussion has been included, where relevant.