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**Sir David Jack CBE FRS FRSE in interview with Dr Max Blythe**
**Oxford, 24 March 1997**
**Interview II**

MB David, in our first interview we got to 1961 and your move to work with Allen and Hanburys. Before we actually take that story sequentially, it would be nice to know where your family story had got to.

DJ Well, by then Lydia and I had two daughters who were born during the 1950s. I can't do the arithmetic but Moira is now forty and Norma is about thirty-eight.

MB So, you were a dad. Did that bring considerable changes to your life?

DJ Well, it changes one's way of living obviously, but only for the good.

MB You enjoyed playing with children and having time out?

DJ Oh yes, although in truth I used to leave early in the morning and get home fairly late at night sometimes, so they would not know me as children anything like as well as they knew Lydia. But weekends we spent together and holidays we obviously spent together and, as far as I know, we were a pretty contented normal family.

MB You told me that you tried to get into the learning process with them?

DJ What I am going to tell you is true and it taught me a great lesson so far as my own work was concerned. We were living by then in Harpenden and Moira had a cloth book with pictures of animals on it and she got jolly good, she knew all these animals because we lived fairly near Whipsnade and she'd seen them all. Lions and tigers were no bother, monkeys, even giraffes and maybe even a hippopotamus, no bother, but in the book there was a little spotted woodpecker and every time we got to it Moira was stuck mainly because they're not so common in Hertfordshire where we lived, at least certainly not around our house, and there were none in the zoo. So, every time we came to this, Moira was stuck and I said to myself, 'I will teach this child the value of orderly thinking from this early age.' 'Are you listening Moira?' 'Yes.' 'Moira, if you had a bird that pecked holes in wood, what would you call it?' And she thought quite a long time and then she said, 'I think I'd call it Peter.' Now, she taught me a great lesson because she answered exactly the question I put to her, because if you don't ask the right question you're unlikely to get the right answer. And secondly, and even more important, she showed me that when there is an obvious answer to a question or a problem which everybody knows to be right, if you can look at that and see something different, which is real and true, almost certainly you're on to something important. And it took my child to teach me that. I'm not sure I learned quite, but the lesson was there for anybody who was prepared to learn it. It impressed me. I've never been quite the same about Moira since by the way!

MB Working as a research and development director, there were quite tough lessons to learn. You had to go a long way in a short time to justify that appointment. Can you take me through the foothills of those years at Allen and Hanburys because I think you didn't find all that seaworthy a ship when you got there?

DJ Well, that's true. But I should tell you that I went to Allen and Hanburys as a research director after having agreed conditions with Mr Maplethorpe, of whom I've talked already, and Sir Harry Jephcott, who was chairman of Glaxo, because I was leaving a secure better-paid job in Smith Kline to come to Allen and Hanburys for the opportunity of attempting to run a research show. So, the conditions were these very simply. Firstly, the one hundred and twenty-two people who were there already were an inadequate number of staff and I asked Mr Maplethorpe could we increase that to two hundred and after discussions with Jephcott they decided they could. And I assured him that if I couldn't find him a new medicine with two hundred people, then almost certainly I could not with two thousand, and by the way I still feel that.

MB You feel that two hundred is a good unit?

DJ Well, as I say, if you can't find a drug with two hundred people, the chances are that you're not going to do it with a lot more anyway. I also told him that if we were successful though, then two hundred was not big enough to be self-sustaining and I would be back for more, but by then of course they would have a medicine that was going to pay for it. The second condition was that we would be given at least five years to show what we could do. Now, that became complicated because within six months of my beginning in November with Allen and Hanburys, Jephcott decided to set up Glaxo Research Limited to integrate all R and D activities in the Glaxo Group, and Mr Maplethorpe told me of this and said that I was going to be a director of that. And I said, 'Well, no, I don't think I am,' because again I had a convenient bolt-hole back into Smith Kline, so there was nothing brave about what I was saying or doing. But I reminded them simply of the conditions and I told Mr Maplethorpe why: that Harry Jephcott, although he saved Glaxo from total failure in the 1920s and 1930s and created a substantial science based organisation, it was almost entirely built on licensed end product. By the 1960s it was almost impossible to license in any useful products. The reason why they could license products in was simply that immediately after the war, there were very few if any truly international companies, so Glaxo could license very worthwhile products, including streptomycin and suchlike things, for sale but on a very limited franchise with licensees from America and other drugs from other places. In the 1960s there was no doubt in my mind that we had to find our own drugs, otherwise we weren't going anywhere. Glaxo had to be innovators and find their own drugs. Now, Jephcott still found that very hard to take. Uncertainty he had had enough of, he had lived through difficult times, so he was not in any way interested in highly speculative research and that's the only kind I had to offer him. So that is why I said no because I could see no point in going along to Greenford every month to be chastised by Jephcott for doing what I thought was the right thing to do. I would rather leave. In any case, Maplethorpe and Jephcott were very honourable men and when reminded of their bargain said, 'Okay, that's what we said, that's what we'll do.' So, I got my extra people up to two hundred and luckily we found our first major drug with the two hundred in 1966 and we'll come to that later, I guess.

MB But you'd stuck your neck out quite a lot?

DJ Not really. I had nothing to lose.

MB But you hadn't got a lot working on the floor of the laboratories when you came to look around in the first six months?

DJ Well, there was not a single viable project in the place. That simplified matters, so we started from scratch. I should tell you that if you go into a place and change everything in sight, you're unlikely to be the most popular man there, and I was not. Over the first year or so, they wondered what fool had come amongst them, this iconoclast knocking down all sorts of traditions. But it was a rigid and original structure and amazingly more than three-quarters of the research budget was spent on anti-infective agents, which was really trivial when compared with the huge investment in Glaxo down at Greenford in antibiotics and vaccines and suchlike. So, for Allen and Hanburys to work on anti-infective agents in that environment was lunatic really. I described it as being like a cairn on top of a mountain; really a cairn doesn't do much for the dignity of the mountain, but is very obvious. So, what I did was to remove that cairn and go to my own wee mountain and try to build it up myself. So, one set up pharmacology-based research, medicinal chemistry and pharmacology, which was complementary to that in Glaxo, Greenford.

MB Just put me on the map, David, with this. Whereabouts were the laboratories and where were you based?

DJ At Ware in Hertfordshire.

MB Good laboratories?

DJ No. The new chemistry buildings were converted from 1900 buildings and I would describe it as English workhouse style really, but on the inside you could turn them into perfectly serviceable laboratories. The pharmacology department, strangely enough, was built on the top of a Roman road and when we dug for a little extension, all sorts of Roman remains were found including a Roman toga, which couldn't have been very functional for the amount of coins dropped about the place. Also, we found a Roman General in his lead coffin looking maybe a bit aggrieved, insofar as a skeleton can, when he was disturbed. But also, we found dog bones and other bones, so we had the oldest established pharmacology department in the business. We had to start again anyway, so one stopped parasitology, one stopped anti-infective work and started a new project, really, not of any great originality, quite honestly, because none of us knew what we were doing. We were learning together and I will explain to you later when we come to it how salbutamol gave us a way of thinking and a way of living, but in the meantime just in case there were things out there to license… God knows I must have travelled a hundred thousand miles looking for a company or somebody daft enough to license Allen and Hanburys with something worthwhile to sell just to keep the show on the road. I didn't find them and luckily, as I say, salbutamol found us because one of the programmes we started was in bronchial asthma in 1963, I think it was. And our starting purpose was very simple. At that time, the most effective bronchodilator was isoprenaline, an analogue of adrenaline, different from adrenaline in that it acted only on one sub-group of adrenoceptors, the

beta receptors. Given by inhalation, it acted very, very quickly but the duration of action was only about one and a half to two hours. So, hugely effective, short acting and in addition, a cardiac stimulant.

MB A problem.

DJ Even by inhalation. So use-limiting with cardio-vascular effects. However, the first starting objective of the project was to make an analogue of isoprenaline which would be stable in the body and which when given by inhalation would be longer acting than isoprenaline, and that is what we set out to do. It was problem which was solved by the Boehringer Group with their compound, oxyprenaline, which is simply the resorcinol analogue of isoprenaline. Given by inhalation it acts for three or four hours: given by mouth it is a bronchodilator but a cardiac stimulant because, like isoprenaline, it is equally active on all beta receptors. The best idea we had in-house as it turned out came from Dr Larry Lunts, who suggested that we make non-catechol analogues, not the resorcinol, because they came from another company. Included amongst these were saligenins and we got a huge surprise because, when we made the saligenin analogue of isoprenaline it was active as a beta stimulant. A bronchodilator, certainly, about one-fifth as active as isoprenaline, which is quite active, but amazingly it was hundreds of times more active on bronchial muscle than on heart muscle. And this was the proof that beta receptors were not all of the same kind and the ones in the heart and the lungs were different - different sensitivities to unnatural beta agonists, the same kind of sensitivity to adrenaline and isoprenaline, but different sensitivities to the saligenins. So, the next drug in that series instead of N-iospropyl is N-t-butyl, which is salbutamol, and it is really a thousand times more active on bronchial muscle than on heart muscle. Now, some people would say that was what they were trying to do, but it's not true because I can tell you that when the first result came on the first compound at that time, the girl concerned, Valerie Cullum, was sent back to do the experiment again because it couldn't possibly be right. That's how expected it was. Then, Roy Brittain, the head of pharmacology went and did it himself and sure enough we had a highly selective agent, the first of its kind, and that led to the Ventolin inhaler. Ventolin by mouth is less effective, but by inhalation it had no use-limiting cardio-vascular side effects and acted like oxyprenaline for three or four hours. So, it was a new kind of anti-asthmatic agent and during the day, three times a day, you had very good control of the asthma with that drug. During the night, the control is much worse. The reason for that is very simple that in the asthmatic during the day there is a natural increase in circulating adrenaline, so that contributes to keeping an open airway. During the night, the adrenaline levels fall and that is why asthma is always worse during the night. By the way, Ventolin turned into a very major product.

MB You put that on the market in about 1969/70?

DJ 1969. By inhalation, 1970, I think.

MB I think you said at some stage, David, that it wasn't marketed all that well. Would that be a criticism you'd keep to on this record?

DJ I think so. The chief reason I have for that is simply that fifteen years after it was on the market, the sales usage was still going up. Now, that's a very slow uptake.

Part of the reason was timid marketing or selling, maybe. Another reason was that it was only very slowly introduced in the world in different countries and the reason for that is that Glaxo had no international development organisation. Arthur Hems, who ran research at Greenford, and I ran research at Ware… our job was to find new entities and get them to the British market. We could do clinical trials wherever we wanted to or whatever we chose to do, but it was not our responsibility to get registration in Germany, France or wherever it was. In fact, at that time we were not even in Germany, I don't think.

MB So, you were let down by marketing?

DJ Well, it was the whole strategy. You see, the group we had then was a consequence of Jephcott's policy of licensing in for sale in the UK and British Commonwealth, former colonies and so forth, so you had a very restricted franchise. So, we didn't have companies in France, not until immediately after the war, in Germany, Japan or the USA. We had nothing and these are the biggest markets in the world, but the reason we were not there was that you had nothing of your own to sell. Ventolin was the first drug that we could sell in every country in the world because it was ours.

MB It was a revolution, wasn't it?

DJ Well, I don't know about a revolution, but so far as Glaxo was concerned, that was the first one that could sell throughout the whole world. Before that had come betamethasone valerate, a topical steroid from Greenford, which could be sold throughout the world except in the North American continent. The reason for that is too difficult to explain at this time, but was as a result of collaboration with the Shering Corporation on steroids and they reserved the right to sell in Canada and USA. So, that was not available for Glaxo. So, the first major drug for Glaxo was betamethasone valerate, which is Betnovate, a topical anti-inflammatory steroid, and the second was salbutamol.

MB Let me just keep you with salbutamol. That must have been a great step forward for your career because you put yourself on the line on a five year guarantee to come up with something and it came right in time. I don't want to get there quite yet, David, because I'm interested in those early beginnings. You said you travelled hundreds and thousands of miles looking for products to be licensed. In those early days when you found that that early workforce hadn't really got a project worth carrying forward, I just wondered how you handled that because that must have been a massive test. You had to go to a board, I suspect, and tell them that there was nothing on the ground?

DJ Well, I don't think boards were terribly interested in that, but having decided that we must stop doing this and this and this, and start doing that, that and that, I remember going to Mr Maplethorpe… by the way, you will hear me talk about Mr Maplethorpe as an act of respect, because he used to urge upon me, 'My name is Cyril. Call me Cyril!' And I used to say, 'Mr Maplethorpe, I cannot call you Cyril, it would be like calling my father Andrew. Now, just take it as a mark of respect and we will get on fine.' In any event, I went to Maplethorpe, who was the managing director and my immediate boss, and I also reported to Jephcott for scientific content,

to explain to him what analysis I had made. This was about six months after I was there, and the analysis I had made was that we were going to stop this and this, and this is what we have to start, and this is what we have to do. Maplethorpe was a very intelligent man but also one of the most impatient man I have ever come across. If you wanted to tell him something you had to get it in within the first two or three minutes, otherwise his attention used to wander. But I can well remember that before I had gone for five minutes or so, he said, 'David, David, can we understand one another. I don't really care what you do, so long as you are successful.' And that was the only conversation I had with the boss at Glaxo about what I should do in research. I realised then that in the Glaxo of that day, once you have reached a certain level in the company, you were on your own and you made your own jump. It's a good discipline. It also means that decisions can be made very quickly because you make them yourself. You have to answer for them perhaps, but you make them yourself, and that I did from the day I became research director at Allen and Hanburys until I retired in 1987 as the research and development director of the whole Glaxo group of companies.

MB But just keeping you to the strategies of that early time, 1961, did you really go in and torpedo people quite quickly? I'm trying to work out the way you approached it?

DJ I approached it most unsubtly. Allen and Hanburys was an ancient crystalline structure and I took a hammer and smashed it, but the only people who went out were the parasitologists who went from Ware to Greenford, to Harefield, still within Glaxo. Nobody was sacked and the pharmacologists and the medicinal chemists we started again, really, from a standing start, which is good.

MB And you didn't get much resistance because you carried them with you?

DJ I wouldn't say I had a lot of happy people about me for a month or two, but in time they came to realise that I was not entirely daft and certainly they were very willing to listen.

MB What I was trying to account for is that with a big shake-up like that and being the new boy, how you managed to take them with you?

DJ Well, they didn't have a lot of choice really because the only way out of the problem was forward, and so we were working into new areas from some areas which had no hope of success. For example, in pharmacology one of the projects was to find a barbiturate antagonist. Why? It would be useful to bring dogs round from barbiturate anaesthesia. Now, the market for barbiturate poisoning in Britain would be, what, £20,000 a year, if that. Absurd. Also, one of the earliest jobs I had in Allen and Hanburys was to go to Cambridge to explain to the professor of veterinary medicine why our barbiturate antagonist had killed his dog because he was daft enough to try it on his own dog. In any case, these kind of projects disappeared to be replaced with other things, but in honesty, again one has to say that I had no guiding principles at that time. I likened myself and my people, who didn't like it, that we were very like a willing hen scratching in a corn yard. If we scratched hard enough we'd find some corn because there was corn there, but we had no way of analysing, like the hen, where the corn is likely to be. So we just had a number of projects and

we just did this and this and this and got happily nowhere until salbutamol found us. We didn't find it, it found us because we found something we weren't looking for, a highly selective agent.

MB But you were looking at dealing with asthma?

DJ Oh yes.

MB I mean, you'd got the strategy of looking for major areas of illness that would give you large international coverage, so that strategy had been put to work?

DJ Asthma was an obvious target. Improvement on isoprenaline… if you could do that, was doing something useful.

MB Did you look in other areas as well?

DJ Yes, we looked at problems of mental illness, cardio-vascular disease and all of these ran into the sand, again because we didn't have guiding principles. But in any case, salbutamol saved the research group from extinction and more important than that, it gave us a way of thinking simply because of this. So, let's say that that's adrenaline and that's salbutamol, the difference is just a wee bit. Adrenaline acts on virtually every cell in the body: heart cells, bronchial muscle cells, cells in the liver, all sorts of things. Whereas salbutamol, which is only four carbons different, had none of the alpha affects of adrenaline and only some of the beta affects. And in looking at these two structures how can structures as closely related as these, how is it possible?

MB You produced a less generalist key?

DJ So, one says very simply how is it possible that salbutamol properties should be so different from that of adrenaline, and the conclusion one came to very simply is that the receptor proteins for beta-2 receptors were different from beta-1. Also, extrapolating from that, if adrenoreceptor proteins are varied in this way, it was a reasonable certainty that the receptor proteins for other mediators were similarly varied - much more varied than we'd ever imagined - so the thing was how do we set out to characterise differences or recognise differences between receptor proteins for the same mediator in different kinds of cells, and that at last gave me at any rate a way of thinking which was sound.

MB That was the model on which so much else was built?

DJ Absolutely.

MB David, you've mentioned beta-1 and beta-2 receptors. Was the work that you conducted actually instrumental in highlighting the existence of those receptor groups?

DJ No, it confirmed that they did exist because before us Lands and his colleagues in Winthrop had found a drug called isoetharine, which was about twenty times more active on bronchial muscle than on heart muscle, but as a catechol it was

still short-acting. They published in 1966, the year we found salbutamol, so we were disappointed that they had identified that the receptors were different, but we were pleased that our compound was very much better than theirs, so ours was the evidence that what they were proposing was sound. Now, once salbutamol went on the market we had some money coming in, so I could go back to Maplethorpe, and in 1968 I put forward a ten year expansion plan for research at Ware, which was really going to be funded by the income from salbutamol and indeed it was. So, the first building we built was opened in 1972 and that I regard as the *annus mirabilis* of Glaxo because in that year our second major asthma drug, which I'll come back to - an inhaled steroid - went on the market under the name of Becotide. So we had one drug which was a bronchodilator, salbutamol, and the other, an anti-inflammatory agent, a steroid, both selectively acting within the lungs. Together, they changed the treatment of asthma over the next ten to twenty years. So in 1972, we opened the new pharmacology laboratory based on income from Ventolin and Becotide went on the market. Also, in that year we started the work which led to ranitidine which was Zantac, and also in that year we started the work that led to the new drugs for migraine and vomiting, which came forward in the past few years, so that was a twenty year job. Ranitidine, Zantac, was rather less than ten years, but all of these started in 1972 because we had some new pharmacology laboratories. These drugs, if you take them all together, substantially make up more than half the turnover in profit of Glaxo today. There were eight major drugs to come through in that period. The eighteen years I spent at Ware were comfortably the happiest working years of my life because we had a good group of people who got on with one another and they were good hard-working people and talented people into the bargain. It may sound immodest, but they were good of their kind. Also very important, they got on with one another. We made decisions for ourselves; we didn't have to refer to the Allen and Hanburys board or the Glaxo board. Once a month there was a development meeting and every six months each major project was reviewed and any advance was reported at the monthly development meeting. So, during this time I was my own director of project developments, acting on my Smith Kline experience, and research director because once I found something, I could put it into development very, very quickly. For example, it couldn't happen today, but when we found salbutamol, it was formulated in an inhaler. The formulation for it was mine thanks to the suspensions I was telling you about earlier. The formulation of that is uniquely different from any other and it avoided a fifteen per cent royalty to Reicher.

MB David, you were saying how quickly products could be developed then?

DJ It could happen very, very quickly. I inhaled this formulation; I'm not asthmatic, and so I knew it wasn't an irritant and I knew it wasn't doing anything dramatic to my blood pressure, but I needed an asthmatic patient. My friend, who was a parasitologist turned pathologist and toxicologist, Desmond Poynter, and who is still a friend of mine, despite everything…I remembered Desmond telling me that once when he opened a coke stove once, a puff of hot air came out full of sulphur dioxide and he went into a bronchial spasm. So, with a Ventolin inhaler in one pocket, I went down to the chemistry lab and I got a cylinder of liquid sulphur dioxide, put it behind my back, went to see Desmond and said, 'Do you mind inhaling this because this is a little bit of sulphur dioxide?' And so on the first day we gave it to him, he went into a bronchial spasm and Ventolin, the salbutamol inhaler, relieved that. The second day, same experiment, except that we gave him the Ventolin first

and it prevented it. That was in a couple of days. We knew we had an effective drug and we knew how long it lasted. Then I went down to see Professor Colin Dollery. I don't know if he's on your list of interviewees but you should think about it if he isn't. In any case, he had a very sensitive body box which measures changes in lung function. We went along there and two of our staff went down there as volunteers, Graham Williams and Ann Raphael. That's how close we were at that time, we knew all the people involved. Ann was a fairly severe asthmatic, Graham not so much so, but an asthmatic all the same. They went down and again within a fortnight of taking the drug Ventolin by mouth, we knew the duration of action, we knew the optimum dose probably both by mouth and by inhaler, and that happened within a month. Now, it takes eighteen months to do that because of regulations both inside and outside the company. People are timid. They don't test drugs on themselves any more and all our drugs, every last one while I was there, I was the first person to take it because I wanted to know what the volunteers were in for.

MB So, with a few volunteers and that kind of test, you could put a product into development?

DJ Yes. Well, it was in development anyway. What I wanted to find out quickly was does it work? At that time it was said, if you came for an interview for a job at Glaxo and you were wheezing you were in at Allen and Hanburys, but we had a panel of about half a dozen asthmatics and they were very trusting people and that's the kind of relationship we had.

MB But that was salbutamol and that was in development very quickly?

DJ Yes.

MB And that really provided a lot of finance for the later projects?

DJ Well, we'd found an effective bronchodilator, but the mainstay treatment of more severe asthma is glucocorticoid, a steroid, and the first of them was cortisone, cortisol, and then the more selectively acting drugs, glucocorticoids, prednisone, prednisolone, betamethasone and so forth. They're given systemically, are highly effective but they have long-term severe side effects, the details of which don't matter here. So, the question was how could we get a selective glucocorticoid action within the airways and obviously you give it by inhalation. So, that's the first thing. You give it by inhalation but the rest is swallowed and if it is absorbed from the gut you get a little bit of selectivity, but not much. So, the second condition was that the bit that was swallowed, if absorbed was inactivated by metabolism in the gut wall or in the liver. So, these are the two conditions that had to be met and we were lucky we had in our hands beclomethasone dipropionate; it's a topical steroid from Glaxo, which was a ready source as a topical, anti-inflammatory skin product. We tested it in our volunteers and we tested first of all the activity of the drug by mouth, the activity of the drug by inhalation, of course - I'm now talking about systemic activity, glucocorticoid activity - and intravenously, solubilised, given intravenously. Now, intravenously gave the maximum answer obviously, and when we found that it was four times more active intravenously than by mouth, then that said to us simply for such a long-acting drug that there is a considerable first-pass metabolism, or the drug (??). It didn't really matter which. We didn't know because we didn't have analytical

methods to determine it with. But on the gross bioassay on ourselves, on the skin it was about six or seven hundred times more active than cortisol acetate and we knew it was a topical anti-inflammatory drug systemically more active by injection than by mouth. So, we were in with a chance and we tried it and it worked out very well. So, that was the first topical anti-inflammatory drug. Our worries were firstly, would it work at all? Would the inner surfaces of the airways be similar to skin? Would you have an anti-inflammatory action? The answer came yes. The second worry though was if it was active in the lungs in the same way as on the skin, then there would be a very big problem because on the skin if you apply such a potent steroid day in and day out, you get inhibition of collagen and elastin production, so you get thinning of the skin. Mine is already thin with old age, but you'd have a hollow where the steroid was applied. And of course if you quietly dissolved away the collagen and the elastin tissue in the lung, you would not be doing a lot of good. So, the question was did we have any reason to believe that the lungs were different from the skin? The answer was yes. When one looked up the natural history of Cushing's disease, which is a natural hypercorticoid activity, then the pathology of the skin showed certainly all sorts of side effects, but when you looked at the post-mortem report of the lungs, they looked okay, so we had reason to go forward. Secondly, we made Cushingoid dogs by giving them high doses by inhalation, they had all the symptoms of Cushing's disease: a change in subcutaneous fat, retention of water, all sorts of things, but the lungs were okay. So, that was another reason for taking it forward. The third worry, of course, is when you inhaled a steroid would you get uncontrolled infections due to suppression of the immune response in the lung. The answer was in the dogs with Cushing's disease, no. If they inhaled beclomethasone dipropionate no, as it turned out. In fact, if anything, the incidence of infection was less, I think simply because there was less inflammation within the lungs and therefore less debris on which bacteria and other organisms could feed. So that it turned out to be a considerable success, and there again that even more than anything changed the treatment of asthma.

MB When you put the two together?

DJ The two come together because one deals with the contraction of bronchial muscle and the other controls the inflammatory process, but it was not as simple as that and as we go on I will explain to you why. You see, the thing that was wrong with salbutamol, the Ventolin inhaler, was that it only acted for about three or four hours. That couldn't get people through the night, so nocturnal attacks of asthma were still common in these patients although they responded to Ventolin. So, if somebody wakes up in the night gasping, they reach out and find their inhaler, inhale it and then they go back to sleep again. So, it was very important if we could, to get continuous beta-agonism not only during the day but during the night, and the problem was how to do that and I will explain to you later how we came to salmeterol because that's a few years on.

MB But, in the Seventies you put the two compounds that you'd found together and made the most effective inhaler system that was on the market?

DJ It changed the treatment of asthma beyond any doubt. By the way, it took about twenty years for the chest physicians of the world to decide that this inhaled steroid was safe after all, and it happens that it's the safest drug I believe that I ever

put on the market for one very good reason. You see, if you have a Ventolin inhaler and your asthma is getting worse, your airways are being filled with mucous and other material, shed epithelial cells and so forth, and all the salbutamol will do is to relax the bronchial muscle but it will not create a clear airway. So, the asthma can get progressively worse if a Ventolin inhaler is the only thing they have, and if it gets very much worse, if that's the only treatment they have, they inhale and inhale it and inhale it and they are found dead with an inhaler in their hand and they blame the inhaler. The problem is not the inhaler. The problem is that they didn't have the anti-inflammatory treatment that would stop them getting into that condition. And in the first literature of the product, I used to write the literature for all my products myself, you find in the data sheet there is a warning to the doctor and to the patients simply that a dose from a Ventolin inhaler effectively should act for three or four hours. If a previously effective dose is obviously acting for less than three hours, the advice to the patient is please go to your doctor because this indicates that your asthma is getting worse and it indicates that you need a steroid. We say that to the doctor as well. It was not a very successful campaign, but it is still the best advice we could give them because we couldn't give them a steroid first because it was forbidden by the drug authorities. It was too dangerous. It took twenty years or so before they changed their mind that okay you start with a steroid. Ironically, when they found that the steroid was safe, almost to the day, they decided that the beta agonist might be unsafe, but I'll tell you more about that later. The reason why I believe that Becotide or inhaled beclomethasone dipropionate was the safest drug ever put is, as I have explained to you, if your asthma is getting worse and you increase the intake of the Ventolin inhaler, you run into more and more trouble, but the inhaled steroid is quite different because if your asthma is getting worse and you increase the dose, even if you become Cushingoid, you're doing the right thing because you are bringing the inflammation under control. So, even if you grossly overdose because in the short term steroids are not toxic, that's why there is an inbuilt safety factor, as long as people understand the nature of the drugs they are using.

MB David, what was the actual date when you put the steroid together with the bronchodilator?

DJ Well, they were separate drugs. By the way, I should tell you because it's very important to acknowledge who did what, the man in Allen and Hanburys who first proposed the use of a steroid of this kind in the lung was a man called Wilfred Simpson, who was our medical director. What I didn't know then was independently in Glaxo, Gordon Phillips and the other medical director, whose name I can't remember at the moment, they also proposed that, but they didn't do anything about it whereas we pressed on and we were dead lucky. It was the only steroid available to us, we tried it and it worked and the use of these two things sensibly did change the treatment of asthma. By the way, beclomethasone dipropionate went on the market, the clinical trials started I guess about 1967/68, after we had found salbutamol, because having found a better bronchodilator, what did we do to improve steroid treatment. And Wilfred came up with that and in 1972, as part of the *annus mirabilis*, this Becotide went on the market.

MB A big year. Like 1966?

DJ In my view, 1972 was, well I keep on saying it and it's all that's left of the Scottish higher Latin, it was an *annus mirabilis* for Glaxo because there were tremendous consequences from that year.

MB David, I'm going to leave that part of the drug finding story for today because you're going to come back and talk very specifically on a separate tape with some illustrations about the pharmacology of asthma treatment. But I don't want to leave the story totally yet, because you've got into the Seventies now, that remarkable year we keep referring to. Was there a chance of you moving to a new appointment and going to Wellcome in the Seventies?

DJ Well, I had two opportunities then. The first was with Wellcome. I fancied my chances as a director of a bigger company and I applied, wrote in, and I was interviewed and highly commended but runner-up to John Vane, who was then a much better-known pharmacologist, obviously. So, there was no chance of my going there because they chose not to have me. What they did have though was the opportunity of joining Rank Hovis McDougall as their research director, the food company, because it did a lot of interesting work actually in plant genetics and also produced Quorn, I think it's called, which is sold by ICI now, the protein made by an *Aspergillus* fungus, I think it is, and again they were doing that work then. Their place was in High Wycombe but I found that when I thought about it, really it wouldn't be right for me. When I drove to Ware in the morning I knew why I was going, I knew I was going to enjoy myself for the most part. If I was driving from my home to High Wycombe, why would I be going? For the money? That is not a good enough reason. Would I enjoy food research as much? I doubted it. So, I told them sorry, I can't come. They pressed me and I said, 'Well, I'm going to make a confession to you. The truth is that I am addicted to drugs.' I don't know whether you've found it yourself, but if somebody offers you a job and you turn it down, they press you harder and harder.

MB So, you stayed with Allen and Hanburys, but you moved closer in the Seventies to working with Glaxo centrally?

DJ Well, I was research director of Allen and Hanburys in 1972 incidentally, and they set up a research company independent of Allen and Hanburys Limited, and I was managing director of this research company. That was from 1972 onwards, and I think it was in 1978 when I was appointed overall group R and D director of Glaxo.

MB That was of the whole empire?

DJ So, I started with one hundred and twenty-two people at Ware and there were one thousand or so at least, by the time I retired. Worldwide there were about three and a half thousand people. So, the job had changed and not half as enjoyable; with two or three hundred people it was more enjoyable.

MB David, we're going to close down for today. Next time we'll have a look at that expansion of your interests, that wider Glaxo research commitment and also we'll make plans for the study of asthma pharmacology.

DJ Okay, but I think you ought to hear the story of how we got to ranitidine. But we were greatly indebted in that case to James Black, because ranitidine, Zantac, was the biggest selling drug ever, as I understand it, but it was a piece of opportunistic research and again a bit of luck, but not in the same league as the 5HT work.

MB Could we just encapsulate that now and put that on the record?

DJ If you'd like to. In 1972 again, when we had a new lab, one of the projects we tackled was control of gastric acid secretion. By the way, the things that were known to induce acid secretion was stimulation of the vagus nerve, which means it's cholinergic and secondly, gastrin which by then had been isolated and pentagastrin was also almost certainly available. So, gastrin was the hormone involved and a chap called Popiavsky also showed that the injection of histamine stimulated acid secretion. There was no doubt in my mind that acetylcholine was an important mediator, but there are acetylcholine receptors all over the body, so selectively to block the receptors for acetylcholine in the stomach was really impossible. That didn't inhibit some people trying to do it, mind you, but it turned out to be impossible. Secondly, I was in no doubt that gastrin was a physiological mediator because its levels rose and fell with the condition of the stomach. But again, you are now dealing with a large molecule, I think 21 or 22 amino acid residues, and blocking the action of that when you don't know which units in it are critical for the binding, well, it's like a lucky dip really. So, we started that nevertheless. I avoided histamine although we knew that Jim Black was working on histamine because I was far from sure that histamine, although it stimulated acid secretion, was a physiological mediator. Jim found the first histamine $H_2$ blockers as they are known. If histamine were not a physiological mediator blocking these receptors, it would simply be a footnote in an advanced treatise on pharmacology. It would have no clinical significance. But it was Jim's drug, burimamide, where he first showed that by blocking the histamine receptors in the stomach, you inhibited a secretion induced by histamine, which is not surprising since that's what you designed the molecule to do. But also you inhibited gastric acid secretions stimulated by gastrin and above all stimulated by ingestion of food, which showed beyond any doubt that histamine is a physiological mediator. Roy Brittain and I went along one evening, it must have been towards November that year because it was a cold, wet and miserable evening, and Jim Black was speaking at Hatfield Polytechnic about his work on histamine. By the way, his publication came out in 1972 *Nature*[1], a famous publication that every pharmacologist should read. Anyway, he showed a chap called Wiley at Kings College, a surgeon, because he had infused into him - he was covered by an $H_1$ blocker, mepyramine, then he had burimamide - and then he had infused into him histamine, infused into him pentagastrin afterwards, and the acid secretion was inhibited in each case. So, the minute one saw that, for goodness sake why are we trying to block gastrin? So, I went in the next day and said, 'Gastrin, just forget it, we'll now work on histamine.' We started then and in 1976 we found ranitidine and that turned into Zantac. Now, ranitidine had the advantage over the Smith Kline compound and that was cimetidine, trade mark Tagamet. Now, Tagamet is a perfectly good drug. Its main weakness is that it does inhibit oxidising enzymes in the liver, which are cytochrome P-450 enzymes, which are important for metabolising drugs like warfarin, phenotoin and all sorts of things. When you have a drug with a small therapeutic margin, if you inhibit this metabolism

[1] Black, J.W., Duncan, W.A.M., Durant, G.J., Ganellin, C.R., and Parsons, M.E., 1972. Definition and antagonism of histamine H2-receptors. *Nature* **236:5347**, 385-390.

you can get toxic blood levels. So, that was a weakness. Another weakness was in high doses that it also blocked androgen receptors. So, in high dose you can get feminizing side effects in man. We were lucky because again, no doubt as somebody will tell you, we set out to find a highly selective $H_2$ block, and in truth we didn't know if such a thing was possible. In fact, we didn't even know that cimetidine had these problems. We were much relieved to find that our drug did not. So, the reason that ranitidine took over was first that it was pharmacologically cleaner. Because of that we could get big doses and safely give big doses. The Tagamet doses schedule was four or even five times a day. We could give at night and morning by giving a big dose and it was David Richards, our medical director, who said we should do that and he had a job convincing me because I felt we could test this drug to destruction, but he convinced me finally and that's what we did. So, we came out with a better drug and a cleaner drug with a much simplified dosage schedule. From then on, Glaxo were in the driving seat. That was the advantage and they followed us to twice a day and we went to once a day. One big dose at night and it worked perfectly well. Again, they followed us. From then on, partly because of the intrinsic merit of the compound but mainly because it was sufficiently clean and you could give really big doses.

MB And that was a lead you got from Jim Black's talk at Hatfield Polytechnic. You just went away and knew?

DJ Well, I don't know that I went away and knew, but that was self-evident then. It was a much easier project than trying to block gastrin because I knew from his work it could be done. They went on and burimamide was the next one, and the next one was cimetidine. Burimamide was active but toxic, it caused agranulocytosis. Cimetidine was much cleaner and was the major drug discovery of the Seventies, beyond any doubt, and that was Jim's second triumph and that is why he got the Nobel Prize. He shared it with George Hitchings and Trudy Elion, but in many ways Jim's achievements were greater than theirs, in my view. Mind you, I am biased. He is a fellow Scot for a start and comes from the same county. When you interview him, he will show you where he was born, which is not very far from Markinch.

MB David, I am tempted at this point, as we are winding down this particular interview to reflect on your rejection by Wellcome for that research and development job and the fact that in the time you remained at Glaxo, you actually provided most of the finance that was eventually to buy out Wellcome?

DJ Well, in all honesty, I don't regard that as an achievement. I think the purchase of Wellcome was bad for this nation really, because when Wellcome was there, we had Glaxo, Wellcome, ICI and Smith Kline Beecham, which was really British based. So we had four major British drug companies which were international. Each of them with the right research direction, in my view, had the capability of becoming big enough, but the minute you fuse any two you've one less. So, that diminished the British pharmaceutical industry and only time will tell whether that was a good move or not, but if, in fact, the new Glaxo Wellcome research is not productive, then you're left with Zeneca and Smith Kline Beecham, who are getting more American by the day. But as a source of wealth creation in this country, the absolute wealth creation of the drug industry may be less, and it is a profitable industry, but not a big one. To make it smaller as a matter of policy was very bad. In

fact, I stood for my indolence at that time to write to Michael Heseltine, who was then President of the Board of Trade, to explain that to him. And also why, in 1972 again, I think it was, Beecham attempted to take over Glaxo. Why? You see you only get a successful takeover if you are buying a company because of their assets and our assets were under-developed drugs and Beecham wanted to buy them. They were turned down by the Monopolies and Mergers Commission as this was not in the national interest, and I wrote to Heseltine explaining that to him. But, of course, the outcome of that was Glaxo went on to be the second biggest drug company in Europe. Beechams solved their problem by a different way. I was saying the least you should do is refer to us again to the Monopolies and Mergers Commission. I got a letter back from one of his assistants to tell me that the next stage was that it would be referred to Brussels for fair trade, but that's not what I was talking about. There was no question of unfair trade if you disadvantage yourself. You can never possibly be turned down on that basis, but in my view it should have gone to the Monopolies and Mergers Commission. Now, had they stayed separate would they have both grown, I don't know? I've reason to believe that they would have done because I did a review of Wellcome's research for them at their request after I retired and the research side of that business was not bad at all. The general management was appalling.

MB David, at that point today, I am going to wind down on this interview. We've got you well into your career with Glaxo and we'll take that up next time we meet.

DJ Thank you.