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Dr Norman Heatley, Hon DM in interview with Max Blythe
Oxford, 28 October 1987

MB Dr Heatley, it's very nice to be talking to you here in Oxford where the bulk of your life and work has been lived, but can I take you first to Suffolk and your origins, your parents and Woodbridge?

NH Yes. I was born and bred in Woodbridge, which is on the estuary of the Deben, which is a very nice place to be because you can sail; it's very good sailing there and I got to know the river extremely well. But my father was a vet and he was really more interested in the large animals, farm animals, than in the small animals and I used to go with him sometimes round the farms, which was very nice indeed.

MB He was more than a vet, from all that I read he was rather a good vet?

NH Yes, he was a good student and I've got his medal somewhere here, but also he ended up as the senior Fitzwygram Prize man for his finals year and that is a competition which is open to the four veterinary schools combined and he happened to win it for 1892. And, do you want the little anecdote about... ? Some visitors were travelling from London to Yarmouth, I think, and they let their little Pekinese out on the journey and the Peke ran into something and damaged its eye. And so when they got to Woodbridge, they asked if there was a vet there and they came to my father, and my father looked at the eye and said, 'Well, really the only thing is to take the eye away.' And the man said, 'Do you mind if I watch?' And my father said 'No, not particularly.' So, the man watched and as my father was just sewing up the eye, the man said, 'Well, I must say you made a very nice job of that.' And my father thought this was rather patronising and so he said, 'Oh, and what's your profession?' And the man said, 'Well, I'm an ophthalmic surgeon!' I was very proud of that because it was nice to ...

MB He was a good man to have around. You got a lot from him?

NH He was a good - yes, I learnt a lot from him. A keen gardener which sort of came back to me when I had a garden of my own and so on.

MB Yes, but he was an intensely practical man?

NH Yes, yes. Very.

MB What about Mother?

NH Well, Mother was - my father was from Cheshire - Mother was on the borders of Norfolk and Suffolk and she was an invalid. She had been one of Arbuthnot

Lane's[1] patients. In fact, she'd had, Lane had sort of removed almost everything that he could from her at one time or another, but nevertheless she lived to the age of seventy-six in spite of this.

MB So, Lane made a pretty good job?

NH Well, my father lived to eighty-six and he was having a prostate operation but an embolism occurred and he died, otherwise he might have gone on. And the thing is, if you want to live a long time, is to choose parents that live a long time too, so we're hoping ...

MB Yes, I have no doubt! Norman, you go to school away from home?

NH Yes. I first of all went to a school in Suffolk which had been quite a good one and then became the nearest thing to the *Lord of the Flies* that I've ever heard of. And then I was encouraged to go onto the south coast because I got bronchitis and that was a very good school indeed, Westbourne House.

MB Can we pin-point your age at that time. What age were you?

NH Yes. I went away as a boarder at seven and a half, a year at the *Lord of the Flies* and then I think two years at Westbourne House. And there were two things, I think, which were perhaps rather important to me. First of all, I had a very good friend there, Christopher Morecombe, who went on later on to Sherborne and was the boy who really befriended and possibly turned on Alan Turing, the mathematician who solved problems at Bletchley and so on, and Christopher Morecombe was such a nice man. I can well understand how Turing... Turing said after he died, because Christopher Morecombe died when he was about twenty-one, he said to his mother 'I worshipped the ground he trod on.'

MB But, he also influenced you as well?

NH Yes. We were the same age and, you know, we could strike sparks off each other. He was a really good, nice man. And the other thing about Westbourne House that I'm very thankful for was an elderly man who used to go round, I think, to other prep schools as well, and he came to this place once a week and he gave a lecture, a sort of one hour lecture with practical demonstrations, on elementary science. It might be volcanoes or chemistry or heat or static electricity, you know, rubbing things on your clothes and so on. And when he did electricity which he did every other year so as to cover the whole generation at school, he would bring his Wimshurst machine and everybody in the school used to look forward to these lectures. It was the real red-letter lesson of the week and we had to write home, you know, and most of the boys, I think, described what Mr Elliott had done last week. This was partly, no doubt, filling up the letter to the required length, but also they were extremely interested and he was a very, very gifted man. He set the level of things at exactly the right level for that age group, which was six and a half to ten and a half, but I'm sure he inspired a lot of people.

[1] Sir William Arbuthnot Lane, CB, FRCS (1856-1948).

MB So, very early on you were beginning to feel a bias towards science?

NH Oh yes.

MB You also, I think, had some good experience in a technical way, a local vicar who had a workshop. Is that right?

MH Oh yes, he was - Canon Wilkinson was, he was a very splendid man. He'd married the second time somebody who I think must have been sort of reasonably comfortably off and he had a magnificent workshop and his house, big house, was full of gadgets and the garden was full of gadgets. He had, he thought he would like to see down the estuary but he was a bit low, you see, the land wasn't as high. Then he realised that he had got some very large trees in his garden. So I went... Well, first of all the sort of thing he would do when I was about fourteen, you see, he would say - I would go and visit him - and he would say, 'Hello, Professor, do you know how to make hinges?' And I would say 'No.' And he would say, 'Well, you come to the workshop and I'll show you how to make hinges.' Which he did, and then he would say, 'Well, now, you are going to make one.' Which I did. And one holiday I went along and he said, 'Oh, come along, I've got something that will interest you.' And he'd joined, he'd made a sort of walkway of planks from the ground up to a platform halfway up one of these high trees, you see, and there were steel cables with links under the planks, and then from the platform halfway up the tree there was another thing like this, you see, which went right up to the tallest tree of all. And he said, 'Well, you just follow me.' So, off he went and, of course, as he walked this dreadful thing sort of bounced about like this and I have a terrible head for heights. We got up to the first platform, then the next one was much worse because towards the end, you see, it was steep and the tree was just swaying about like that then. And the last six feet were up a completely vertical ladder through the platform and one had to sort of get oneself over this edge, as it were, going up there, and I wondered how on earth I'd ever get down, but I did get down. Here I am, in fact.

MB Yes, but you could see the estuary?

NH Yes, you got a wonderful view of the estuary just like his friend, Leonard Heywood, who was dying of cancer but had a great deal of fun with a very powerful telescope and could... he said 'I see all sorts of things that people don't think I see with this telescope.'

MB So, by the time you go to Tonbridge, Norman, a science career is really on the map. That's right, isn't it?

NH Yes, I think so, yes.

MB Was Tonbridge a real help before ....?

NH Oh yes, Tonbridge was very well endowed. It was one of the Skinner Company schools and science was particularly good. Good labs, very good teachers, I owe a lot to the teachers there.

MB And then, of course, to Cambridge?

NH And then to Cambridge.

MB Can you tell me a little bit about Cambridge because that was an important time?

NH Well, it was a splendid time.

MB What year did you go up?

NH 1929. And I couldn't resist rowing. I'd decided not to do any games, but I took walks and saw these chaps rowing and I had rowed at Tonbridge and so, rather foolishly, because I'm much too light, you see, I said I'd do this. Well then, the next term I developed glandular fever or some kind of swelling of the glands and that really rather knocked me out for about, I mean, it was about four years before I could play tennis again and that sort of thing, and I think for that reason I was away from school for one or two terms, I think two, I'm not sure. But anyway, I took three years over the part one and then I did a fourth year in biochemistry.

MB Right. So natural sciences followed by biochemistry?

NH Yes, followed by biochemistry.

MB And then a decision to do research at Cambridge, to stay there for some ...

NH Well, no, it was a difficult time, you see, early thirties. One wrote lots of letters to, you know, to Bemax, to Burroughs Wellcome, all that sort of thing and then I was lucky enough to get a DSIR [Department of Industrial and Scientific Research] grant. But before that, Hopkins was the professor, Gowland Hopkins[2] and he had a very good technician who from time to time used to be seen looking at his throat, you see, and he thought he was getting cancer and this was nearly always followed by a spell in the local mental hospital. And Hoppy sent for me one day and said, 'You know, James, I'm afraid he's not well. I've seen him looking at his throat again and I feel somehow that this time he'll have to be inside for quite a long time. Would you like to be my assistant? Don't tell me now, just go away and think about it.' And I said, 'Well, I don't need to think about it, I'd be proud and delighted.' But anyway, James, his technician, recovered and never went away and remained his faithful and excellent technician.

MB So, you were done out of that?

NH So, that didn't happen, that one, but ...

MB Hopkins must have been a remarkable man. Did you get to know him at all well?

[2] Sir Frederick Gowland Hopkins (1861-1947).

NH Not particularly well, no, not particularly well. But he was, of course, he was a great man and the interesting ...

MB What happened instead of this ....?

NH Well, instead of that I managed to get a DSIR grant and stayed on and did a PhD in Cambridge. And then, again, it was not easy to find jobs and I had become very interested in microchemical methods including, of course, the estimation of carbon, nitrogen, halogens etc. by Pregl's method and there were very few labs doing that work. There was one at Oxford, Willer(?) and Strauss had set up, and I think some firms, perhaps ICI had their own lab, but I, most people used to send their stuff to Germany and that was a nuisance, you know, postage and so on. And I thought it might be a good idea to set up in this field and I'd made plans to go to Graz which was where Pregl's methods were taught and so on, but then I got the DSIR grant which was ... No wait a minute, that's, I'm not quite sure… That did happen, I'm not making that up, but I've got the chronology wrong somehow because as I was just getting to the end of the PhD, [Ernst] Chain who had come to work with [Howard] Florey asked me on Florey's behalf if I would come to Oxford and, of course, I was delighted to do that and I've been here ever since.

MB To the William Dunn School?

NH To the Sir William Dunn School.

MB What was the first job that you were going to work for Chain or for Florey?

NH For Chain. Florey was, in fact, away I think for about six months; he'd taken time off to go to Australia, so I was working with Chain. And Chain had a good idea for a piece of research and that was that everyone - I think everyone - believed that a tumour had one kind of metabolism and normal tissue had another, and it was known that one could paint the skin of a rabbit's ear, for example, with carcinogens and Chain's idea was to study the metabolism of the epithelium and, to see, at one end you had normal tissue and if you painted it long enough you got tumours. What changes occurred? First of all, histological ones and then metabolic ones. Was there a sudden conversion? Well, the whole thing broke down because tumours had exactly the same metabolism as normal skin and this hadn't, this had been missed, because nobody particularly measured normal skin, we had to have special micro-methods to do this, of course, because they had studied things by slices. Now you can slice up tumours quite well and you can slice up liver and kidney and so on, but you are not really comparing like with like because tumours are ectodermal, I think, I'm not too sure, and the other tissues, liver, kidney and so on are mesodermal. So the whole thing collapsed, not through any fault of Chain's, but it was quite an interesting and useful bit of information to have found out.

MB And you contributed to this, you made some apparatus for Chain?

NH Yes, it needed a micro-respirometer which I was rather proud of but, of course, it was superseded by these electronic methods of measuring oxygen.

MB But, at that time it worked quite well?

NH Oh yes, I did hundreds and hundreds of experiments and it was about, oh, about two hundred and fifty times as sensitive as the Warberg apparatus and it was nearly as easy to set up and you could do nearly as many things as you could with a Warberg. You could mix solutions, you could add things and so on, you could fill it in with whatever gas mixture you liked and so on and do all the metabolic studies.

MB So, this was a good start to your work with Chain?

NH Yes. Yes, that was a useful piece of apparatus.

MB How did you get on with Chain as a person?

NH Well, I knew him slightly at Cambridge and I'm always very grateful to him for getting me to Oxford, but we weren't really temperamentally suited, shall I say. And when my term was up at the Dunn School, my three years, I was going to Copenhagen to work with Linderstrøm Lang and Holter who had done extremely elegant work measuring things on a very small scale and I was going to take my respirometer and see what could be done there. But, of course, the war came, that was just October, September or October 1939, and Florey asked me if I'd stay on and help him design apparatus and that was something I jumped at. But I then said, 'Well, look, I don't think I can accept this if it means working with Chain.' And he said, 'Well, that's all right, you'll be responsible to me, nobody else.' And so I was delighted.

MB Norman, I don't want to take you too deeply into the link with Chain but obviously it was an important part of the development of your work in the Dunn School, that early phase with Chain, but can you give me a little bit more about how this relationship turned slightly sour and you were not ...

NH Well, I think we were temperamentally unsuited for a start and Chain had been brought up in the German method where the *Geheimrat* says this and you clicked your heels and said, 'Yes, Sir.' And he wanted, I think, to work in the same way and he wanted absolute obedience from his people. No, perhaps that's untrue because he did work with others quite amiably and quite satisfactorily, but we spent such a lot of time arguing about things which shouldn't have been discussed and it was a bad relationship at the end.

MB Right, so not comfortable?

NH Uncomfortable, yes.

NH So, you go to work though for Howard Florey?

NH Oh, that was a different thing altogether; Florey was, you could absolutely rely on anything he said or promised absolutely. He was very much concerned for the people working in his lab, both research, junior research people, and staff and the

more I saw of him the more I admired and liked him right up until the end of his life.

MB A life-long association, a very great pleasure?

NH Yes.

MB Norman, I have to come to the great part of the story, that perhaps by the time you had transferred from Chain to Florey you hadn't expected that the great part of the story is the penicillin part?

NH Yes. I had the incredible luck to be there at the right place and the right time and I started doing simple little bits of apparatus, but within a matter of days of joining Florey, he said, 'I want to teach you how to assay penicillin.' And this was almost the first I'd heard of it and you might say well, it's an unknown substance, nobody's talked about it, how would, are you sure you'd remember if somebody mentioned it. Well, I jolly well would because about eight years before at Cambridge, there had been a lecture during which somebody had talked about penicillin and they just mentioned it as an inhibitor of bacterial growth and I was sufficiently interested to go and hunt up the *British Journal of Experimental Pathology* in which Fleming's paper was published. And that wasn't easy, it wasn't in… well, I couldn't find it in the university library, we didn't have it, and I had to go to the pathology lab which certainly, you know, made me remember. But, anyway, Florey showed me how to do these assays which was a rather elaborate dilution method where everything had to be kept sterile and your solution that you wanted to assay had to be sterile to start with, it had to be filtered perhaps if it wasn't sterile, you see. And so I gradually got sucked into the story and I developed a method which really was very similar, as I found in later years on thinking about, to one that Fleming had developed. And Fleming's method was to take petri dishes with agar in them, to seed them and to cut out holes, remove the agar, and put a mixture of melted agar plus what he was looking at in here in the holes and then incubate the plates. And you get a zone of inhibition around the holes, but that again, you see, needed them to be sterile otherwise the plate got overgrown. And Fleming never used it in a quantitative way. Then Florey told me of a method he'd used in 1929 in which he had drilled holes in the back of a petri dish, in the bottom of a petri dish, closed the holes with rubber stoppers, poured the agar and when it was set, you removed the rubber stoppers, turned the plates upside down and put his solution in the top. Now, that got rid of the problem of the plate being overgrown by contaminants because contaminants couldn't get through the agar. And I made one or two of these things that Florey had used and then I thought wouldn't it be much easier just to have a reservoir, say, little cylinders on the top. And that turned out to be a good deal easier and was in fact used a great deal for assaying penicillin, not only by the Oxford group but by others.

MB So, you sank shafts of glass tubing into the agar gel?

NH No, they rested on top.

MB On top?

NH They rested on top. You just put them in the flame for a moment and then

there was a sort of a 'pssssst' as you laid them on top and that sealed them on but without sinking in.

MB But, this was after the bacteria ...

NH After the bacteria had been sown, you see ...

MB ...culture had been sown?

NH Then, you put your solutions in these cylinders and incubated it and the bacteria grew over the whole plate, you got a lawn of growth except for circular zones, and I think I've got a picture of that too.

MB Right. When did you get deeply involved in the production of penicillin? This was assaying. When did you start? Everything all of a sudden started to go, the need for a lot of penicillin; when did that arise?

NH Well, that was almost at the same time because ...

MB What I'm saying is that all of a sudden from it being a curious and a pleasant study of something that might inhibit bacterial action, all of a sudden it became a thing that was desperately important.

NH Oh, that would be, I suppose, within a matter of about three or four months.

MB Right. What changed the situation?

NH Well, its great antibacterial potency, the fact that it was, as far as one could see, non-toxic - non-toxic to isolated leucocytes, which was important. And the work was going on on many fronts. The yield was pathetically small and essentially what you had to do was to grow the fungus on layers of medium, about one centimetre and a half thick, something of that order, for, say, ten days at a temperature of about twenty- four degrees centigrade and so you needed a lot of vessels to grow this. And the medium - we used the medium which had been used by some people, [H] Raistrick and [P W] Clutterbuck and [R] Lovell in 1932 - it was a very simple, almost inorganic medium: sodium nitrate, a source of nitrogen, and glucose, and so on. Since the containers had to incubate for, say, ten days and you wanted to get a batch off every day, so that meant you had to set up ten lots and so the vessels were a great... there was a shortage of vessels. And the stuff which was harvested was handed over to Chain and he tried various methods of purification and so on. And at the same time some was given to the bacteriologists, who found that quite a range of bacteria were sensitive and others weren't. Then simple chemical work was done. Was it destroyed by metals? Was it destroyed by acid, by alkali and so on? And a general study of its properties. And then in, about six months after that, in March, Chain did a test which he considered one of the most important tests, namely, he got some of the very scarce stuff we had and got somebody to inject it into two mice. Well, they didn't die and Chain considers that this was a very crucial experiment which showed that the stuff was non-toxic, you see. Well, there's no record of how much penicillin these things contained and strychnine and arsenic are non-toxic if you take little enough of them.

Chain had quoted no activity for these samples that he got someone to inject and I've tried to find out what their probable potency was. At that - my notebooks aren't here - but at that time there was something like thirteen batches made round about that date which might have been the ones he injected and their potency ranged from, I think, something like from nil - one batch was inactive altogether - from nil up to probably something like twenty or thirty units per milligram. So, it didn't really show whether the stuff was toxic or not, but anybody ...

MB With zero units it would hardly be very good proof.

NH No, quite. Well, we don't know what the potency was. Well, anyway, Chain ....

MB Can you just pin-point that date for me?

NH Yes, March 19th.

MB That was in 1939?

NH 1940, because the work - well, I joined the work at the outbreak of war, October 1 1939. Well, this was… Chain shouldn't have done this because Florey was away; he didn't consult him or anyone else and the stuff was very scarce and he may well have used up practically all of the available material at that time. Florey had been waiting, trying to accumulate enough to do a mouse protection experiment and that was done a couple of months later on May 25th, that was a Saturday, and here we have a sort of summary of that experiment. Eight mice were taken and four of them were controls and four of them were given penicillin. Now, all of them were given 110,000 strep [streptococci] which had been made more virulent, they'd been passaged, and that was given intraperitoneally at zero time. Then one hour later two of the mice were given ten milligrams of a certain preparation and two others were given five milligrams ...

MB Of the penicillin?

NH Of the penicillin. And then the ones which had had the five milligrams received doses at about two hour intervals and that penicillin was given subcutaneously which is important because if it had been given in the same route as the streps it might merely have acted as a disinfectant in the peritoneum, you see, so that was important. Well, after about seven or eight hours, the controls which had had no penicillin were all looking very sick and after thirteen hours, I think, the first one died and then an hour or so later two more died and the last of the controls died after about sixteen hours.

MB A full cemetery of crosses for the controls.

NH That's right, and a nice grouping, I'd say. But these survived, they survived; the first one survived for four days, another for six days - those were the two which had had just ten milligrams. The others which had had five divided doses of twenty-five milligrams ...

MB A more elongated course?

NH Yes, one lived for thirteen days and the other survived indefinitely. So, that was a very exciting experiment.

MB There was a great buzz around that experiment, I believe, it was very exciting?

NH Well, yes, very exciting. And the next... you see, Florey was really… nobody in peacetime would have dreamt of setting up this kind of experiment at the weekend because you want to see what happens over a matter of two or three days at least. But, so he, Florey, and Chain and I think possibly Mrs Jennings[3] who later became Florey's second wife, were there on the Sunday and all very excited and they decided to press on and make as much stuff as possible.

MB Looking back, Norman, this was a time when it was really becoming quite clear the medical implications of this?

NH Well, it was a jolly good indication. I mean, there are pitfalls; you may find that - you see, guinea pigs for some reason, it's a bit toxic to, penicillin is rather toxic. But no, it was very promising indeed and the job was to make enough of it and for that we needed more vessels and we took every kind of container we could think. It had to be sterile, you see, the least infection would destroy the penicillin and we used flasks and medicine bottles on their side, and trays and pans and things of that sort, biscuit tins. And then we managed to get sixteen old-fashioned bed-pans, the ones with a spout, from the Radcliffe, that's all they let us have. But they were splendid vessels because we could get a litre and a half of medium in them, you see, and the spout, you see, they were just like gigantic tarel flasks. However, sixteen wasn't enough and eventually we thought well, we must get some special things and the obvious place to write is to Pyrex or to some laboratory supplier. And we told them what we wanted, a shallow layer which could be sterilised and kept sterile and Pyrex said that, yes, they could make these things, but the mould would cost £500, that was apart from the cost of each one, and the order would take six months. Well, in those days, I mean, six months was a long, long time and it might easily spread out to two years or never if that particular plant had got bombed, you see. And then we had the idea of perhaps making them of ceramic and we got these things made by a firm in Burslem which are a sort of abstraction of an old-fashioned bed-pan, you see, the spout... And they were made of cheap ceramic, glazed inside, and each of these would hold a litre with about, in an appropriate depth, I think, about 1.3 centimetres, and they could be stacked on top of each other, you see, when they'd been set up and seeded. But another benefit we hadn't really thought of was that when autoclaving you could stack them this way and you made very good use of your space, of your autoclaving space. And then when you had autoclaved them you had to seed them and if you stacked them like this, you see, you could have your sterile suspension spores, just squirt it in there, put this back, and go along the line, whereas if we'd had them the other way, they'd have been too close, so they were ...

[3] Dr Margaret Jennings. She married Howard Florey in June 1967.

MB So, that was how it was done?

NH Yes, and it was done by a firm called James MacIntyre and Company from Burslem.

MB Right. To your design?

NH Well, Florey, when I suggested ceramics, Florey said, 'Yes, I have a colleague, I know somebody in the Potteries called J P Stock,' who, I think, was a cardiologist and he wrote to him or telephoned him. Stock sent a telegram back saying James MacIntyre would do these and James MacIntyre suggested somebody went up to discuss it. We had sent them drawings and I was sent up and I couldn't see them the first day because the trains were held up with bombing and so on, but the next day they'd actually got three of these things made, you see, two of this pattern but with different kinds of spouts and slight modifications. And I said, 'Well, this is absolutely splendid, but could you make them with a spout which is like this spout,' you see. And they said, 'Oh, yes.' And he took a pocket-knife out of his hand and took a piece off and said, 'How's that?' Just a little bit off.

MB Just made-to-measure?

NH And there we were. They weren't, of course, fired, you see, they'd been made ... and it's an interesting process, what do they call it, slip-casting, I think. I don't know whether it's worth going into that but I remembered this from one of the Royal Institution Christmas lectures for children on ceramics. Well, what you do. Supposing you want to make a teapot, you make a mould with your teapot inside and then you take the mould carefully apart, take the teapot out and put the mould together and then you fill the whole cavity with slip which is just a fluid suspension of clay. The mould is porous and abstracts water from a thin layer of the inside of the cavity and then you pour out the slip that's left and you let the thing inside harden a bit and then you take the mould apart and there is your teapot, you see. Then you let it harden a bit more and then you bake it and that's essentially, that's in fact the process used with these. And I think we had something like seven or eight hundred of these from them and I believe they only cost 7/6d, which seems ridiculous.

MB For all of them?

NH For each one, each one. But, there was no charge for the mould, you see, as there would be for the glass.

MB But, these were the first real production pots?

NH Well, that solved that problem, growing them in shallow layers. We wanted more labour and this was almost impossible to obtain, at least male labour, and females had never been admitted to the Dunn School before. But there was one very nice technician there, Donald Callow, whose sister was training to be a nurse and had had a very bad time in Birmingham and was sent home for a few weeks to recover and he said, 'Would you like, do you think... I think Ruth could do this.' So, Ruth came along and she was the first of a number of girls who were all, with one exception

possibly, extremely good and they never grumbled at having to come in on a Sunday or a Saturday, or a Saturday afternoon.

MB And they all grew penicillin?

NH Well, they did more than that. They made it up, trundled it down, got it sterilised and then inoculated the thing. And then they were all incubated in the operating theatre, which could be readily heated to the right temperature, and then they harvested the medium and for a while they replaced it with fresh medium because we'd found that you could do that up to, well, thirteen times.

MB Leave the mould in the pots ...

NH Leave the mould in the pots, put in fresh medium with careful precautions, and we had a little arrangement for taking the liquid off. I seem to have lost that. Perhaps it was, anyway, that doesn't matter, it was just a simple arrangement for tilting these things up and we had a sort of pistol that when you pulled the lever it sucked the stuff up through a bag to filter it and at the same time blew sterile air into the container so that we wouldn't get it contaminated. Well, that took care of the labour and we did have a very good technician, George Glister, who came before the girls, and he was very good at training the girls and getting the best out of them. And then he stayed in the lab for some years, I think, and eventually was asked to go and take a responsible position in the penicillin factory at Speke which was being made, and I think he ended up managing director of that and he played an important part in that.

MB Norman, can I just take two or three details in. I've heard of a story and you can tell me whether this is true or false or whatever of 'dusty scientists'. Does that mean anything?

NH Well, I think I know what you mean. I hadn't heard of that particular expression, but do you mean when people rub some of the fungus in their pockets?

MB Yes. Why was this?

NH Well, this was, I suppose, when the war was in a rather unhappy phase and Florey, who was a cynic, constructive and a good cynic, said, 'Well, we may see the Panzers rolling down Headington Hill yet, so there's no harm in just rubbing this in a few pockets and in your linings and so on of a suit or two in case, if the worst happens, if somebody gets away, they'll be able to recover the fungus.' Nothing did happen, of course.

MB And the spores were in the jackets?

NH The spores were in the jackets, very easy to recover, as long as you didn't send your suit to the cleaner!

MB So, this is the start of the story, the work with the mice showing the potential of penicillin, then the need for high productivity because the need to test it more and probably to go towards clinical trials with humans, but great difficulties in achieving

the right kind of extraction of the penicillin with the right speed?

NH Yes. Well, that was solved rather satisfactorily by a process of solvent extraction. If you acidify your crude culture fluid containing penicillin and shake it up with ether or amyl acetate or other organic solvents, the penicillin largely passes into the ether phase, then you can remove the lower layer, the water in there, and add some clean water which is just faintly alkaline or kept alkaline by adding more alkali, and shake it up with the ether and the penicillin would go back from the ether, back into water.

MB So, in those alkaline conditions it went back to the water?

NH That's right.

MB Leaving the impurities in the ether?

NH Well, there were all sorts of impurities, you see. The sugars, the gums and the proteins and the salts wouldn't go into ether and then certain fat soluble things would, I suppose, but they would tend to stay in the ether when you back-extracted into water. So, it got rid ...

MB So, the first lot of water took away one set and then the ether a second set of impurities and then you are back to water?

NH Yes, you are back in water with a lot of impurities removed and also by shaking, say, x litres of the crude culture fluid with, say, a fifth of the volume of ether, you could concentrate it and then you could shake the ether with, say, a quarter of a volume of dilute alkali, so you end up with twenty times, most of your stuff in one-twentieth of the volume. So, that was useful but there were two snags. One was that when you acidify penicillin it starts being destroyed, so you have to keep the solution cool and you have to work quickly. The second thing is ...

MB So, you worked in a cold room?

NH Yes, we used to work in, with big separating funnels and sort of bottles modified for that purpose in the cold store, lots of sweaters and overcoats and things, just sitting there waiting for the emulsion to settle. And that was sometimes very slow and presumably some destruction would go on even then, although most of the stuff would be in the ether phase. And we got over that by building a rather temperamental piece of apparatus for doing it at room temperature. It consisted really of breaking the solution, cooling the crude penicillin, acidifying it just before entering a column in the form of droplets, which sank through this column and yielded up the penicillin to the amyl acetate contained, or ether contained, in the column. And the column had a slow counter-current flow of fresh solvent and the penicillin-rich solvent came out at the top. There were quite a lot of snags that had to be overcome.

MB This was another piece of apparatus you could use at that time?

NH Yes, but we had to have several shots at getting it to work properly. And then,

that was working for a year or so and a very much better idea was thought, I think by Florey. I think Florey had the idea and then he and [Dr A Gordon] Sanders built the plant to do this. Essentially, it was the same process. You acidify the stuff and then you mix it, first of all it was all done with, you know, sort of home-made stuff. I had nothing to do with this thing at all because I was in America, but the fluid was tipped into a bath and from there it was pumped up by one of these little garden fountain pumps over a milk cooler and from there it was fed into milk churns and then amyl acatate was added and an amount of acid and then the things were mixed by a paddle with holes in it. And the idea was not to get as little emulsion as possible but to let it go as much as it wanted. And then the emulsion was passed through a Sharples centifruge, you know, like a milk separator, which separated it cleanly into penicillin-rich solvent and spent watery phase, which went down the drain. And then since you'd got over the troublesome step with the emulsions being formed very simply, the penicillin-rich solvent could be extracted by a very simple process, in milk churns, back into chloroform or into ether. And a lot was worked up in this plant and later on a firm in the East End of London, Kemball, Bishop [and Co.], used to send up lorry-loads of milk churns and they were put through this, you see, and, anyway, that was later. But the first human trials were done at the end of 1941, no, at the end of 1940. A patient who was dying of cancer was asked if they would, if she would, allow them to try this new drug and she went into a rigor and this looked very bad. But Ted Abraham managed to purify the stuff by chromatography and one could cut out of the chromatogram the fraction containing the penicillin and certain impurities, but not the pyrogenic one, so that was all right. Then, it was a question of getting enough material and the first case, as you may remember, was this unfortunate policeman who had scratched the corner of his, mouth with a rose-thorn and had got a heavy staph[ylococcal] and strep[tococcal] infection of his scalp and his orbit and his arms and indeed one of the bones, and so on, and was very sick indeed and was not expected to live more than a few days. Well, he was given penicillin by Fletcher[4]. Fletcher was the sort of liaison with the Radcliffe [Infirmary, Oxford] and he made a miraculous recovery; his temperature fell, pain went off, he looked much better and so on, but alas the supply of penicillin was exhausted and he relapsed and died.

MB Norman, can I just ask at that point, what kind of daily dosage is involved at that stage?

NH Oh, I think between five and fifteen thousand units every two hours or three hours, intravenously or intramuscularly.

MB Right. And this represented a tremendous amount in production?

NH Yes, in production. That would be something like, oh, perhaps twenty-five or thirty litres of pooled - no, it would be more than that because you never got a complete recovery. So, the stuff was in very, very short supply, you see, and from then on all syringes were taken to pieces and rinsed and the penicillin was recovered from them. And the urine was collected, to the disgust of the ward sisters who didn't like their fridges being used for storing patients' urine, but it had to be to keep the destruction down, and that was worked up. And Florey then decided never to start an

[4] Dr Charles Fletcher (1911-1995). Nuffield Research Student, Oxford, 1940-42.

experiment until he thought he had enough stuff to treat, to continue the treatment.

MB How did you get more? How was this achieved?

NH Well, we had these vessels coming along, the stuff could be worked up quite well and then after the first extraction, further purification was, up to a certain rather low level, was straightforward.

MB But, it must have been obvious that you needed to go into fairly high production rates by that time?

NH Yes. Well, we did, yes, and thanks to the girls and George and people, there was enough to test on six patients. No, I think another... I'm never quite sure whether the policeman, Albert, I forget his name [Alexander], was one of the six, but there were six patients who were treated and showed quite astonishing recovery. Two of them eventually died: one through an accident which had nothing to do with penicillin, and the other one didn't… again, there wasn't enough stuff, but that was the policeman. But it was quite clear that here was something very important and Florey, of course, tried to get firms interested, but it's quite understandable that they had… they were full of wartime orders, they didn't really want to take on an unknown substance which had only been tried in six patients, they wanted to do further work and so on. And after a bit Florey was visited by a friend from the Rockefeller Foundation on a sort of routine visit and to cut the story short the Rockefeller supported him and suggested that he should go over to the States and try to get the commercial firms interested. America wasn't at war then, you see, and I was lucky enough to be taken with him because I'd got all the notes about growing the stuff and what had been tried and what hadn't and so on and the various things we did, you see.

MB And so effectively you and Florey went over and really initiated a penicillin industry in America?

NH Well, I suppose you could say that, but the Americans were a very… they'd had a little work done by a man called Martin Dawson in New York and this had been published, but he'd used his penicillin to treat a case of bacterial endocarditis, which unfortunately is not a very sensitive strep; [*Streptoccocus*] *phyllidans* is not very sensitive to penicillin, and he hadn't been successful. Yes, Florey went over and just visited a number of firms who were very interested. Nearly all the firms were interested; some were very interested, Merck, Squibb - I can't give names because I don't know them all - Commercial Solvents was an early one, and Florey didn't mind whether so-and-so got a patent or not. This was, patenting was a question which had come up in England. Chain was very keen to patent it, but ...

MB Florey just wanted it produced?

NH Florey wanted it produced. Florey was prepared to try and get it patented but there wasn't any money for this purpose, for that purpose, and it's very doubtful that you could have drawn up a patent which would hold water, which would hold.

MB Norman, we are running towards the end of our time now. Just one final

point: the clinical trials - I know you commented on them before - they couldn't have ever taken place these days, could they? In a few words...

NH Oh yes. Well, yes, that was, if the Committee for the Safety on Medicines had to be in existence, penicillin wouldn't have been eligible for testing and so we were immensely lucky that it didn't exist in those days. And there was so much luck in the thing. I mean, if it had been tested in guinea pigs, this is very well brought out in some remarks by Gordon ...

MB But, anyway, the luck was colossal?

NH The luck was colossal.

MB Norman, we are getting towards the end of the interview and I have to thank you very much for going through those rather remarkable years of early penicillin work. Thank you very much.

NH Thank you.