

The Committee on the Safety of Drugs: a personal account by Professor Bill Inman

Professor William H W (Bill) Inman (1929 -2005), qualified in medicine at Cambridge in 1956. After a short period in clinical practice, he became a medical adviser to Imperial Chemical Industries. In 1964 he joined the Ministry of Health's Committee on Safety of Drugs as Senior Medical Officer, later Principal Medical Officer. He was principally responsible for developing its voluntary reporting system of adverse reactions to drugs, and became Medical Assessor of Adverse Reactions Sub-Committee. He devised a number of procedures and protocols to detect risks of drug treatment, and played a part in developing both national and international drug safety monitoring.

Interview conducted by Dr Stephen Lock, for the History of Twentieth Century Medicine Group, February 1996

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Dr Stephen Lock: One of the key figures in the early days of regulating new drugs in the United Kingdom is Professor Bill Inman. Sadly he had bad polio when he was a medical student and he now has to spend all his time in a wheel chair, and so I went down to see him at his home outside Southampton to talk about the beginning of the Committee on the Safety of Drugs. So can you tell us how it all started?

Professor Bill Inman: I suppose the first indication of trouble was 1956 when Dr Heinrich Mückter of Chemie Grünenthal invented thalidomide. It was marketed in this country in the following year as Distaval and in Germany as Contergan and two or three years passed really before Bill McBride in Australia spotted an association between thalidomide and congenital abnormalities. In the same year Dr Widukind Lenz said he'd seen 52 babies in Germany with these limb problems. At the time I was working at ICI in their medical department and I discussed this at meetings in the Association of Medical Advisers in the Pharmaceutical Industry (AMAPI) and so it was known that I was interested in setting up some sort of scheme to monitor new drugs. Out of the blue a letter came from Sir Derrick Dunlop at the end of 1963, inviting me to show an interest in the new Committee which he was forming.

Lock: The Committee had been set up by then?

Inman: It had already been established. As far as adverse reactions were concerned the total number of yellow cards was the contents of one shoe box, literally, when I joined, and I would in fact have been in right at the beginning had I not been late starting – I was ill. I had been working for ICI for about five years by that time. My career was very much dictated by the fact that I had had polio as a medical student and it seemed that it was dermatology, psychiatry or something like laboratory work, which didn't appeal to me. And I had an ICI background, as it had been in the family since the early 1920s. My father was a founder member of the company.

Lock: So you got to the Committee in 1964, and what happened then?

Inman: Eventually arriving in 1964, by which time yellow cards were just beginning to trickle in and there were various bits of publicity to encourage that. Sir Derrick Dunlop himself wrote a letter to all doctors, circulated it with yellow cards, and they started to come in. I can't remember the exact rate but it was a thousand a month easily, maybe more than that. Derrick Dunlop was the Chairman of the main Committee and he operated three Subcommittees. The first was a Subcommittee on Toxicity – the Chairman of that was Professor Frazer; the second was the Clinical Trials Subcommittee, which was chaired by Bob Hunter; and the third was Adverse Reactions with Leslie Witts. I think it was really the Subcommittees that the attention was focused on when things went wrong as with the Pill and with asthma deaths and so on. We got most of the press attention.

Lock: Leslie Witts was the distinguished professor at Oxford?

Inman: He was a specialist in blood dyscrasias and I think that was felt to be one of the target areas we might get involved in. I liked him very much indeed. He was very quiet, very considerate, a perfect gent, in fact. I was very fond of him.

Lock: And who else was working there?

Inman: At the moment I can recall, it's now nearly 30 years, Ekke Kuenssberg, a GP in Edinburgh, Owen Wade who at that time was in Belfast, Bill Mushin in Cardiff – an anaesthetist and Michael Linnett. And Roy Goulding put in an occasional appearance from the National Poisons Information Service.

Lock: How exactly did you work?

Inman: The keystone of the whole operation was the yellow card, which was a very simple business reply card, folded double and glued round the edge for security and confidentiality, and these were issued periodically to doctors who were encouraged to report any suspected reaction to a new drug and any serious reaction to any drug, however old or new it was. And it was an entirely voluntary system. They didn't get paid for it and on the whole, I think, they responded very well, but of course the yellow cards really grossly underestimated the probable numbers of events which were occurring. The first drug that struck us as dangerous was benziodarone, used in heart disease, and it quite obviously caused jaundice. The company was persuaded to remove that voluntarily without any pressure. It was kept under wraps. There wasn't much publicity. We didn't seek publicity. Another good example is Dytransin which was the trade name for ibufenac which is still on the market. Exactly the same thing. Two waves of jaundice occurred, once when they issued it to hospitals and again when they issued it to general practitioners. Boots had no difficulty taking that one off the market straightaway.

Lock: When the drug was taken off the market, did you issue warnings to GPs

Inman: Several times. We issued the Adverse Reactions Series, which pharmaceutical companies called the Yellow Peril. The first was on monoamine oxidase inhibitors. We put up one on chloramphenicol which wiped out aplastic anaemia virtually, except for the odd patients who'd used the stuff on holiday in France or Spain if they got a cold and came back to die in England.

Lock: And then there was the Pill.

Inman: The Pill first impacted about 1965 when there were odd anecdotes in various journals. I think the first was from a man called Jordan in the West Country. He described three cases, probably pulmonary embolism, and by the beginning of 1966, the estimated incidence was what you'd expect from the Registrar General's figures if we had 100 per cent reporting. Clearly, we didn't believe that we were getting 100 per cent reporting. So we had a prima facie case that the Pill might be causing thrombosis. With some difficulty I organized a national study, picking out all deaths within the childbearing age group that would occur in 1966. I had to wait for them to occur and follow them up. By that time I had recruited a team of field workers – we called them Derrick's Dolls – they were personable, mostly young, doctors who visited the general practitioners to get the information at first hand, which the doctors appreciated. We got the cause of death from death certificates, and I used the same team to follow up the yellow card reports. So these girls went out and collected I think about three or four hundred cases and at the beginning of 1967 there looked like at least a six-fold, maybe an eight-fold, excess of Pill users. We took living controls, at the same practices, and this was a major first for the Committee.

Lock: When was this published?

Inman: It was eventually published in 1968. But quite a lot happened before that. Way back in 1965, before we had even shown that there was a statistically valid case against the Pill, I had already spotted a difference between mestranol and ethinyloestradiol which I thought was possibly chemical. I didn't do very much about it until considerably later. Late in 1966 Leslie Witts and I went to the MRC to try to encourage them to set up parallel studies, because one set isn't enough, and we did it with great difficulty. They were persuaded to do a study looking at hospital admissions, not deaths. And we persuaded the College of General Practitioners to do the same thing and they did a study, a small one, mainly on superficial venous thrombosis in general practice.

Lock: What was the difficulty? You said you had some difficulty.

Inman: Well, they didn't really seem to be very interested.

Lock: The MRC wasn't interested?

Inman: Not at first, no. We had to make two visits to them altogether. But once I got some data to show them they were a little bit more impressed. This basically was Richard Doll and Martin Vessey, whom I hadn't met at that time. So we got together and these three different studies were supposed to be published early in 1967 as an MRC Report. But the Royal College of General Practitioners had in the meantime jumped the gun. In order to be in first, they published their little series so we were forced, I think, to publish the MRC Report prematurely. This was May 1967. Anyhow to cut a long story short the Vessey and Doll paper and our paper, by Martin Vessey and I, were published on the same day, in the same edition of the British Medical Journal, and things then quietened down a bit after the initial media response. I went back to the yellow cards. I had about three or four thousand of them by that time, and they used to go home in a suitcase every night and were arranged in piles according to first the dose, the chemical, the age of the women, how many children they'd had, and suddenly the penny dropped that where the two hormones were equally distributed in the market, and I got that data from the Intercontinental Medical Statistics Ltd, there was a 52:48 per cent split.

There was a huge relative excess, of the larger doses, irrespective of what chemical it was. And at that stage I hadn't looked at progesterone and I advised the authorities not to publish anything until we'd had time to do that. But Mr Crossman wanted something to say in Parliament and just before Christmas in 1969, 'something' as you'd say in America 'hit the fan' and the Committee was heavily criticized.

Lock: Can you tell us just a bit more about this. Because there was a leak, wasn't there, to Chapman Pincher of the Daily Express?

Inman: Yes. I predicted that if we held a conference with members of industry, because they are legally obliged to inform their masters in America, then the FDA would have the story within 24 hours. I also predicted that there would then be an automatic leak to the Washington Post through Mr Morton Mintz. I think they used him as a sort of safety valve, really to take the heat out of some of these things. But I was wrong because Chapman Pincher had it a day earlier. And the doctors hadn't been informed. The Committee was then forced to issue an urgent Yellow Peril, which is a piece of A5 paper typed on an ordinary typewriter, and tried to fob that off as one of the leaflets in their Adverse Reactions Series. This fooled nobody and the doctors were even more insulted after receiving this pathetic little bit of paper. The end of the story really was I got the nickname of 'father of the minipill' in respectable circles and 'Bill the Pill' in the eyes of the industry, who weren't too pleased about this. It's alleged that a lot of women came off the Pill. George Godber, and I never knew whether he was fooling or not, claimed nine months later that I had caused a slight eruption in the population. I said 'Well, you know, I am a man that can still move around, I'm probably the father of a lot more than I bargained for'.

Lock: So this almost brings us to the end of the Committee on Safety of Drugs? Then we get the Medicines Act?

Inman: The main paper on oestrogen dose was published in 1970 as soon after the Christmas furore as we could get it out, by which time I had been to Sweden and to Denmark and got all their data and these showed exactly the same thing. Then from September 1971, I think it was, the Medicines Act became operative and everything changed.

Lock: What do you think the main lessons we learnt from this period?

Inman: I think I learnt three things. First of all, the value of independence; secondly, the need for transparency, the ability to communicate freely with the people outside; and thirdly the need for more information about the efficacy of drugs. If I take the last one first, I think that was a serious defect in the Act, probably initiated by pressure from the industry, but many countries now insist that a new drug has to have a margin of superiority or to be very considerably safer than existing drugs. In other words, you have got to have the complete equation—relative safety and relative efficacy, and the Medicines Act really prohibits these considerations. As far as the independence is concerned, I always felt that it was a great mistake to expect doctors and other scientists working in the department to be loyal to a scientifically independent committee on the one hand and to the Minister of the day on the other hand. There may be perfectly good reasons why ministerial decisions apparently clash with the scientific decisions and if they were separate these problems wouldn't arise. I think the doctors now working at the Department find themselves more as medical

advocates rather than being free to communicate scientifically.

Lock: Thank you Bill very much.

Inman: My pleasure Stephen, thank you very much.