REVIEW

50th anniversary of the first clinical trial with ICI 46,474 (tamoxifen): then what happened?

V Craig Jordan

Dallas/Ft. Worth Living Legend Chair of Cancer Research, Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Correspondence should be addressed to V C Jordan: vcjordan@mdanderson.org

Abstract

Following the discovery and approval of the oral contraceptive, the pharmaceutical industry sought new opportunities for the regulation of reproduction. The discovery of the first non-steroidal anti-oestrogen MER25, with antifertility properties in laboratory animals, started a search for 'morning-after pills'. There were multiple options in the 1960s, however, one compound ICI 46,474 was investigated, but found to induce ovulation in subfertile women. A second option was to treat stage IV breast cancer. Although the patent for ICI 46,474 was awarded in the early 1960s in the UK and around the world, a patent in the USA was denied on the basis that the claims for breast cancer treatment were not supported by evidence. A trial at the Christie Hospital and Holt Radium Institute in Manchester, published in 1971, showed activity compared with alternatives: high-dose oestrogen or androgen treatment, but the US Patent Office was unswayed until 1985! The future of tamoxifen to be, was in the balance in 1972 but the project went forward as an orphan drug looking for applications and a translational research strategy was needed. Today, tamoxifen is known as the first targeted therapy in cancer with successful applications to treat all stages of breast cancer, male breast cancer, and the first medicine for the reduction of breast cancer incidence in high-risk pre- and post-menopausal women. This is the unlikely story of how an orphan medicine changed medical practice around the world, with millions of women's lives extended.

Key Words

- ▶ breast
- ▶ endocrine therapy
- ▶ estrogen receptor
- ▶ hormone structure/function
- ▶ SERM

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Introduction

History is lived forward but is written in retrospect. 'We know the end before we consider the beginning and we can never wholly recapture what it was to know the beginning only (CV Wedgewood, *William the Silent*). That is unless one has lived through the evolving applications of ICI 46,474 (tamoxifen)'.

Tamoxifen, used as a long-term adjuvant therapy, burst onto the international scene in the 1990s ([Early Breast Cancer Trialists' Collaborative Group 1998](#)). The Oxford overview analysis of the international adjuvant clinical trials in breast cancer, was the brainchild of Richard Peto who successfully obtained the cooperation of every

principal investigator of adjuvant tamoxifen clinical trials worldwide. They would all provide their raw data for inclusion in the overview analysis that would be updated every 5 years. The publication in 1998 ([Early Breast Cancer Trialists' Collaborative Group 1998](#)) not only focused specifically on the worth of tamoxifen as a targeted therapy that saved lives, cheaply and effectively, but also addressed whether there were any unacceptable major side effects. The clinical evidence was clear: tamoxifen was only effective as an adjuvant therapy in oestrogen receptor (ER) positive breast cancer and longer adjuvant therapy (5 years) was better than shorter (1–2 years) therapy.

Concern about an increased incidence of fatal endometrial cancer was calculated to be manageable. A gynaecological examination before adjuvant tamoxifen therapy became the medical standard of care.

Powles *et al.* (1989) took a bold step by initiating a pilot trial to deploy tamoxifen to prevent breast cancer in high-risk women. A decade later, this novel strategy, based on translation research (Jordan 1976b) and the observation that tamoxifen reduces the development of contralateral breast cancer during adjuvant therapy (Cuzick & Baum 1985), was supported by the publication of three randomized clinical trials (Fisher *et al.* 1998, Powles *et al.* 1998, Veronesi *et al.* 1998) and a complimentary study by Cuzick *et al.* (2002). All demonstrated that tamoxifen could significantly reduce the incidence of primary breast cancer. The Food and Drug Administration (FDA) in the USA approved tamoxifen as the first medicine to reduce the risk of breast cancer in pre- and post-menopausal women. A similar approval by the National Institute for Health and Care Excellence (NICE) followed in the UK. A blockbuster medicine was born for international use and ‘tamoxifen’ became a household word worldwide.

Despite the eventual enormous medical and financial success of tamoxifen, this medicine was not a preplanned priority of the discoverer and manufacturer, Imperial Chemical Industries (ICI), Pharmaceuticals Division (Jordan 2003, 2006) headquartered at Alderley Park, Cheshire UK (Hill 2016).

Here, we will embark upon a journey through the essential grafting of unplanned interpersonal relationships across continents and professional friendships that together produced the absolute commitment of a few individuals, who made an orphan drug come alive. This is that story.

An international search for a ‘morning-after-pill’ following the success of the oral contraceptive

On June 23, 1960, The FDA approved the use of the oral contraceptive. This simple pill, a mixture of an orally active synthetic oestrogen and progestin, change the world, and has the distinction of being the first drug to be approved for human use without a disease. This feat of pharmacology would not have been possible without first solutions being found to create orally active oestradiol and progesterone analogues, in the decade before clinical trials of the pill started in 1955. But laboratory testing was all-important too.

In 1944, Drs Gregory Pincus and Hudson Hoagland chose to create a private research institute dedicated solely to the search for an oral contraceptive. This was the Worcester Foundation for Experimental Biology (WFEB) in Shrewsbury, Massachusetts. They hired Dr M C Chang to be their principal reproductive biologist for the project, to provide evidence, from animal models, to justify the selection of an appropriate synthetic progestin. Dr John Rock was in charge of clinical testing and this was successful. However, the support of Margaret Sanger, a social activist for female contraception, and the wealthy philanthropist Katherine McCormack were essential for progress in medical science to occur. As a result, the WFEB was forever referred to as the ‘home of the oral contraceptive’. (Speroff 2009) We will revisit the WFEB again.

In the late 1950s, a young endocrine biologist with the Merrell Company in Cincinnati, Ohio, Dr Len Lerner, discovered the first non-steroidal anti-oestrogen MER25 (Fig. 1) (Lerner *et al.* 1958). He went on to discover a triphenylethylene-based anti-oestrogen called clomiphene (Fig. 1) (Holtkamp *et al.* 1960). However, the finding that these simple compounds were post-coital contraceptives in laboratory rodents, resulted in multiple companies discovering their own potential ‘morning-after-pill’. The international pharmaceutical companies, including ICI Pharmaceuticals Division at Alderley Park, Cheshire, initiated research programmes to harmonize with the times in the era of ‘make love not war’ in the early 1960s. An occasional morning-after-pill would have a market for millions.

Unfortunately, a contraceptive in a mouse or a rat did not predict the properties of a morning-after-pill in young women. In fact, the medicines clomiphene (Greenblatt *et al.* 1961) and tamoxifen (Klopper & Hall 1971) induced ovulation and guaranteed the very thing they were designed to prevent!

Dr Arthur L Walpole (Fig. 2) (Jordan 2006, Hill 2016) was the head of the Alderley Park fertility regulation programme that discovered ICI 46,474. Dr Dora Richardson (Fig. 2) was the talented organic chemist who meticulously separated the geometric isomers of the triphenylethylene named ICI 46,474 (*trans* isomer) and ICI 47,699 (*cis* isomer) (Fig. 1) (Bedford & Richardson 1966). The molecules were found to have opposite pharmacological actions: the *trans* isomer was an anti-oestrogen but the *cis* isomer was an oestrogen (Harper & Walpole 1966). The pharmacology was further complicated because ICI 46,474 was an oestrogen in mice but predominantly, an anti-oestrogen in rats; ICI 47,699 was an oestrogen in both species.

Figure 1

The comparative structures of early non-steroidal anti-oestrogens. Triparanol, a cholesterol-lowering medicine, marketed in the early 1960s, is illustrated to demonstrate the similarity of structure with the first non-steroidal anti-oestrogen MER25. The structure of the anti-oestrogen tamoxifen and its oestrogenic-cis isomer are compared with the geometric isomers of clomiphene.

However, before publication in industry, patents must be written and submitted worldwide. The patent was stated clearly and awarded in the UK in 1965 (and everywhere in the world except for the USA). The patent (1965 as UK patent GB1013907) stated: 'The alkene derivatives of the invention are useful for the modification of the endocrine status in man and animals and they may be useful for the control of hormone-dependent tumours or for the management of the sexual cycle and aberrations thereof. They also have useful hypocholesterolaemic activity'.

The patenting difficulties for ICI in the USA, was that the Merrell Company had conducted defensive patenting on all triphenylethylene derivatives and had clinical evidence that clomiphene, in a small number of breast cancer patients, had positive clinical outcomes (Herbst *et al.* 1964).

Walpole had a longstanding interest in carcinogenesis and cancer research (Jordan 1988a) and had previously collaborated with Dr Edith Patterson (Walpole & Paterson 1949) at the Christie hospital in a study of high-dose oestrogen to treat breast cancer. This is where ICI

Figure 2

The principal staff members in the Fertility Control Program at ICI Ltd. Pharmaceuticals Division. From left to right: Arthur L Walpole (Walop) the head of the fertility control programme, Dora Richardson, the chemist for the programme charged with synthesizing test compounds and Michael J K Harper the reproductive biologist who tested compounds in laboratory animals.

Pharmaceuticals Division would discover the value of tamoxifen for the treatment of Stage IV breast cancer (Cole *et al.* 1971).

A new anti-oestrogenic agent in late breast cancer an early clinical appraisal of ICI 46,474

The goal of the clinical study was to provide definitive evidence that the anti-oestrogen ICI 46,474 had potential for the treatment of metastatic breast cancer. Not only would response rates be documented in patients, who had previously been treated with high-dose hormone therapy (paradoxically high-dose oestrogen therapy was the standard of care since the mid-1940s (Haddow *et al.* 1944) but also side effects would be monitored closely. Harper and Walpole (Harper & Walpole 1967) were well aware that ICI 46,474 was anti-oestrogenic in rats with oestrogen-like effects but was predominantly oestrogen in mice. Administration to monkeys revealed anti-oestrogen actions. Would ICI 46,474 be an anti-oestrogen in breast cancer patients?

A total of 46 post-menopausal patients received either 10 mg or 20 mg daily of ICI 46,474 for longer than 3 months. Eleven of the 46 patients received 10mg daily and four were found to respond. Nineteen patients failed to respond, and 17 patients had indeterminate or incomplete responses. In 7 of the patients judged to respond, there was healing of a malignant ulcer or a malignant infiltration regressed. Pulmonary metastases in two patients resolved and a lytic bone metastasis in one patient reosified. Overall, 10 patients (22%) showed a clear response. In the 46 patients, a total of 19 side effects were noted with hot flushes and gastrointestinal intolerance being the most frequent. Only two patients stopped therapy, but one was found to be unable to take tablets of any kind.

The response rates of the 46 Stage IV breast cancer patients given ICI 46,474 were compared with hospital records of breast cancer patients treated with either high-dose oestrogen (64 patients) or high-dose androgen (60 patients). Response rates were comparable: high-dose oestrogen (25%), high-dose androgen (16%) and ICI 46,474 (22%). By contrast, the discontinuation rate for side effects favoured ICI 46,474: high-dose oestrogen (18%), high-dose androgen (8%) ICI 46,474 (4%).

Concerning routine blood test, no alterations persisted but one observation was important. Estimates of cholesterol and desmosterol ratios were normal.

This was a positive finding that would impact on extended adjuvant therapy with ICI 46,474 in the future.

The historical background, that created a clinical catastrophe in the US, is worthy of note. In the 1950s and 1960s coronary heart disease was a major priority for the pharmaceutical industry. In the 1960s the Merrell Company marketed a product triparinol (Fig. 1), to reduce the levels of circulating cholesterol (Hollander *et al.* 1960) but was found to cause acute cataract formation (Laughlin & Carey 1962). This toxicity was linked to the accumulation of desmosterol as a consequence of blocking cholesterol biosynthesis (Avigan *et al.* 1960).

By comparison, clomiphene an unseparated mixture of *cis* and *trans* geometric isomers (Fig. 1) did produce increases in desmosterol in animals. This led to the decision by Merrell, not to pursue the use of clomiphene for the treatment of breast cancer.

With this breast cancer treatment database in 1972, surely the patents for tamoxifen would be issued in the US. But no. Nevertheless, it was a year that would decide the fate of ICI 46,474.

Around Easter 1972, all the clinical research projects were reviewed at a meeting at Alderley Park. The objective was to allow the marketing team to assess the commercial value of ICI 46,474. A new fact had come to light; the industrial synthesis and purification of the pure *trans* isomer was complex and lengthy. The treatment of a number of gynaecological conditions, the induction of ovulation (competing with the established agent clomiphene), and as a palliative agent for the treatment of Stage IV breast cancer after the menopause, were the major topics evaluated to provide a realistic projection of commercial success.

In May 1972, at a meeting to decide the future development of ICI 46,474, few advantages could be recommended to develop the medicine for human use. By contrast, reasons not to proceed were profound: the drug could not make a profit to ever reimburse manufacturing and development costs. The breast cancer application was bleak as only one in three Stage IV breast cancer patients would respond but only for a year. Pricing against the standard of care high-dose oestrogen therapy, was an issue as oestrogen therapy, was very cheap. Additionally, a worldwide marketing strategy seemed remote as the country with the most lucrative market, the USA, still had not awarded a patent despite the definitive study at Christie published in 1971 (Cole *et al.* 1971) and a follow-up study in progress on dose responses by Dr Harold Ward to be published in 1973 (Ward 1973). Who would market a product in the USA without a patent?

It was Dr Arthur Walpole who made his views known to the Division Medical Director, and the Division Chairman, because he would not be present at the critical meeting in 1972. Based on the lack of profitability of ICI 46,474 the Deputy Chairman, Eric Hoggarth proposed the project be terminated. It was then suggested, by the Medical Director, Colin Downey, that it would not be good for the image of ICI Pharmaceutical Division, if the product was not made available. The project remained alive but with little enthusiasm (Hill 2016). Nolvadex (tamoxifen) was approved for the treatment of metastatic breast cancer in the UK in 1973.

Despite having no patent, tamoxifen was passed to ICI's new American subsidiary Stuart Pharmaceuticals in Wilmington, Delaware. Here, Lois Trench became (Fig. 3) the drug monitor for tamoxifen to obtain approval from the FDA. It was 1972 and the stage was set to start translational research that would propel tamoxifen to become the first targeted therapy in cancer that would save millions of women's lives. Mothers would see their children grow up and grandmothers would see their grandchildren grow up.

Life is what happens to you when you are making plans to do something else!

As a teenager, I was obsessed with chemistry, and in a moment of weakness my mother allowed me, at the age of 12, to convert my bedroom into a chemistry laboratory – a real chemistry laboratory! Experiments could get out of hand: I nearly killed myself with chlorine gas and I repeatedly threw experiments out the bedroom window, leaving the curtains on fire. My mother had a philosophical view: at least we know where he is!

I continued my education after Moseley Hall Grammar School in Cheshire, in the Department of Pharmacology at the University of Leeds. I was thrilled to learn medicinal chemistry and pharmacology. I took to it like a duck in water. But what to do to gain further experience in pharmacology during the summer holidays?

I lived in Cheshire near Alderley Park, ICI Pharmaceutical Division. In 1967 I had read in Nature that Dr Steven Carter, at Alderley Park, had discovered an natural product that made cancer cells extrude their nucleus (Carter 1967). Very interesting! Why not work at Alderley Park in the summer, but how to get a job? I decided to take the bus from my home in Bramhall to the gates of Alderley Park. I knew there was a phone box there, so I put through a call to Dr Carter and I told him

Figure 3

The 3-day event at Northwestern University honouring Professor V Craig Jordan as the inaugural Diana, Princess of Wales Professor of Cancer Research. Lois Trench (left) was the clinical monitor for tamoxifen in the USA who achieved FDA approval in record time on December 31, 1977. Professor Elwood V Jensen (right), pioneer in estrogen receptor discovery in breast cancer, former Director of the Ben May Cancer Research Laboratory at the University of Chicago, former Director of the Worldwide Ludwig Institute for Cancer Research, Zurich, Member of the National Academy of Sciences and Lasker Award winner.

about my plan to work with him! 'Next time you are back from the University of Leeds, arrange to come and see me for an interview' 'I am outside the front gates of Alderley Park now', I replied – I was in and got the summer job.

It was during this time, I met two scientists who would shape my future career.

In the laboratory across the hall from Dr Carter's laboratory, was Dr Arthur L Walpole's laboratory with his technicians Rosemary Chester and Barbara Valcaccia. He and Dr Michael JK Harper had just published their discovery on a new anti-oestrogen ICI 46,474 and its actions as a post-coital contraceptive in rats (Harper & Walpole 1967). Mike Harper (Fig. 2) had since left ICI Pharmaceuticals Division and had gone to the WFEB to study prostaglandins as contraceptives. We will meet Mike Harper later.

Next door to Steve Carter's laboratory was the cardiovascular laboratory headed by Dr Michael Barrett who had taken over from Dr James Black (years later to be my mentor), who had discovered β blockers for adrenaline and H₂ blockers for histamine. Five years later Barrett, Walpole and Harper would, together, shape my future career in cancer pharmacology and support my translational research ideas for the clinical use of tamoxifen.

In 1969, armed with a first class honours degree from the University of Leeds, Department of Pharmacology, and a scholarship from the Medical Research Council (I was on

the waiting list, but someone returned their scholarship. I was the last lucky person to have funding for PhD training in the country!). I had chosen to address a revolutionary idea. My supervisor in the Department of Pharmacology, Dr ER Clark had read that the ER was a soluble protein and could easily be extracted from the uteri of immature rats (Toft & Gorski 1966, Toft *et al.* 1967). He explained that I would extract and purify the ER and crystallize the protein with oestradiol or a non-steroidal anti-oestrogen, take the crystals to the Astbury Department of Biophysics for x-ray crystallography and discover the mechanism of action of a drug; in this case a failed contraceptive! I rapidly discovered that this would not work (molecular biology had to be invented to create a part of the pure ER protein, that is, the ligand-binding domain). Most importantly, all the then available anti-oestrogens had too low affinity for the ER (Korenman 1970). In fact, low-affinity binding was believed to be a requirement for a non-steroidal anti-oestrogen to block estrogen action. High-affinity anti-oestrogens had to be discovered in 1977 (Jordan *et al.* 1977) to achieve the X-ray crystallography of an anti-oestrogen ER complex. This was partly achieved nearly 30 years later (Brzozowski *et al.* 1997) at the University of York by Rod Hubbard and an international team of scientist. Obviously, this project was not possible to be accomplished, even by an ambitious PhD student in the late 1960s!

Instead, I was steered, by Dr Clark, towards a study of the structure–function relationships of the non-steroidal anti-oestrogens. Then the unexpected occurred. Dr Michael Barrett (remember him from ICI, Alderley Park) accepted the position as Chair of the University of Leeds, Pharmacology Department and he became Professor Barrett. As a PhD student, I chose to give lectures in pharmacology and Professor Barrett talent spotted me to be a member of his faculty as a lecturer, with an annual salary of £1995. But first, I had to have my PhD examined and I had to go to America for 2 years to get my BTA (Been to America).

However, Professor Barrett discovered that no one in the UK wanted to waste their time reading a thesis on ‘failed contraceptives’. He solved that problem by inviting Dr Walpole, from Alderley Park who, after some issues with the University about ‘being from industry’, accepted.

Dr Barrett also solved the problem of my BTA. He arranged for me to work for 2 years as a visiting scientist at the WFEB with his friend from Alderley Park; Mike Harper (Fig. 2). He was in charge of a research programme on prostaglandins (he was also a copatent holder of ICI 46,474). I remember his trans-Atlantic phone call to me very well ‘Can you come in September, will \$12,000 a year tax free be sufficient, and will you work on prostaglandins?’

‘YES, YES, YES’ was my reply and I rushed off to the library to find out what ‘prostaglandins’ were! I had a big grin on my face all day as I had just been offered a job for more than three times my Leeds lecturers’ salary but with no tax!

When I arrived at the WFEB, I discovered that Mike Harper had arranged to leave *immediately* to be Director of Contraception Research at the World Health Organization in Switzerland. I was introduced to my new supervisor Dr Edward Klaiber. He was an MD interested in the clinical aspects of male reproduction. He explained ‘you can do anything you want as long as you get funding, but you must work on prostaglandins for some of the time to justify your salary’. As a completely inexperienced, newly graduated PhD student who only knew about failed contraceptives, there were no real alternatives. I was a pharmacologist with a goal to complete significant research to get a drug on the market to treat cancer. Why not consider ICI 46,474 for the treatment of breast cancer? Naturally I knew nothing of all of the struggles to keep ICI 46,474 alive at Alderley Park during 1972, but a phone call to Dr Arthur Walpole filled in the gaps. He could not fund me in the USA, but he arranged for me to be contacted by Lois Trench (Fig. 3) the newly appointed drug monitor for ICI 46,474.

This started a relationship with ICI Pharmaceuticals division and Stuart Pharmaceuticals that achieved the impossible in translation research and Lois with FDA approvals. But how was I to start a career in cancer research?

As luck would have it, one of the Giants of ER in breast cancer was to visit the WFEB. He was Dr Elwood Jensen (Fig. 3). Director of the Ben May Cancer Research Laboratory, at the University of Chicago. Although I had not changed the world of science with my PhD in failed contraceptives, we spent an afternoon going over every page of my thesis. I told him what I hoped to achieve with ICI 46,474 by converting it into a breast cancer drug. I was thrilled when he agreed to help me in my quest, he arranged for me to visit the Ben May laboratories to learn analytical techniques with his chief technician, Sylvia Smith, to determine the breast tumour ER. His right-hand man, Dr Eugene DeSombre taught me the dimethylbenzanthracene (DMBA)-induced rat mammary carcinoma model, so I could establish, for the first time, a translation research strategy for ICI 46,474 on the brink of becoming tamoxifen. The DMBA-induced rat mammary carcinoma model was the standard laboratory model (Huggins *et al.* 1961) used to study potential anti-cancer agent. At that time in 1973, I could never have entertained the thought that Elwood and

I would be the winners (2002) of the inaugural Dorothy P Landon AACR prize in Translational Research for extraordinary accomplishment in translational research (Jensen & Jordan 2003) and colleagues as members of the National Academy of Sciences in the USA. I was a new post-doctoral visiting scientist at the WFEB with no publications!

Tamoxifen was launched in the UK in September 1973. But in the USA, it was still Mission Impossible. The US Patent Office was not persuaded by the Christie study (Cole *et al.* 1971) or with the additional clinical study of Dr Harold Ward on the value of tamoxifen to treat Stage IV breast cancer (Ward 1973). Stuart Pharmaceutical/ICI Pharmaceuticals Division chose to move ahead with ICI 46,474, a medicine with no patent protection.

When I first met Lois Trench in 1973, she was just back from the Soviet Union, where she had been a member of the US women's rowing team. Lois was a focused competitive athlete with a will to win. Her task was to obtain FDA approval for tamoxifen in record time. She did, and tamoxifen was FDA approved for the treatment of Stage IV breast cancer in post-menopausal women on December 31, 1977.

Lois's strategy was to ensure that the science behind tamoxifen's mechanism of action should drive clinical applications. To this end, she provided a collection of frozen breast cancers for me at the WFEB. With these, I planned to establish, once and for all, that tamoxifen blocked the binding of oestradiol in the breast tumour ER. To a pharmacologist, this was simple drug-receptor pharmacology, but other scientists had been unsuccessful in demonstrating this necessary first step in receptor pharmacology. The paper was approved for publication in the *European Journal of Cancer* in 1975 (Jordan & Koerner 1975).

Lois and I travelled to meetings of the Eastern Cooperative Oncology Group in Miami in 1974 and subsequently at Jasper National Park in Alberta. There, I presented my views on the future potential of tamoxifen not only to treat Stage IV breast cancer but also to prevent breast cancer. I had been putting the DMBA rat, mammary carcinoma model, to good use at the WFEB. I had data! As a result, Lois offered to sponsor my attendance at the International Congress of Steroid Endocrinology in Mexico City in the summer of 1974. The abstract (Jordan 1974) and the subsequent publication in the *European Journal of Cancer* (Jordan 1976b) would be the first to demonstrate the potential of tamoxifen to prevent breast cancer in women. The proof of this translational research, plus a mechanism to block the ER from being activated to

make breast cancer grow, were the clinical trials designed and published by Trevor Powles, Umberto Veronesi, Bernard Fisher, and Jack Cuzick.

Before I left the WFEB, in the autumn of 1974, I learned an important scientific lesson for future career development in academia. Dr Eliahu Caspi made an appointment for me to meet him to discuss my future. Dr Caspi was a senior member of the WFEB and a major contributor to research on steroid biosynthesis. The meeting did not go well but the lesson was learnt. He stated he had been charged with my evaluation for a position to stay at the WFEB rather than return to the University of Leeds. He explained that productivity in prostaglandin research with a post-doctoral fellow Dr Daniel Castracane and my clinical research with a WFEB alumnus Dr Tom Pokoly, was apparent to all. Also, there was my nascent research with the failed contraceptive ICI 46,474 to become a drug to treat breast cancer. However, he had examined my Curriculum Vitae and there were no publications at all! It was the summer of 1974. Stunned by this turn of events, I replied 'but I haven't discovered anything yet!' His advice to me was life-changing 'tell them the story so far. Each paper should be linked to other related studies to create a theme for a topic. In this way, you will become known for a research area'. I did not get an offer for a job at the WFEB, but I already had a tenure track appointment in the University of Leeds, Department of Pharmacology. Most importantly, I had learned an important lesson; I set about correcting this deficit. As a result, I built a bibliography of my 2 years during my BTA with a number of refereed papers: prostaglandins and tamoxifen. I have never stopped writing papers ever since. In 2002 I was the inaugural Dr Eliahu Caspi Memorial Lecturer in Chemical Biology at WFEB now part of the University of Massachusetts. His advice to me made this honour possible.

A translation research strategy at the university of leeds and discoveries

I was supported by my Department Chairman Professor Michael Barrett and most importantly Dr Arthur Walpole to create a translation research path for tamoxifen. Walpole was committed to my goals by continuing to act as scientific liaison with Alderley Park during the next 5 years of our University of Leeds/ICI Pharmaceuticals Division/Joint Research Scheme. Their investment in my laboratory and development of my research ideas would put the pieces in place for future clinical development and

all my new career opportunities. I had two unanswered questions that I chose to address at Leeds.

Question 1: At the WFEB, I was surprised that tamoxifen was such a potent anti-oestrogen *in vivo* but it only had a low binding affinity for the ER. Tamoxifen also had a strange species-specific pharmacology: it was a weak partial oestrogen agonist in rats with predominantly anti-oestrogenic properties but in mice it was an oestrogen (Harper & Walpole 1966). What is the pharmacology of the identified metabolites of tamoxifen in animals and humans (Fromson *et al.* 1973a,b)? Perhaps there was species-specific metabolism to oestrogens?

Question 2: Is it possible to cure animals with DMBA - induced rat mammary carcinoma? Dr Marc E Lippman was Head of the Breast Cancer Program at the National Cancer Institute in Bethesda, MD. Lois Trench at the new ICI Americas, had ensured that Marc was aware of their new anti-oestrogen tamoxifen going into clinic trial in order to obtain FDA approval. Marc would dissect the mechanism of action of tamoxifen in breast cancer. In 1975 he stated in his publication (Lippman & Bolan 1975), that tamoxifen was cytotoxic at high concentrations on the growth of the ER-positive cell line MCF-7. Could I demonstrate the cure of an animal tumour model with tamoxifen?

At the University of Leeds, I built my first tamoxifen team to address the answers to my questions supported by unrestricted funds (i.e. I was an independent university investigator not a contractor for ICI Pharmaceuticals Division). The members of my team were the final year pharmacology degree students who would conduct a one-term final year research project but then they would either become a PhD student sponsored by an ICI Pharmaceutical Division scholarship or would be employed as a technician in my laboratory. My laboratory was funded by the Yorkshire Cancer Research Campaign and ICI Pharmaceuticals Division, through my grants.

Our progress was assessed and monitored by Dr Walpole, Drs Alan Wakeling (Fig. 4) and Barry Furr (Fig. 4) and their staff members at Alderley Park. Most importantly, the clinical monitor for tamoxifen, Dr Roy Cotton, was essential for success. He played a critical role in our productivity at University of Leeds. I was asked what would be the most important factor for the success of my tamoxifen team. My reply was the game changer. I asked for unlimited Alderley Park rats to be sent weekly to the medical school at the University of Leeds. This Roy Cotton did, with rats for both DMBA-induced rat mammary carcinoma studies and immature rats to study the pharmacology and mechanisms of action of tamoxifen metabolites. These rats were chauffeured weekly to Leeds,

Figure 4

Alderley Park colleagues with whom Dr Jordan worked during the/ University of Leeds tamoxifen team between 1974 and 1980, left to right: Dr Alan Wakeling who, with chemist Jean Bowler (Fig. 5) created a new group of medicines called Selective ER Disruptors (SERDs) (Wakeling *et al.* 1991), Alec Pleuvry, the principal individual who guided the business plan for tamoxifen through medical meetings and collaborations, Dr Barry Furr, Reproductive biologist who assumed the leadership role of the new 'cancer research programme' for breast and prostate cancer. He became the Chief Scientist at Alderley Park. In 1984, Drs Furr and Jordan wrote the 'state of the art' review of all that was known about tamoxifen (Furr & Jordan 1984). Dr Sandy Todd has the distinction of being the genetic result of two Nobel laureates: his father Lord Todd (affectionately known as Lord Todd Almighty) and his grandfather on his mother side was Sir Henry Dale. Dr Todd focused on the international business plan for tamoxifen.

for 5 years. The ICI executive car fleet was normally used to run VIP's back and forth between Manchester Airport, Alderley Park and their hotels in the area. Years later I was picked up at Manchester Airport on a visit to Alderley Park. 'Excuse me sir, are you the Professor Jordan who worked at the University of Leeds?' Yes, I replied. 'Well I used to chauffeur rats to you every week for years'. There is only one reply, 'Thank you very much!'

The answers to my questions developed quickly as we had an excellent evaluation system. Every 6 months my Leeds tamoxifen team would travel to Alderley Edge near Alderley Park and we would spend a couple of days on each visit. We wrote a report and made presentations as a cohesive group. Years after the programme finished, I was told by the Research Director, Dr Brian Newbold (Fig. 5) that ours was the most successful joint research scheme they had ever had. So, what was achieved?

Question 1: Can the pharmacology of tamoxifen metabolites explain the unusual species-specific actions of tamoxifen in mice and rats? Dora Richardson provided two hydroxylated metabolite of tamoxifen: 4-hydroxytamoxifen and 3,4-dihydroxytamoxifen. In

Figure 5

Jean Bowler, the chemist at ICI Pharmaceuticals Division, who synthesized fulvestrant pictured with Brian Newbold the Research Director.

the ligand-binding assay of rats, mouse or breast tumour cytosols (a homogenized protein extract of tissue spun down in a centrifuge to create a protein solution) we discovered (Clive Dix and Graham Prestwich actually) that the hydroxylated metabolites bound to the ER as tightly as oestradiol. This was unheard of in the scientific literature at the time (Korenman 1970, Skidmore *et al.* 1972), and I demanded repeat determinations to ensure there were no dilution errors. It was a discovery!

When tested in immature female rats, the metabolites were both anti-oestrogens but more potent than tamoxifen. Never before had high-affinity anti-oestrogens been found. The idea that non-steroidal anti-oestrogens fell off the ER because of low affinity was no longer plausible. To a pharmacologist, it was the structure of the anti-oestrogen and the position of the anti-oestrogen side chain that determined anti-oestrogen action at the ER. My plan was to use structure–function relationships to prove that tamoxifen was being metabolically activated to a metabolite that bound to the ER and the metabolite was really the active agent. However, all this had to wait as our collaboration with the University of Leeds/Alderley Park Research Scheme needed to obtain my agreement to avoid problems with patent issues in the USA in 1976.

Lois Trench and I had maintained communications during the time she was battling successfully to get FDA approval for tamoxifen in America. She was also the

Godmother to my daughter Alexandra. Lois requested I present the basic science tamoxifen talk at the symposium she had organized in Key Biscayne in Florida in 1976. This was to encourage Dr Bernard Fisher and the NSABP to consider adjuvant tamoxifen to treat breast cancer (Jordan 1976a).

During the telephone call to Alderley Park from Leeds, I agreed to say nothing about my work on the metabolites as the legal people were still trying, unsuccessfully as it turned out, to get the patent for tamoxifen in the USA before FDA approval. The disclosure that tamoxifen was metabolized to a super-anti-oestrogen would complicate progress with tamoxifen and commercialization. I had already written up our work for publication at Leeds in 1976 and was ready to submit, but I now agreed to give Dr Sandy Todd (Fig. 4) at ICI my manuscript and delay submission for a year to allow Alderley Park to patent all known metabolites of tamoxifen just in case they were found to be important.

A year later, I was informed I could submit my work for publication, and it became my most cited article in laboratory research. We subsequently proved that tamoxifen was metabolically activated to 4-hydroxytamoxifen (Allen *et al.* 1980) that contributed to anti-oestrogen action *in vivo*. A similar study of structure function relationships *in vitro* (Lieberman *et al.* 1983) actually identified the ER signal transduction pathway as the central mechanism for estrogen/anti-oestrogen action. This was important, as there were several competing theories of anti-estrogen action at the time in the early 1980s.

What I was to discover later, was that it was the policy at ICI Pharmaceutical Division, that all compounds entering clinical trial testing, would also have all known metabolites patented just in case it was discovered that the potential medicine was a pro-drug. It seems that there had been a previous case that a medicine had been patented and used successfully, but a competitor patented and marketed the active metabolite. That was never to happen again. However, the initial lack of patenting of tamoxifen's metabolites, demonstrates how the company continued to have little faith in the success of tamoxifen. If tamoxifen was unsuccessful and was abandoned, why waste time and money patenting metabolites. Few were believers!

Nevertheless, the discovery of the metabolic activation of tamoxifen to an anti-oestrogen with high-binding affinity for the ER did have more important implications for new uses for the 'failed contraceptives' never before considered. In the 1980s, the tamoxifen team

at the University of Wisconsin discovered the new drug group of Selective Estrogen Receptor Modulators (SERMs) (Jordan 2019).

Another win for the University of Leeds/Alderley Park Joint Research scheme was the idea that substitutions in the 6 and 7 position of oestradiol could be useful to carry an alkylating group to the nucleus of breast cancer cells to kill the target (Jordan *et al.* 1981). Though this did not come to pass, the idea was pursued successfully by Drs Jean Bowler (Fig. 5) and Alan Wakeling, (Fig. 4) who together discovered a new group of medicines to treat ER-positive breast/cancer: Selective Estrogen Receptor Disruptors (SERD). An early candidate ICI 164,780 was first tested in transplantable tamoxifen-resistant breast cancer cells *in vivo* in immune-deficient mice (Gottardis *et al.* 1989) at the University of Wisconsin. This success in a relevant animal model of acquired resistance to tamoxifen was followed by fulvestrant. The SERD is a non-cross-resistant anti-oestrogen that destroys the tumour ER. This publication (Gottardis *et al.* 1989) proved the concept that SERDs could be a viable second-line therapy following acquired resistance to tamoxifen as an adjuvant therapy. And so it was in clinical trials a decade later. Indeed, the field of breast cancer treatment was redirected towards the idea that 'no estrogen at all' was better than the oestrogenic tickle of tamoxifen. Aromatase inhibitors now took the lead with three companies competing for market share with exemestane, letrozole and anastrozole (and prices many times higher than tamoxifen).

Question 2: Can adjuvant tamoxifen treatment cure some rats with mammary cancer? To answer the question my experimental plan was to induce mammary tumours in 50- to 65-year-old female rats with 20mg of DMBA dissolved in 2 mL peanut oil and then 4 days later, start to treat animals for either a month with tamoxifen (equivalent to a year in a patient, the then-current duration for adjuvant clinical trials of tamoxifen in women) or continuous tamoxifen treatment for 5 months (i.e. 5 years). The winner was 5 months of continuous treatment with 90% of animals remaining tumour-free. Even enormous daily doses of tamoxifen for 1-month, that is, a year in patients, eventually resulted in all animals developing at least one tumour (Jordan & Allen 1980). Tumours appeared when tamoxifen was cleared from the body. The solution was to keep giving tamoxifen as an adjuvant therapy.

However, first I presented my new strategy of long term adjuvant tamoxifen was superior to short term adjuvant tamoxifen at a symposium at King College, Cambridge 28–29 September 1977 (Figs 6 and 7) (Jordan 1978). This was organized by ICI Pharmaceuticals

Division for doctors in the UK as a 2-day educational symposium. Unlike my positive experiences with the now, ICI America with Clinical Cooperative Groups in America between 1973 and 1974, there was less acceptance of the contribution of translational research within clinical community in the UK in the 1970s. Part of this stemmed from the real concern that tamoxifen, unlike combination cytotoxic chemotherapy, did not kill cancer cells. The view was this palliative therapy should be reserved for the end of life. Nevertheless, the data for the translational research was published (Jordan *et al.* 1979, 1980b, Jordan & Allen 1980, Jordan 1983, Tormey & Jordan 1984), and presented at major meetings within the next 2 years. Luckily, two clinical trialists Drs Helen Stewart and Michael Baum (Fig. 7) had plans, but no recruitment, to initiate long-term adjuvant tamoxifen trials. These important contributions (Nolvadex Adjuvant Trial Organisation 1985, Scottish Cancer Trials Office 1987) both demonstrated survival advantages for patients treated for longer than 1 year of adjuvant tamoxifen. This was before the Oxford overview analysis provided undeniable evidence of the potential for long term adjuvant tamoxifen to save lives (Early Breast Cancer Trialists' Collaborative Group 1998). However, my DMBA tumour studies would, within a few months of the Cambridge meeting, change the course of my career.

At the end of the 1970s, a month after the King College meeting in 1977, Lois Trench at ICI Americas organized a grant for Dr Douglas Tormey (Fig. 8) at the University of Wisconsin Comprehensive Cancer Center, to allow me and my family as well as Graham Prestwich, my talented technician in the University of Leeds/ICI Pharmaceutical Division Joint Research Scheme, to spend 3 months in Wisconsin conducting experiments. In reality, it was to establish whether there was sufficient evidence to offer me a job.

Armed with my latest data shown at the King College meeting in September, Graham and I met in Madison after I had spent weeks telling him how wonderful the campus was and how much fun we would have.

It was October 1977 and the worst winter in living memory with snow falling every day. We had no car so just staying alive at the bus stop before the bus came was a challenge. Be that as it may, the opportunities were there for the taking. Dr Harold Rusch (Fig. 8), the founding Director of the Cancer Center was also the Founding Director of the world-famous MacArdle Laboratory for Cancer Research. What I did not know was that Dr Rusch had recently lost his daughter to breast cancer and he had regrets that he had focused his career on identifying the causes of cancer and

A

Figure 6

The first report of the effectiveness of continuous (long-term) tamoxifen treatment to prevent the development of rat mammary carcinoma versus no treatment. In additional experiments (Jordan & Allen 1980) a 1-month treatment equivalent to a 1-year adjuvant therapy in women was not effective in the DMBA-rat mammary carcinoma model. This was published following the Kings College meeting September 1977.

not enough time on innovative treatments. I gave my talk of my vision to target breast cancer through the tumour ER, treat breast cancer with surgery and then use long term adjuvant tamoxifen therapy (based on my DMBA model-no publications yet) and raised the possibility of preventing breast cancer (again based on my DMBA publication (Jordan 1976b)). Afterwards, I discovered that this strategy was just what the new Cancer Center needed. Tamoxifen was soon to be on the market in the USA based on Lois Trench's timetable for the end of 1977. The University of Wisconsin Comprehensive Cancer Center would have a translational research plan to implement.

I was offered a job with, as it turned out, rapid promotions up the academic ladder (Assistant Professor 1980–1983, Associate Professor with tenure 1983–1986, Full Professor and Director of the Breast Cancer Research and Treatment Program at the WCCC (1986–1991). But first, it was back to the Department of Pharmacology at the University of Leeds.

B

as the drug is cleared from the body. Therefore in this case Tamoxifen would appear to have a suppressive effect rather than a tumour specific killing effect.

Continuous treatment

The effect of ovariectomy on day 28 after DMBA followed by no further treatment was compared to a continuous Tamoxifen therapy (50 mcg/day) from day 28. By 150 days all 20 rats in the control group had tumours. In the ovariectomized group tumours started to appear by 150 days after DMBA and at 200 days after DMBA only 45% of the rats in the group were tumour free. Thus ovariectomy appears to retard tumour development rather than completely protect the animals from the carcinogenic process. The Tamoxifen-treated

group by comparison produced a few tumours by 100 days after DMBA but then no more and by 200 days 90% of the rats were tumour free.

Conclusions

These studies show that, as in the human situation, once the tumours have become established it is difficult to effect a complete cure with Tamoxifen treatment.

The oestrogen receptor appears to play a role in the control of tumour growth in this particular model, although we cannot precisely predict how the tumour will respond to treatment. It does seem though, that if oestrogen receptors are low or absent then the tumour is probably hormone independent and the anti-oestrogen will be ineffective. By contrast to the treatment of animals with a large tumour burden, a short course of Tamoxifen treatment during the early development of tumours will produce some protection of the animal by suppressing the small foci of deranged cells. Perhaps most effective though is a continuous course of Tamoxifen therapy which appears to be very effective in suppressing tumour development.

Our data in the DMBA-induced rat mammary carcinoma model suggests that an adjuvant type of treatment is effective in controlling tumour growth and development and would warrant the establishment of controlled clinical trials.

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Figure 7

Reduction in the number of rats with a tumour after continuous treatment with Tamoxifen.

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The end of an era but the creation of a blockbuster not once but twice

Dr Arthur Walpole had died suddenly on July 2, 1977. He never knew of the enormous success of the medicine that he had fought so hard to create. He had not only been my PhD examiner for my thesis on 'failed contraceptives', but the member of staff at Alderley Park in 1972 who ensured I would receive funding from ICI Americas and meet Lois Trench the drug monitor for ICI 46,474 now tamoxifen, in the USA. He brought me into the loose team of committed individuals who wanted to make ICI 46,474 into a medicine to treat breast cancer. It was he and I who created the University of Leeds/ICI Pharmaceutical Division joint research scheme 1974–1979. Overall, this focused translational research programme built on the clinical database for the treatment of Stage IV breast cancer and Walpole fought, successfully, to keep the momentum going despite all expectations of non-profitability. It was born an

Figure 7

Participants at the breast cancer symposium in September 1977 at Kings College, Cambridge, England. Professor Michael Baum chaired Dr Jordan's session and during the discussion declared that they had arbitrarily chosen to use 2 years of adjuvant tamoxifen in the future. The trial had not opened. Dr Helen Stewart was a participant and there was a plan to initiate recruitment of patients to examine toxicity issues with 5 years of treatment. Similar studies were initiated in Wisconsin and subsequently published (Tormey & Jordan 1984, Tormey *et al.* 1987). The publication of the Scottish trial of 5 years of adjuvant tamoxifen treatment vs no adjuvant treatment but tamoxifen treatment at first recurrence, in the Lancet (Office 1987) publication on 25 July 1987 (Dr Jordan's birthday) was a wonderful present to demonstrate the power of translational research.

orphan drug, but with a mechanism of action (Jordan & Koerner 1975) and a bold evidence-based treatment plan of longer is better than shorter for adjuvant therapy (Jordan *et al.* 1979, 1980a,b, Jordan & Allen 1980) worked in clinical trials (Nolvadex Adjuvant Trial Organisation 1985, Fisher *et al.* 1987, Scottish Cancer Trials Office 1987).

His memorial service was held at his church in Adlington outside Wilmslow and it was there that Dr Brian Newbold told me that he would keep the University of Leeds/ICI Pharmaceutical Division joint research team active. However, the impossible happened – again!

Figure 8

In 1984, Dr Jordan organized a 3-day symposium to review and publish all that was known about non-steroidal anti-oestrogen (Jordan 1986). This photograph shows the principle supporters and faculty participants in Dr Jordan's nascent Breast Cancer Program and tamoxifen team in Wisconsin. L/R back row Dr Gerald C Mueller (early investigator of oestrogen action before the discovery of the ER, McArdle Laboratory), Dr Jack Gorski (pioneer in first visualizing the ER using sucrose gradient analysis; his work was the original inspiration of Dr ER Clark, Dr Jordan's PhD supervisor; Department of Biochemistry) Dr Jordan, head of tamoxifen team, Dr Doug Tormey (former head of the Breast programme at the NCI and Dr Jordan's principal clinical collaborator) bottom row seated Dr Harold Rusch (Founding Director of both the McArdle Laboratory of Cancer Research and the Wisconsin Clinical Cancer Center) Dr Paul P Carbone (Director, to be, of the Wisconsin Comprehensive Cancer Center and leader of the Eastern Cooperative Oncology Group).

Sales of tamoxifen worldwide were increasing, and all manufacturing of the tablets occurred at an ICI plant outside Macclesfield. With Lois Trench's success for FDA approval on 31 December 1977, orders for the export of tamoxifen to the USA started to climb. The orphan medicine tamoxifen was starting to become a blockbuster.

In recognition of this major achievement, ICI Pharmaceuticals Division was awarded the Queen Award for Technological Achievement in July 1978. This was celebrated, at a luncheon at ICI Pharmaceuticals, Alderley Park. Only two hundred and thirty handpicked employees, who had been directly involved to accomplish this milestone in drug discovery and development, were invited. I discovered that I was the only nonmember of ICI staff invited to attend. My invitation was in recognition of my translational research work that provided the future road map for drug development. Dr Roy Cotton, the successful initial clinical drug monitor for tamoxifen (who also shipped my rats to Leeds), and I dined at the same table (Fig. 9). Barry Furr (Fig. 4) welcomed me upon my arrival after being chauffeured from Leeds to Alderley Park. Always the supporter, he invited me to the VIP cocktail reception to meet the Directors and the Lord Lieutenant of Cheshire.

Figure 9

The Queen's award for industry is an exceptional honour for a company who has excelled. The celebration is only for those considered to have been instrumental in making the award a reality, that is, tamoxifen. A carefully selected group of 230 employees were present and Dr Jordan was the only one invited from outside of the company. The figure shows the front page of the Alderley Park company newspaper SCAN and Dr Jordan's personal invitation. The luncheon table photograph shows Dr Roy Cotton and Dr Jordan opposite of each other and unfortunately, Dr Sandy Todd hidden behind Dr Jordan (right). A better photograph of Dr Todd is in Fig. 4.

At the Department of Pharmacology at the University of Leeds, I had created my first tamoxifen team. In alphabetical order the undergraduates who excelled by contributing to the refereed journal publications were: A C Abbot (M Phil Student), K E Allen Porter (née Naylor) (undergraduate and research technician), M M Collins (undergraduate), C J Dix (undergraduate then ICI Scholar PhD Student), T Jaspan (intercalating medical student obtaining a pharmacology degree), G Prestwich (undergraduate then research technician), L Rowsby (undergraduate then research technician). Total 25 publications.

Before I returned to Wisconsin in 1980, I spent 1979 in Bern, Switzerland responsible for constructing and creating a Ludwig Institute for Cancer Research.

During this year, I visited clinicians around the world supporting the Ludwig Breast Cancer Trials. I quality controlled all their ER laboratories and established lifelong friendships.

Back to America to study 'the good, the bad and the ugly' of tamoxifen that resulted in the discovery of selective oestrogen receptor modulators

Anna T Riegel (née Tate) and I arrived in Madison, Wisconsin to start my second tamoxifen team in January 1980. Anna had been awarded a Fulbright/Hays scholarship to complete her PhD in 3 years at the

McArdle Laboratory. I was her thesis supervisor in the Department of Human Oncology. The path to progress was daunting but within 3 years we had a vibrant laboratory with about 18 tamoxifen team members in all consisting of PhD students, post-doctoral fellows, technicians, and student helpers in the laboratory. The story of the Wisconsin tamoxifen team and their accomplishments have recently been told in detail (Jordan 2019) and will not be retold in detail here. The members of the Wisconsin tamoxifen team in the latter half of the 1980s are shown in Fig. 10.

Nevertheless, it is important to recount the critical importance of the Wisconsin tamoxifen team for the future of drug discovery in women's health. Our initial focus was an examination of 'the good, the bad and the ugly' of tamoxifen. The clinical plan was long-term adjuvant tamoxifen treatment and chemoprevention. Unfortunately, little was known of the pharmacology and toxicology of tamoxifen. The good developed from the translational research that occurred when Paul Carbone and Doug Tormey embraced my translational laboratory evidence that longer adjuvant tamoxifen therapy would be better than shorter therapy (Jordan *et al.* 1980a,b). Doug and I initiated a pilot clinical studies in the late 1970s and these was published in the 1980s (Tormey & Jordan 1984, Tormey *et al.* 1987). Dr Carbone decided, in the early 1980s, that all adjuvant tamoxifen patients would receive extended therapy. Tamoxifen did not develop metabolic tolerance during long term (10 years) adjuvant therapy (Langan-Fahey *et al.* 1990) and was not metabolized to oestrogens in species (the mouse) that exhibited oestrogenic action in the target tissue, that is, uterus and vagina (Lyman & Jordan 1985a,b, Robinson *et al.* 1991).

However, our conceptual breakthrough depended on our observations using the athymic mouse transplanted with human MCF-7 ER-positive breast cancer (Jordan & Robinson 1987).

Tamoxifen, an anti-oestrogen, blocked oestrogen stimulated tumour growth but caused increases in uterine weight in the same mouse (Jordan & Robinson 1987). Target site specificity, not metabolism, was responsible for oestrogen/anti-oestrogen effects in target tissue. In inbred strains of mice that had a high incidence of spontaneous mammary tumours, tamoxifen prevented mouse mammary tumours (Jordan *et al.* 1990, 1991) but the uterus grew with tamoxifen. Oestrogen target tissues were being switched on and switched off around the body. Immune-deficient mice bitransplanted with a breast and a human endometrial tumour responded to tamoxifen by blocking oestrogen stimulated breast cancer growth, but endometrial cancers grew, and tamoxifen was not an anti-oestrogen (Gottardis *et al.* 1988). This observation attracted international attention (Jordan 1988b, 1989) and eventually, it was recognized that patients should be screened for preexisting endometrial cancer before adjuvant tamoxifen treatment was employed. But our biggest surprise was the effect of tamoxifen and a failed breast cancer drug, keoxifene (later to be renamed raloxifene) on bone. Unexpectedly, both anti-oestrogens built bone rather than the anticipated pharmacology of decreasing bone density with anti-oestrogens (Jordan *et al.* 1987). This observation was confirmed (Turner *et al.* 1988) and critical for the application of tamoxifen as a preventive for breast cancer in high-risk women. The development of osteoporosis was unlikely in post-menopausal women.

Figure 10

Members of the Wisconsin tamoxifen team (approx. 1988). Front row, left to right Shui-Yuang Jiang (PhD Student), Meei-Huey Jeng (PhD Student), Dr Craig Jordan, Marco Gottardis (PhD student), Cathy Murphy (PhD Student), Dr liuchi Ino (visiting Professor from Gunma University Japan who became President of the Japanese Breast Cancer Society), Chris Parker (ER assay technician), Mary Lababidi (Head technician of the ER laboratory), Mark Johnson (radioimmunoassay), John Pink (molecular biology technician to become a PhD student).

Translation clinical research at Wisconsin (Love *et al.* 1992) and subsequently elsewhere (Powles *et al.* 1996) confirmed the laboratory findings (Jordan *et al.* 1987) that tamoxifen increase bone density in patients. Additional clinical studies confirmed the hypocholesteremic action of tamoxifen (Love *et al.* 1990, 1991) as noted in ICI's original patent.

So, at the close of the 1980s at Wisconsin, a new concept was to emerge in animals and women that non-steroidal anti-oestrogens could switch on and switch off sites around the body. The same ER was being modulated by an unknown mechanism. This mystery was subsequently solved by O'Malley and his group at Baylor College of Medicine (Smith *et al.* 1997). Tissue site ER regulators became an essential part of the oestrogen signal transduction pathway.

The proposition in 1990 for the clinical value of SERMs was stated as follows: 'We have obtained valuable clinical information about this group of drugs that can be applied in other disease states. Research does not travel in a straight line, and observations in one field of science often become major discoveries in another. Important clues have been gathered about the effects of tamoxifen on bones and lipids; it is possible that derivatives could find targeted applications to retard osteoporosis and atherosclerosis. This ubiquitous application of novel compounds to prevent diseases associated with the progressive change after menopause may, as a side effect, significantly retard the development of breast cancer. The targeted population would be post-menopausal women in general, thereby avoiding the requirement to select a high- risk group to prevent breast cancer' (Lerner & Jordan 1990).

Today there are five FDA approved SERMs, all with discovery links to work done in Wisconsin: tamoxifen (Jordan 2019), toremifene (Robinson *et al.* 1990), raloxifene (Gottardis & Jordan 1987, Jordan *et al.* 1987), bazedoxifene (Robinson *et al.* 1988), and ospemifene (Jordan *et al.* 1983) (Figs 11 and 12). So, if it is not written down, it never happened. What was the total of publications at Wisconsin? – 245, thank you Dr Caspi for your lesson!

The impact on drug discovery by the success of tamoxifen

The patent situation with tamoxifen in the USA resolved with the award of the US patent in 1985. A chain of events, not considered to be imaginable, occurred when ICI Pharmaceutical Division sued the Patent Office in the USA, but the Judge upheld the Patent Offices rejection.

Figure 11

Late in its clinical use, tamoxifen was found to induce rat liver cancer (Greaves *et al.* 1993). No clinical evidence was found over 20 years of Oxford overview analyses, that patients treated with tamoxifen developed liver cancer. By contrast, chlorine on the ethyl substitution at the double bond to produce toremifene resulted in no rat carcinogenesis (Williams *et al.* 1997). Toremifene is FDA approved to treat Stage IV breast cancer. The discovery of metabolite Y in patients treated with tamoxifen (Jordan *et al.* 1983) resulted in the finding of any equivalent metabolite from toremifene. Ospemifene is FDA approved for dyspareunia.

However, in the same year, tamoxifen was declared the adjuvant treatment of choice for breast cancer by the National Cancer Institute (Consensus Conference 1985). There, was, however, a caution that no recommendations could be made about the duration of therapy. This was a work in progress based on translational research (Jordan 1983).

The surprise was this, in 1985, the Federal Court of Appeals ordered the Patent Office to grant the patent, which it did in August of that year. At that time US patents were granted from the date of patent award not from the date of original filing (i.e. 1965).

At this point, in the latter half of the 1980s, I was asked to speak at many medical events and these naturally contained patients. I recall one occasion that an angry patient rose to exclaim 'Dr Jordan you are advocating

Figure 12

The value of knowledge of the pharmacological properties of tamoxifen's hydroxylated metabolite (Jordan *et al.* 1977). This led to raloxifene for the prevention of osteoporosis/breast cancer (Gottardis & Jordan 1987, Jordan *et al.* 1987) and bazedoxifene (Robinson *et al.* 1988), in some countries for the prevention of osteoporosis and with conjugated equine estrogen for the amelioration of menopausal symptoms.

5 years or more of tamoxifen adjuvant therapy. This is ten dollars a day so in a year that is nearly \$4000. Who can afford that?' How the world of modern cancer therapy has changed!

The newly granted patent had a life in the USA until 2002. This lucrative patent started just as the patents on tamoxifen were running out worldwide. Tamoxifen was the adjuvant endocrine therapy standard of care with no competition. It was a blockbuster in the USA alone and the only medicine to have patent protection in lucrative markets for a total of 37 years!

This revenue stream, for a medicine never expected to succeed (except by the tamoxifen loyalists of the early 1970s), drove the development of ICI Pharmaceutical Division to undergo a metamorphosis to become first Zeneca and then AstraZeneca with an early run of successful agents to treat endocrine-related cancer (goserelin, fulvestrant, bicalutamide, and anastrozole) and establish itself as a world-class pharmaceutical company and a leader in cancer therapeutics.

Indeed, but for the coincidence of my 2 years at the WFEB in 1972–74 and establishing a lifelong professional

and personal friendship with Angela and Harry Brodie (Jordan & Brodie 2007, Abderrahman & Jordan 2017, Abderrahman & Jordan 2018), it is unlikely that the aromatase inhibitors would have sprung into life, in pharmaceutical companies around the world.

Tamoxifen's blockbuster success as a long-term adjuvant therapy, that saved lives, was an unanticipated advance by the medical community in the 1970s and the idea that tamoxifen would be the first targeted therapy via the ER was certainly not accepted initially by all in the medical establishment in the UK. One of my medical colleagues in London, was less inclined to be persuaded about the relevance of the ER in tamoxifen's mechanism as there was no correlation of responses to ER breast tumour levels in the NATO trial (Nolvadex Adjuvant Trial Organisation 1985). As a result, all patients received tamoxifen. I like to think that more good than harm came of that.

Tamoxifen had to succeed in a big way, and this was aided by the reduced side effects observed with tamoxifen in the Christie trial (Cole *et al.* 1971), the Queen Elizabeth Hospital Trial (Ward 1973) and the later Mayo Clinic randomized clinical trial in the USA (Ingle *et al.* 1981). Indeed, without the low incidence of side effects with tamoxifen, and little or no effect on desmosterol, it is unlikely that the clinical community would ever have used an anti-oestrogen as a long-term adjuvant therapy for the treatment of breast cancer.

The SERMs owe their birth to the discovery of the high-affinity metabolite of tamoxifen 4-hydroxytamoxifen (Jordan *et al.* 1977, Allen *et al.* 1980a). The strategically located hydroxyl of the anti-oestrogen binds to the same site in the ER ligand-binding domain as the 3-phenolic hydroxyl of oestradiol (Brzozowski *et al.* 1997) that is used for high-affinity binding by 4-hydroxy tamoxifen (Shiau *et al.* 1998). That hydroxyl is replicated in the SERMs raloxifene and bazedoxifene (Fig. 12).

Millions of women worldwide owe their lives to the tenacity of Dr Arthur L Walpole to keep ICI 46,474 alive until the evidence was accumulated that tamoxifen could save lives.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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