

Tamoxifen as the first targeted long-term adjuvant therapy for breast cancer

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Abstract

Tamoxifen is an unlikely pioneering medicine in medical oncology. Nevertheless, the medicine has continued to surprise us, perform, and save lives for the past 40 years. Unlike any other medicine in oncology, it is used to treat all stages of breast cancer, ductal carcinoma *in situ*, and male breast cancer and pioneered the use of chemoprevention by reducing the incidence of breast cancer in women at high risk and induces ovulation in subfertile women! The impact of tamoxifen is ubiquitous. However, the power to save lives from this unlikely success story came from the first laboratory studies which defined that ‘longer was going to be better’ when tamoxifen was being considered as an adjuvant therapy. This is that success story, with a focus on the interdependent components of: excellence in drug discovery, investment in self-selecting young investigators, a conversation with *Nature*, a conversation between the laboratory and the clinic, and the creation of the Oxford Overview Analysis. Each of these factors was essential to propel the progress of tamoxifen to evolve as an essential part of the fabric of society.

Key Words

- ▶ breast
- ▶ endocrine therapy

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Introduction

‘Science is adventure, discovery, new horizons, insight into our world, a means of predicting the future and enormous power to help others’ (Hoagland 1990).

– Mahlon Hoagland, MD, Director, Worcester Foundation for Experimental Biology (1970–1985).

Tamoxifen (Imperial Chemical Industries (ICI) 46 474; Harper & Walpole 1967, Cole *et al.* 1971, Klopper & Hall 1971) is an old medicine with origins unlikely to predict pioneer or breakthrough status (Jordan 2003, 2006, Maximov *et al.* 2013). I was the least likely schoolboy to go to university (University of Leeds) but subsequently selected a career path ‘to help develop a drug to treat cancer’ (Poirot 2011). At the time, this was not a popular or even reasonable career path as treatments were primitive

and invariably unsuccessful (except for childhood leukemia). Tamoxifen and I became the ‘odd couple’, but nobody cared in the 1970s, as combination cytotoxic chemotherapy was predicted to cure cancer. Be that as it may, tamoxifen slowly ‘arrived’ and advanced on the clinical scene in the 1970s but only as an orphan drug after all but being abandoned by the pharmaceutical industry. This old medicine never went away and continues to provide surprises (Davies *et al.* 2013, The aTTom Collaborative Group 2013). Through the application of experimental science in cancer therapeutics (I was, and remain, a pharmacologist first), questions were asked, but *Nature*’s replies were unanticipated. However, *Nature* does not lie, and if the controls are correct, and it is

reproducible, then one is compelled to re-evaluate the implications for medicine. The science of tamoxifen became 'a means of predicting the future and enormous power to help others' (Hoagland 1990). This is that story.

In 1977, I presented an invited lecture at a medical symposium held by ICI Pharmaceuticals Division at King's College, Cambridge. I described a new strategy to treat breast cancer (Jordan 1978). This was to use tamoxifen, a palliative agent then used in the final stages of breast cancer as a long-term adjuvant therapy, but this was not the fashion. Already adjuvant therapy with cytotoxic chemotherapy was showing promise (Fisher *et al.* 1975, Bonadonna *et al.* 1976) on the way to cures. The clinical strategy was considered sound. The primary tumor is first removed with a mastectomy, then nonspecific cytotoxic chemotherapy is given for many months afterwards to destroy the micrometastases scattered unseen around the patient's body. Destruction of micrometastases would produce cures.

During the 1970s, I was supported by both ICI Pharmaceuticals Division and the Yorkshire Cancer Research campaign to explore the mechanism of action and clinical opportunities for ICI's orphan drug tamoxifen (Jordan 2006). Tamoxifen, a nonsteroidal antiestrogen, was no better than high-dose estrogen or androgen therapy (Cole *et al.* 1971, Ward 1973, Morgan *et al.* 1976, Ingle *et al.* 1981) as a treatment for metastatic breast cancer and was available as a palliative therapy in the UK and other countries (except the USA) to treat metastatic breast cancer in postmenopausal women. Only 'fewer side effects', and higher cost, separated tamoxifen from the other 'hormone therapies' (Cole *et al.* 1971, Ward 1973, Ingle *et al.* 1981). No cures were anticipated as the 'hormone therapies', as they were then called, were only effective in 30% of patients for a year or two. The medicine would not be approved in the USA for the treatment of metastatic breast cancer until December 1977 and chances for economic success for ICI Pharmaceuticals Division were hovering just above zero.

The experimental results I presented (Jordan 1978) at the medical symposium at King's College demonstrated that long-term tamoxifen treatment was superior to short-term treatment in suppressing rat mammary tumorigenesis (Fig. 1). At the time, numerous adjuvant trials of 1-year adjuvant tamoxifen were proposed for the simple reason that tamoxifen treatment only controlled breast cancer for a year (Hubay *et al.* 1980, Ribeiro & Palmer 1983, Ludwig Breast Cancer Study Group 1984, Cummings *et al.* 1985, Ribeiro & Swindell 1985, Rose *et al.* 1985). The new concept presented presaged any clinical trials of more than

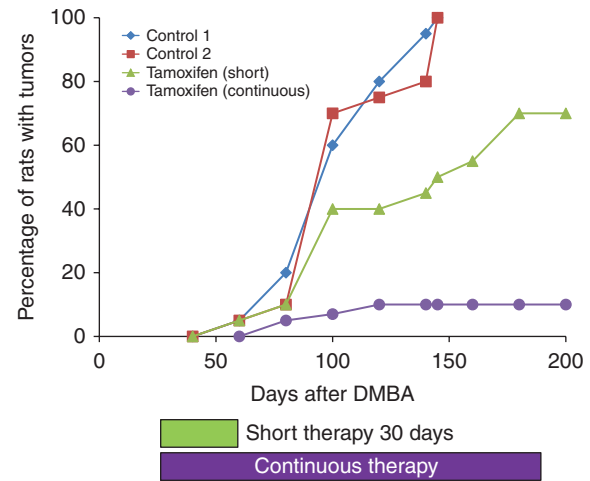


Figure 1

The use of the dimethylbenzanthracene (DMBA)-induced rat mammary carcinoma model to demonstrate that longer or continuous therapy with daily tamoxifen (50 µg s.c. injection) was superior at preventing the appearance of mammary tumors when compared with short therapy of 30 days. Female Sprague-Dawley rats that are 50 days old were each given 20 mg DMBA by gavage in 2 ml peanut oil. In nontreated control groups of 20 animals, all rats had multiple palpable tumors by 150 days. The model design for therapy groups first administered DMBA at 50 days of age but the 30-day or continuous treatment was delayed for 30 days to permit initiation and promotion of mammary carcinogenesis to occur. The goal was to establish whether a short 30-day course of tamoxifen (estimated to be equivalent to 1 year of adjuvant tamoxifen in patients) could destroy the deranged microscopic cancer cells in the mammary glands or whether continuous therapy was required for complete tumor control and suppression. Continuous therapy is necessary. The strategy was to use tamoxifen only in patients with ER-positive tumors (Jordan & Koerner 1975) and use continuous therapy. This new strategy was first reported at the medical symposium held by ICI Pharmaceuticals Division at King's College, Cambridge, September 1977.

1 year of adjuvant tamoxifen and proposed that an appropriate clinical strategy for adjuvant tamoxifen treatment would be for extended or indefinite tamoxifen administration. My catch phrase at medical meetings was 'tamoxifen forever'. However, the proposal was immediately controversial. Attendees at the conference (Fig. 2) challenged the fidelity of the dimethylbenzanthracene (DMBA)-induced rat mammary carcinoma model I was using, as it did not replicate human micrometastatic dissemination. Worse still, 'your strategy is dangerous!' It was universally known by the clinical community that tamoxifen would only be effective for <2 years in one-third of patients when used to treat metastatic disease in postmenopausal women. 'You're proposing we give long term or indefinite adjuvant tamoxifen to women, some of whom are already cured, so you can prevent a recurrence. Your treatment strategy may, in fact, encourage premature



Figure 2

The participants of the medical symposium held by ICI Pharmaceuticals Division at King's College, Cambridge, September 1977. The author (top) presented the new strategy; Prof. Michael Baum (right) was the session chair and leader of the proposed NATO trial that was planned to advance the current 1-year adjuvant tamoxifen trials to a 2-year treatment period. Helen Stewart (left) was in the audience and had plans to compare placebo and tamoxifen at first recurrence with 5 years of immediate adjuvant tamoxifen in the Scottish trial. Both trials (the NATO and Scottish trials) were to demonstrate, for the first time, survival advantages of adjuvant tamoxifen used for longer than 1 year.

drug resistance and we will have wasted a valuable palliative drug by using it too soon'.

Immediately after the King's College meeting, in October 1977, I had been invited to visit the University of Wisconsin Clinical Cancer Center in Madison by Paul Carbone (Director) and Doug Tormey (Head of the breast program) to spend several months doing collaborative research. I presented my ideas about long-term adjuvant tamoxifen therapy – a new strategy with a drug that was not yet on the market in the USA! I was immediately offered a job at the Cancer Center and asked to move to Madison. Doug Tormey, based on my lecture, decided to continue his patients on indefinite tamoxifen (Tormey & Jordan 1984,

Tormey *et al.* 1987) and an Eastern Cooperative Oncology Group adjuvant protocol of indefinite tamoxifen was subsequently approved (Falkson *et al.* 1990). But first, I spent a year designing and creating the Ludwig Institute for Cancer Research in Bern, Switzerland. I was provided with a large travel budget as I was asked to quality control estrogen receptor (ER) assays (Jordan *et al.* 1983) for the Ludwig Adjuvant Tamoxifen Trials (regrettably only 1 year, Ludwig Breast Cancer Study Group (1984)). As a gamble, I decided to submit an abstract to the Adjuvant Therapy of Cancer II meeting in Tucson, Arizona, organized by the late Syd Salmon and Steve Jones. We now had much more data to support the proposal to use long-term tamoxifen as a long-term adjuvant therapy and I hoped, maybe, I would be lucky and get my abstract accepted for presentation. Imagine my surprise to find myself in the opening session sandwiched between the clinical greats of cancer research. The talk went well and was quickly published (Jordan *et al.* 1979) for global distribution to the clinical community. At the meeting, I was able to enlarge my circle of colleagues in clinical breast cancer research but one 'premonition' is worthy of mention. After my talk, Lois Trench, whom we will meet again later, turned to her colleagues in the marketing department of ICI Americas and exclaimed 'you have no idea what Dr Jordan has just announced with his talk on indefinite adjuvant tamoxifen. This will be a blockbuster!' And so it was. Those first animal experiments provided a scientific justification and road map for all subsequent long-term adjuvant clinical trials with tamoxifen that were to show unanticipated large survival advantages for patients (EBCTCG 1998 and EBCTCG 2005) and consistent decreases in death rates from breast cancer in national statistics (Peto *et al.* 2000, Berry *et al.* 2005).

There is no better example of the value of long-term adjuvant tamoxifen therapy than the recent reports of the Adjuvant Tamoxifen Longer Against Shorter (ATLAS; Davies *et al.* 2013) and adjuvant tamoxifen treatment offers more (aTTom; The aTTom Collaborative Group 2013). Until these trials of 10 years of adjuvant tamoxifen, it was well established that 5 years of tamoxifen is dramatically superior to no treatment (Davies *et al.* 2011), but ATLAS and aTTom compare 5 vs 10 years of tamoxifen. The conclusion is that 10 years of adjuvant tamoxifen cause a superior decrease in mortality than 5 years of adjuvant tamoxifen (Davies *et al.* 2013). However, the question that must be raised is why mortality only decreases for the 10-year treatment group in the decade after tamoxifen is stopped? To seek the answer to this paradox, that should not occur with a

palliative nonsteroidal antiestrogen that blocks ER-mediated estrogen-stimulated growth of micrometastases (no drug, no action!), we have to return to the origins of tamoxifen, follow the interconnected events in translational research, and identify the factors that allowed tamoxifen to triumph.

In retrospect, the essential components to achieve the full potential of tamoxifen in the clinic were: a commitment to excellence in drug discovery, investment in a young self-selecting investigator, keeping an open mind with the conversation with *Nature*, and maintaining an active conversation between the laboratory and the clinical investigators. Laid over all of these essentials was the creation of the recurrent Oxford Overview Analyses of adjuvant trials by Sir Richard Peto and his team. This process formed the fundamental foundation to create the ATLAS trial based on firm clinical evidence and acts as a continuing catalyst to provide scientific support for aTTom. Finally, there is another dimension best described as seeing an opportunity, being in the right place at the right time and be willing to train yourself to be talent-spotted. Slightly different circumstances or a different decision or meeting can change everything: the play of professional chance. 'Sliding Doors', starring Gwyneth Paltrow and John Hannah, is an excellent film based on the premise that by just missing or catching a tube train in London, a life can be altered forever. The film then portrays two parallel lives to the conclusion. In the spirit of 'Sliding Doors', I will retell the progression of the aforementioned interconnecting components that created the tamoxifen of today.

A commitment to excellence in drug discovery

Following the chance discovery of the first nonsteroidal antiestrogen ethamoxotriphenol (MER25) by Lerner *et al.* (1958) at the William S Merrell company in Cincinnati and the finding that there was post-coital antifertility activity in laboratory animals (Segal & Nelson 1958), numerous companies immediately began synthesizing and screening for suitable compounds for use as 'morning-after pills'. Contraceptive research was the 'hot' topic and fashion in the wake of the approval of the oral steroid contraceptive 'to regulate the menstrual cycle' in 1960. A range of nonsteroidal compounds became available but one, clomiphene, induced ovulation in women – it guaranteed what it was planned to prevent! Clomiphene (Greenblatt *et al.* 1961) subsequently found sustained use in medicine for the induction of ovulation after a 5-day course, in subfertile women. However,

clomiphene increases desmesterol levels, which is associated with cataract formation (Avigan *et al.* 1960, Laughlin & Carey 1962), and there was no further development for long-term therapy.

Drs Mike Harper and Arthur Walpole (Fig. 3) tested the antifertility properties of a range of compounds related to clomiphene at ICI Pharmaceuticals laboratory at Alderley Park near Macclesfield, Cheshire. The compounds were made by a talented organic chemist, Dr Dora Richardson (Fig. 3). Compound ICI 46 474, the antiestrogenic *trans* isomer of a substituted triphenylethylene, did not increase desmesterol (Harper & Walpole 1967) but like clomiphene was also found to induce ovulation (Klopper & Hall 1971). By coincidence, I was a summer student working in the nascent cancer research laboratory opposite Dr Walpole's fertility control laboratory in 1967. Alderley Park is just ten miles from my home where I grew up in Cheshire. Walpole was the Head of the Fertility Control Program at ICI Pharmaceuticals Division but was subsequently to play an essential role to ensure the successful development of ICI 46 474 as a cancer treatment. This was because Walpole had long-standing interest in cancer research (Jordan 1988) though he was required to work in what was judged to be the more fertile field of contraception. I was to meet Walpole again 5 years later in 1972, but this time he was the examiner of my PhD thesis entitled 'A study of the structure function relationship of substituted triphenylethylenes and triphenylethanes'.

Self-selecting young investigator

I started my lifelong 'love affair' with triphenylethylenes in 1969 when I chose to accept a PhD project to crystallize and study the X-ray crystallography of the ER complex liganded with an estrogen and antiestrogen. Jack Gorski (Toft & Gorski 1966, Toft *et al.* 1967) had just published a series of papers in the *PNAS* showing that the ER (ESR1) protein could easily be extracted from rat uteri. My PhD supervisor, in the Department of Pharmacology at Leeds University, was Dr Edward (Ted) Clark, a brilliant and exciting lecturer in medicinal chemistry with encyclopedic knowledge and a long-standing interest in estrogens. 'It will be simple' he said. 'You will extract and purify the rat uterine ER and crystallize it with an estrogen and an antiestrogen and do the X-ray crystallography up the road at the Astbury Department of Biophysics'. Well that did not work (the whole ER complex has yet to be crystallized!) and I switched to study the structure–function relationships of triphenylethylene antiestrogens – the failed contraceptives. Although this would prove to be a sound

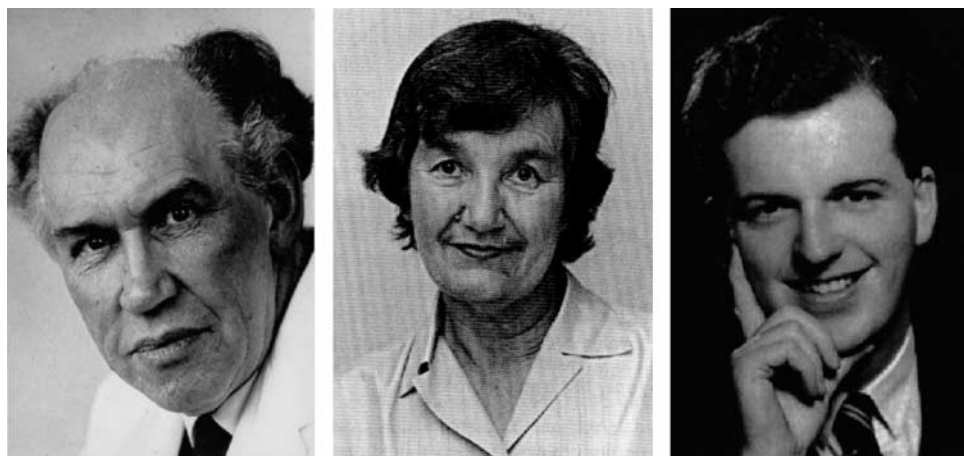


Figure 3

The principal players in the discovery of ICI 46 474 at ICI Pharmaceuticals Division, Cheshire, UK in the 1960s that eventually evolved into tamoxifen a decade later. Arthur Walpole (Walop; left) was the head of the Fertility Control Program tasked with the mission to discover safer compounds to 'regulate the sexual cycle'. Dora Richardson (center) was the team organic chemist who synthesized all of the isomers of the triphenylethylene derivatives that would be tested as antifertility agents in rats by Mike Harper and the team reproductive endocrinologist. Arthur Walpole would

be the author's PhD examiner, scientific supporter, and administrative link to ICI until his untimely death on 2nd July 1977. Dora Richardson would provide the metabolites of tamoxifen to the author to be tested as anticancer agents and Mike Harper would offer the author a 2-year BTA (Been-To-America) at the Worcester Foundation, MA. Each individual was generous with important opportunities, investment, and support for a young investigator starting their adventure to investigate 'failed morning-after pills' as important future therapeutic agents in women's health.

foundation for a future, at the time no one was recommending careers in failed contraceptives!

During the 3 years of my PhD studies (1969–1972), armed with a Medical Research Council scholarship, I was talent-spotted by Prof. Michael Barrett, the new Chair of Pharmacology (a cardiovascular pharmacologist from ICI Pharmaceuticals Division) appointed in 1970. As an undergraduate, I had created, organized, and led our student society, named the Medean Society after the sorceress Medea who created magic potions to protect Jason (of Argonaut fame) from death as he completed his impossible tasks to retrieve the Golden Fleece. She was, it seems, the first to create effective chemopreventive agents!

Prof. Barrett recognized that I had talent for organization in science and, as a graduate student, I chose to create lectures for parent teacher organizations in the Leeds area schools on drug abuse. I strongly believed in public service, as reinvestment in the community was important to 'pay back' the investment of my free education. These lectures were also presented, at Prof. Barrett's insistence, to the undergraduates as I was also closely connected with the Leeds City Police Drug Squad as an advisor. Thirdly, Prof. Barrett was aware that I had been talent-spotted to be on the advisory staff for the Deputy Chief Scientist (Army) and one of my duties was to present drug abuse lectures for Army units throughout the country. In this role, I was Reserve Army Officer. I was

focused on the perils of drug abuse and worked with the police. As a PhD student, I was researching the regulation of the sexual cycle with pharmacological agents, and I was an Army Officer advisor to the Deputy Chief Scientist (Army). In USA (1972–1974), I would often be asked to give talks in the community (the English accent went over well!), so I would preface my talks by stating that my career was based on drugs, sex and violence (with apologies to the 'sex, drugs and rock and roll' in the sixties; I was, however, actually a drummer in a rock band as a teenager!).

In 1972, Prof. Barrett now saw potential in me as a new staff member in his new Department of Pharmacology. I found myself as a prospective lecturer in Pharmacology, but first I had to complete my PhD in 'failed contraceptives'. During my interview for the lecturer's job, it was stated and required that I should spend 2 years in USA to acquire new scientific skills and return to invest the new knowledge back in Leeds University following my BTA (Been to America).

Prof. Barrett and the administration were, however, challenged to find an examiner for my PhD on 'failed contraceptives'. All approaches were declined – nobody cared as this was a topic considered of no significance. Prof. Barrett turned to his former colleague at ICI Pharmaceuticals Division, Dr Arthur Walpole, head of the Fertility Control Program to be my external examiner.

The university administration was initially resistant to having 'someone from industry' as an examiner; but, fortunately for me and, perhaps, the future of tamoxifen, the administration finally agreed. Indirectly, the door had opened for the development of ICI 46 464, the failed contraceptive to evolve into the 'gold standard' tamoxifen for the adjuvant treatment of breast cancer.

Dr Mike Harper, the reproductive endocrinologist at ICI Pharmaceuticals Division who had completed all of the biology of ICI 46 474, was Mike Barrett's friend but was now heading a research program at the Worcester Foundation for Experimental Biology in Massachusetts. I remember my transatlantic telephone call with Mike Harper. 'Can you come in September, will \$12 000 a year be OK, and will you work on prostaglandins?' 'Yes, yes, yes' I replied and went off to the library to find out what prostaglandins were! My examination with Arthur Walpole went well, but I had not anticipated that our lives would be intertwined for the remaining years of his life. I now found myself off to USA for 2 years as a Visiting Scientist (1972–1974).

I arrived at the Worcester Foundation, the home of the oral contraceptive, with the invitation and plan to work with Mike Harper on a 'once-a-month contraceptive'. However, when I arrived I found he had accepted a job as Head of Reproduction at the World Health Organization in Geneva, Switzerland. I was told I could do any research I liked for the next 2 years as long as some of it involved prostaglandins. I was confronted with a daunting task as a brand-new PhD graduate – start my own laboratory as an independent investigator, find my own funds, and hire and train a technician. Her name was Susan Koerner and she was spectacular. She was included as an author on my early papers.

I had always wanted to be involved in the discovery and development of drugs to treat cancer, so perhaps here was my opportunity. I was a pharmacologist, but do what you know and all I knew about was triphenylethylenes and the ER so a phone call to Arthur Walpole gained his support to aid in turning ICI 46 474 into a prospective breast cancer drug. What I did not know at that time was that ICI Pharmaceuticals Divisions had reviewed all the clinical data on ICI 46 474 in March 1972, and the decision was made to stop development for clinical use as there was no financial reward to be accrued for the treatment of metastatic breast cancer or as another inducer of ovulation (Jordan 2006). Arthur Walpole had tendered his resignation and sought early retirement. He would, however, remain at Alderley Park if ICI 46 474 was advanced for approval for clinical use as an orphan drug

for the treatment of metastatic breast cancer and the induction of ovulation. 'Sliding Doors' occurred for me in September 1972 with Mike Harper going to Geneva and me calling Arthur Walpole. Walpole supported me to receive an unrestricted research grant from ICI Americas and introduced me to the lady who became my lifelong friend – Lois Trench. She was the new drug monitor in charge of developing ICI 46 474 in the USA and she succeeded. She recruited me as the scientific consultant for ICI Americas to advocate tamoxifen to clinical trials groups (ECOG and the NSABP) for clinical testing. I returned to Leeds University in September 1974 as a lecturer in pharmacology with much work to accomplish. I had omitted to publish my work and had to catch up. Remember: if you do not publish, it never happened and you cannot claim the credit (only in your mind!).

Investment in young investigators

In 1974, Dr Roy Cotton was the clinician in charge of the development of Nolvadex (ICI 46 474, tamoxifen) for ICI Pharmaceuticals Division. He was my contact person with an agenda to devise a way for the Clinical Department to support my work at Leeds. He was inspirational and through his innovation advanced tamoxifen to become a 'pioneering medicine'. He devised a way for 'flexible support' that had minimal cost for ICI Pharmaceuticals Division or his clinical budget, but was to create a foundation for a blockbuster medicine for women's health. Roy Cotton provided hundreds of rats from Alderley Park stocks in Cheshire for my work at Leeds University. He arranged for continuous supplies of rats to be chauffeured to Leeds Medical School every week between 1975 and 1978 to complete dozens of experiments on the mechanism of action of tamoxifen, metabolism, the strategy to deploy tamoxifen as the first chemopreventive, and as the first targeted long-term antiestrogenic adjuvant therapy. The paper entitled 'Use of the DMBA-induced rat mammary carcinoma system for the evaluation of tamoxifen as a potential adjuvant therapy' (Jordan 1978) was the first to propose publically that 'longer was better than shorter adjuvant therapy' published in the *Reviews of Endocrine-Related Cancer*. The Yorkshire Cancer Research Campaign also provided essential support to this young investigator, without which we could not have supported our staff and students and bought essential equipment that demonstrated tamoxifen bound to the ER (Jordan & Prestwich 1977). Strange as this seems today, the ER was an unpopular and unproven mechanism of tamoxifen action for the clinical

community in the UK and for the next 10 years, the ER assay we use today was not accepted in the 1970s–1980s in the UK. The good news was that instead of doing an ER assay, every breast cancer patient received tamoxifen anyway, and as a result untold numbers of lives were saved with tamoxifen from the beginning.

Conversation with Nature

In 1975, Marc Lippman published (Lippman & Bolan 1975) that tamoxifen was a competitive inhibitor of estrogen-stimulated growth of MCF7 breast cancer cells. Lois Trench in USA had provided me with a selection of frozen breast cancers to measure ER, and in 1975 we showed that tamoxifen blocks estradiol binding to the human tumor ER (Jordan & Koerner 1975). Now back at Leeds, I was refining another publication, started at the Worcester Foundation (Jordan 1974) that tamoxifen prevented rat mammary carcinogenesis (Jordan 1976b). At that time, chemoprevention of breast cancer was a ‘forlorn hope’. Indeed, Michael Sporn had only just invented the new word (Sporn *et al.* 1976). I decided instead to turn to the issue of adjuvant therapy with tamoxifen. Marc Lippman stated in a line of his paper (Lippman & Bolan 1975) that high doses of tamoxifen were tumoricidal for MCF7 cells, so we decided to put it to the test *in vivo*.

When I was at the Worcester Foundation, I spent a day (and dinner) with the late Elwood Jensen, the then Director of the Ben May Laboratory for Cancer Research in Chicago, when he visited the Foundation in September 1972. He was a new member of the Scientific Advisory Board for the Foundation, appointed by Mahlon Hoagland, the new Director in 1970. I accepted Elwood’s offer to go to Chicago in the summer of 1973 to learn ER assay techniques and the DMBA-induced rat mammary carcinogen model. Both techniques were essential for the job to be completed, to find new and novel clinical strategies for tamoxifen.

Back at Leeds some 3 years later, I devised a model that, in my naïve view, would replicate adjuvant therapy with tamoxifen despite the fact that it was not a real model of human disease. There was no real model, so there was no choice but to use what was available. My reasoning was as follows. If DMBA was administered to 50-day-old Sprague–Dawley rats, then all animals would develop tumors within 150 days. I planned two strategies initially: give the DMBA at 50 days of age and then treat daily with increasing doses of tamoxifen starting 30 days after DMBA but only for 1 month. A month in a rat’s life is about a year for a human: what was proposed for current adjuvant trials with

tamoxifen (Hubay *et al.* 1980, Ribeiro & Palmer 1983, Ludwig Breast Cancer Study Group 1984, Cummings *et al.* 1985, Ribeiro & Swindell 1985, Rose *et al.* 1985). The results show that there was a delay in tumorigenesis but then tumors appeared later with at least one tumor per rat (Jordan & Allen 1980, Jordan 1983). However, there was a clue as the higher the daily dose, the larger the delay in tumorigenesis. As it was known that tamoxifen had a long biological half-life (Fromson *et al.* 1973a,b), then I reasoned that tumorigenesis proceeded only after the drug was cleared following short-term treatment. We tried another approach, earlier or later after DMBA – earlier was better to prevent tumorigenesis (Jordan *et al.* 1979). So if the drug needs to be there to prevent the microfoci of deranged rat mammary epithelial cells from growing into tumors, then is long-term tamoxifen treatment superior to short-term therapy? The results showed that indefinite tamoxifen vs shorter tamoxifen are shown in Fig. 1 (Jordan 1978, Jordan *et al.* 1979, Jordan 1983). We had asked the question of what is the best way to give ‘adjuvant tamoxifen’ in the DMBA model and we did not get back the answer we expected but it was a consistent answer. No drug, no antiestrogen action – long-term therapy was the way to go. Conversion of the rat model to clinical practice: 5 or more years of adjuvant tamoxifen would be a superior adjuvant strategy than the planned 1-year of treatment.

Neither did we get the answer we anticipated when we tested the potent metabolite of tamoxifen 4-hydroxy-tamoxifen (Jordan *et al.* 1977) in the same model against tamoxifen (Jordan & Allen 1980). We had initially discovered that tamoxifen could be metabolically activated by 4-hydroxytamoxifen in our collaboration with ICI Pharmaceuticals Division, but I agreed to a delay in my publications for a year (Jordan *et al.* 1977) while ICI Pharmaceuticals Division sought to patent the metabolites. It was anticipated that there was little likelihood of successful development of tamoxifen to a financially rewarding product so there had been no need to follow protocol, waste time and money, to patent the metabolites. I was told years later, that the clinical staff at the beginning of the 1970s was told not to spend too much time on tamoxifen!

We tested the better antiestrogen, 4-hydroxy-tamoxifen, just in case we had found a better breast cancer drug. However, it turned out to be a less effective antitumor agent than tamoxifen in our model (Jordan & Allen 1980). The hydroxylated metabolite was cleared too quickly, simple pharmacology. Tamoxifen can be detected for up to 6 weeks after treatment stops. So it seems that tamoxifen maintained a supply of the active metabolite

as the potent drug but the less potent parent acts as the depot that saturates a patient's body. Nevertheless, the metabolite experiments with 4-hydroxytamoxifen again showed that longer was better than shorter (Jordan & Allen 1980). Keep the drug there constantly: no drug present, no action. This was the principle that we advanced to the clinical community starting that day at King's College, Cambridge, in 1977.

A conversation between the laboratory and the clinic

My love for chemistry was always focused on what organic chemistry can do to create medicines to defeat disease. That for me was the guiding principle first created by Prof. Paul Ehrlich at the dawn of the 20th century when he created the first chemical therapy (chemotherapy) to cure syphilis (Baumler 1984). I seized upon the principle with alacrity in my teens with the desire to find molecules to treat cancer. This was pharmacology and 'failed contraceptives' were both my 'Sliding Doors' and my opportunity. But unless you train yourself and learn to be ready to seize the opportunity, it will vanish as quickly as it appeared. It is a moment in time governed by factors that you cannot control but determination and discipline will aid your quest for success. In my case, the topic was definitely not fashionable so nobody cared or very few. The 'few' were happy amateurs who wanted to contribute to human health when the majority considered 'another hormone therapy' a waste of time and resources. In my case, it was said I had poor career judgment because more than once the topic would crop up that if tamoxifen failed, then I would have nothing. It is true that tamoxifen would most certainly fail today as tamoxifen was unexpectedly proven to cause liver cancer in rats in the early 1990s (Greaves *et al.* 1993). This was some 20 years after clinical use started! Testing of the toxicology of an agent for cancer treatment is trivial but, for a medicine for healthy women (chemoprevention), the rules rightly change and major long-term toxicity testing occurs. No company today would develop tamoxifen knowing it caused cancer. But *Nature* gave the right answer if you were a rat (Greaves *et al.* 1993) and the right answer for women in the invaluable overview analyses that show no increase in liver cancer (Early Breast Cancer Trialists' Collaborative Group 1992, 2005).

Because pharmacology is about '*the enormous power to help others*', I chose to move my career into clinical cancer research through clinical cancer centers in the United States. The opportunities to learn and contribute to

oncology at the University of Wisconsin Comprehensive Cancer Center are a tribute to Paul Carbone, Doug Tormey, and David Rose each making my recruitment happen. I chose to train myself. Actually, it was Lois Trench who initiated all of the process back in 1977 and funded studies through ICI Americas for me to travel to Madison for 3 months to see if I could be recruited. ICI Pharmaceutical Division also deserves the credit for encouraging my career development into clinical research. They provided a decade of support to my laboratory (1973–1983), to pay staff, students' scholarships (Clive Dix rose rapidly to be Research Director for Glaxo, and Anna Tate Riegel is an endowed Prof. in Oncology at Georgetown), laboratory supplies, 'free rats', and most importantly Arthur Walpole did not take early retirement but remained at ICI Pharmaceuticals Division as my link for my University of Leeds/ICI Pharmaceuticals Division Joint Research Scheme until his untimely death on 20th July 1977. He never saw the success of tamoxifen; but, our connection made the possibility of success a certainty (this is, however, only the wisdom of hindsight!).

At the King College meeting around this time, I met Prof. Michael Baum (Fig. 2) who was now to chair my session and introduce me. In the discussion of my paper, he mentioned that he had arbitrarily planned to use 2 years of adjuvant tamoxifen, thereby advancing ahead of the numerous 1-year trials (Hubay *et al.* 1980, Ribeiro & Palmer 1983, Ludwig Breast Cancer Study Group 1984, Cummings *et al.* 1985, Ribeiro & Swindell 1985, Rose *et al.* 1985). Bernie Fisher in USA planned to do the same and advance to 2 years following the NSABP symposium in Key Biscayne Florida organized by Lois Trench in 1976. I gave the pharmacology of tamoxifen talk (Jordan 1976a), but I promised ICI Pharmaceuticals Division that I would not speak about 'metabolites'! Tamoxifen, as I mentioned earlier, was not to be FDA approved until December 1977 in USA, so that step was a priority for the company and I strongly believed this was also a priority for women's health with breast cancer.

Michael Baum and John Patterson, now the clinician responsible for tamoxifen, taking over from Roy Cotton, worked to come up with an imaginative acronym for this group's adjuvant 2-year trial to be sponsored by ICI Pharmaceuticals Division. It was called the NATO group to make American clinicians think it was an American trial and read the results. The acronym stands for 'Nolvadex Adjuvant Trial Organization' and the NATO group has the distinction of being the first to detect a survival advantage for patients taking adjuvant tamoxifen (Baum *et al.* 1983, Nolvadex Adjuvant Trial Organisation 1983).

Helen Stewart (Fig. 2) was in the audience at King's College in 1977. As it turned out, she would be running what was to be known as the Scottish trial led by Sir Patrick Forest and sponsored by the Medical Research Council (the same group who sponsored my PhD at Leeds University 'failed contraceptives'; I will forever be grateful as their investment really paid off!). The Scottish trialists were in the process of deciding whether patients could tolerate 5 years of tamoxifen. If so, their trial was then to start accruing patients to be randomized to 5 years of adjuvant tamoxifen or placebo and tamoxifen at first recurrence. Their results were published on 25th July 1987 (Scottish Cancer Trials Office (MRC) 1987) (coincidentally my birthday!) with significant survival advantages for early tamoxifen vs later use of tamoxifen upon recurrence. The animal studies therefore were '*a means of predicting the future*' when presented at King's College a decade earlier. For me, the '*power to help others*' was important as I subsequently traveled to speak at literally hundreds of clinical meetings worldwide. The clinical colleagues who became lifelong friends are too numerous to list but those close friends and colleagues in breast cancer research, Bill McGuire, Monica Morrow, and Gabriel Hortobagyi, deserve special recognition here for the part each was to play in my life.

By the mid 1980s, clinical trials slowly started to demonstrate some benefits of tamoxifen but, in the main, the trials were too small to declare 'breakthrough' as 'hormone therapy' was not curing everyone – chemotherapy would do that. Well perhaps but now enter the meta-analysis.

The Oxford Overview Analysis

Dr Craig Henderson tells the story of the first overview analysis (Henderson 1999). The overview was conducted by Sir Richard Peto, Sir Rory Collins, Richard Gray, and the team from the Clinical Trials Unit, Oxford University, in 1984. There were two main camps of randomized trials: the Europeans were cautious about the toxicity of cytotoxic chemotherapy and the American skeptical that a palliative 'hormone therapy' could aid survival. The results presented in a hotel at the Heathrow Airport in the mid-1980s showed that chemotherapy or tamoxifen improved disease-free survival and overall survival to about the same extent but in premenopausal and postmenopausal patients respectively. Since then, analyses have occurred in 1990 and 1995 and at regular intervals thereafter to this day. The value of seeing an analysis of all the data permitted the prevention trials with

tamoxifen to advance as inhibition of contralateral breast cancer in adjuvant tamoxifen trials was consistently at 50% and safety with endometrial cancer in postmenopausal women was much less significant than feared. Also, the concern about tamoxifen-induced rat hepatocarcinogenesis was not translated to human treatment trials. The trends observed with 1, 2, and 5 years of adjuvant tamoxifen predicted 'even more' was going to be better. There would have been no ATLAS trial or a focus on unanticipated outcomes without the overview analysis. *Nature* was also to tell us something unanticipated about decreasing mortality with tamoxifen. If tamoxifen is classified as a nonsteroidal antiestrogen that blocks estrogen-stimulated growth of micrometastases as a cytostatic agent, then why does stopping tamoxifen at 5 years not cause recurrence? No drug, no effect. Instead it causes a continuing decrease in mortality after stopping the antiestrogen. We know that stopping tamoxifen too soon, i.e. at 1 or 2 years, regrettably reduces the numbers of lives saved. But why?

The legacy of long-term adjuvant tamoxifen

The full story of tamoxifen has recently been told (Maximov *et al.* 2013). Through study of the pharmacology of tamoxifen, its metabolites, and its ubiquitous use for the treatment and prevention of breast cancer, several other significant advances in therapeutics and women's health have occurred.

The introduction of long-term adjuvant tamoxifen therapy mandated an examination of the development of acquired resistance to tamoxifen in the laboratory. At the time, in the mid 1980s, there were some cell culture studies of resistance, but the finding that opened the door to understand the evolution of acquired resistance to tamoxifen treatment was the transplantable model of acquired resistance in athymic mice (Gottardis & Jordan 1988, Gottardis *et al.* 1989). These studies also lead to the discovery that tamoxifen could control the growth of breast cancer but causes the growth of pre-existing endometrial cancer (Gottardis *et al.* 1988). Different tissues responded to tamoxifen in different ways: in the breast it was an antiestrogen; but in the bones, endometrium, and the regulation of circulating cholesterol, estrogenic actions were predominant (Lerner & Jordan 1990, Jordan 2001). These observations gave the medicine selective ER modulators (SERMs). There were no SERMs in 1990, only tamoxifen was classified as a nonsteroidal antiestrogen to treat breast cancer (Jordan 1984). Today, there are numerous SERMs (tamoxifen, raloxifene, bazedoxifene,

toremifene, ospemifene, and lasofoxifene) for a wide variety of indications. That story has recently been told (Jordan 2013).

An understanding of the evolution of acquired resistance to tamoxifen (Yao *et al.* 2000, Jordan 2004, 2008) also led to the discovery of the new biology of estrogen-induced apoptosis that not only has clinical applications to treat antihormone-resistant breast cancer (Ellis *et al.* 2009) and explain how estrogen replacement therapy can reduce the incidence of breast cancer in long-term estrogen-deprived (>10 years after menopause) women (Anderson *et al.* 2012), but also can explain the reason why tamoxifen therapy for >5 years can dramatically reduce mortality after stopping therapy. The woman's own estrogen may destroy selected and vulnerable clonal micrometastases (Wolf & Jordan 1993).

The idea that longer therapy with adjuvant tamoxifen in patients with ER-positive breast cancer was not fashionable at the start. This is the way it is with most new concepts in any discipline. The clinical strategies of using 1 year of adjuvant tamoxifen (Hubay *et al.* 1980, Ribeiro & Palmer 1983, Ludwig Breast Cancer Study Group 1984, Cummings *et al.* 1985, Ribeiro & Swindell 1985, Rose *et al.* 1985) were clinically sound in the late 1970s because clinical experience using tamoxifen to treat metastatic breast cancer showed that treatment was successful in a minority of unselected cases for <2 years. Suggesting a treatment strategy for indefinite adjuvant tamoxifen treatment was destined to fail at 2 years – but it did not. I believe that the reason lies in the fact that metastatic disease is too established and can readily subvert the stress caused by preventing estrogen-stimulated growth. It is also a matter of bulk and vascularization that aid the survival of breast cancer cells in metastatic disease. But micrometastatic disease is apparently indolent and not well established but survives through slow and deliberate microscopic steps to select cells with acquired resistance that evolves very slowly through phases of resistance to reach unstable and vulnerable clonal populations over 5 years of treatment. It takes this long in the laboratory (Yao *et al.* 2000) and physiological estrogen will now cause rapid tumor regression (Wolf & Jordan 1993, Yao *et al.* 2000). But what if estrogen from the patient now triggers estrogen-induced apoptosis in the adjuvant tamoxifen trial of 5 years or more (Early Breast Cancer Trialists' Collaborative Group 1998, Jordan 2008, Davies *et al.* 2013)?

Is there direct evidence that the new biology of estrogen that causes apoptosis gives us profound mortality decreases after tamoxifen is stopped? Yes, I believe so. We know (Anderson *et al.* 2012) from the Women's Health Initiative

estrogen-only trial that there is a profound decrease in the incidence of breast cancer and mortality for women treated with estrogen in their 1960s when compared with placebo. Estrogen kills estrogen-deprived occult cancer cells more than a decade after menopause (Obiorah & Jordan 2013). None of this science would have been revealed but for the fact that long-term adjuvant tamoxifen advanced from a laboratory concept in the late 1970s (Jordan 1978, Jordan *et al.* 1979), through clinical trials, to be enhanced as a reality by the Oxford Overview Analyses (Davies *et al.* 2011). Today, we have a successful clinical strategy with the results of ATLAS (Davies *et al.* 2013) and aTTom (The aTTom Collaborative Group 2013). Further lives are saved with a cheap effective medicine that never went away. The science of long-term adjuvant tamoxifen was indeed '*an adventure, discovery, new horizons, insights into our world, a means of predicting the future, and enormous power to help others*' (Hoagland 1990).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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