Chapter 2
Tamoxifen Goes Forward Alone

Abstract Tamoxifen (ICI 46,474), the trans isomer of a substituted triphenyl-ethylene, was discovered in the fertility program at Imperial Chemical Industries, Pharmaceuticals Division, Cheshire, England. The plan was to use tamoxifen to regulate fertility, but this failed and interest refocused outside the company for applications to treat breast cancer. The initial application of the nonsteroidal antiestrogen was for the treatment of metastatic breast cancer in postmenopausal women and by the 1980s tamoxifen had replaced high-dose diethylstilbestrol therapy. Efficacy when compared with diethylstilbestrol was similar, but tamoxifen had fewer side effects. No other antiestrogens were developed by the pharmaceutical industry, as this was not considered a financially lucrative development strategy.

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” (C.V. Wedgewood, William the Silent). That is, unless one has lived through the evolving applications of tamoxifen.

Tamoxifen (ICI 46,474; Nolvadex), a nonsteroidal antiestrogen, started life as the endocrine treatment of choice for advanced breast cancer [1]. Adjuvant therapy with tamoxifen also proved to be effective [2] because a sustained survival advantage is noted for women with node-positive and node-negative disease. The Food and Drug Administration (FDA) approved the use of tamoxifen as an adjuvant therapy with chemotherapy (1986), as an adjuvant therapy alone (1988) in node-positive postmenopausal patients and pre- and postmenopausal node-negative patients with ER-positive disease (1990). Tamoxifen is used to treat breast cancer in men (1993). However, remarkably tamoxifen was also approved to reduce the risk of breast cancer in women at high risk (1998). Tamoxifen was also FDA approved for treatment of ductal carcinoma in situ (DCIS) (2000). No other cancer therapy is so widely approved and had so dramatic an impact on cancer care. Tamoxifen is,
however, one of those remarkable examples of a drug originally designed for one primary purpose that fails but is then steered by dedicated scientists toward a recognized secondary application where it becomes enormously successful.

The chief credit for the discovery of tamoxifen in 1962, and its subsequent application as an orphan drug treatment for metastatic breast cancer, must be given to Dr. Arthur L. Walpole (Fig. 2.1), then head of the fertility control program for Imperial Chemical Industries (ICI) Pharmaceuticals Division. Tamoxifen was identified as an effective postcoital contraceptive in rats [3–5] and there was a distinct possibility that antiestrogens could be developed as “morning-after” pills [6]. However, the basic pharmacology and physiology of ovulation and implantation are critically different in women and rats. When tamoxifen was tested in patients in preliminary clinical studies, it was found to induce ovulation rather than reduce fertility [7, 8] and so is marketed in some countries for the induction of ovulation in subfertile women [1].

The ovarian dependence of some breast cancers has long been recognized [9, 10] and the first antiestrogens [11, 12] were shown to be effective in their treatment, but the drugs then available were considered to be too toxic for chronic use [13–15] (Table 2.1). By the end of the 1960s, the direct role of estrogen in breast cancer growth was further substantiated with the description of ERs in breast tumors [18–20] and the subsequent clinical correlation with hormone dependency [21, 22]. However, clinical research with tamoxifen was not based on the ER but on proven antifertility activity as an antiestrogen in the rat. Walpole encouraged the clinical testing of the antiestrogen tamoxifen at the Christie Hospital and Holt Radium Institute in Manchester [16]. He had a long interest in cancer research [23] but also wanted to determine whether tamoxifen was an estrogen or an antiestrogen in humans because of the link between estrogens and breast cancer growth. A subsequent dose response study was published by Dr. Harold Ward [17]. But in 1972, ICI Pharmaceutical
Division chose to abandon clinical development because there would be no financial gain for the limited applications in the treatment of metastatic breast cancer where only one in three patients respond for, on average, 2 years [24].

This chapter will trace the “resurrection” and development of tamoxifen for the treatment of advanced breast cancer in postmenopausal patients and consider the unusual set of circumstances that set the stage for the subsequent success of tamoxifen as a long-term adjuvant therapy in patients with node-positive and node-negative disease. In 1990, the fashion was to change again with a plan to test the worth of tamoxifen as a preventive in women at risk for breast cancer [25–27]. Much of the basic laboratory work in animal models was conducted in the period 1974–1992. This produced a strong rationale to move forward with clinical trials and the meticulous evaluations of pharmacology of tamoxifen (Fig. 2.2). This is our story.

### ICI 46,474: The Early Years

In 1958, Lerner and coworkers described the first nonsteroidal antiestrogen MER 25. The drug was tested in clinical trials but proved to be toxic at the high doses required [28]. A successor compound, clomiphene (also known as chloramiphene or MRL41) (Fig. 2.2), now known to be a mixture of two geometric isomers with opposing biological activities, was a postcoital contraceptive in rats but was developed only clinically as a fertility drug [29] (see Chap. 1).

To understand the obstacles that had to be overcome before the successful clinical development of tamoxifen, it is necessary to recapture the mood of the times in the 1950s/1960s. Coronary heart disease was a primary target for drug development and was proving to be a lucrative market. However, one product—triparanol (MER29) (Fig. 2.2)—was to become a cause célèbre and a major issue in the relationship between product safety and regulatory authorities. Indeed, this case was taught to Craig Jordan as an undergraduate at Leeds University, in the Pharmacology Department (1965–1969), to illustrate how drug development can go very wrong.

#### Table 2.1 Comparison of the early chemical experience with antiestrogen as a treatment for metastatic breast cancer

<table>
<thead>
<tr>
<th>Antiestrogen</th>
<th>Daily dose (mg)</th>
<th>Year</th>
<th>Response rate (%)</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethamoxytriphetol</td>
<td>500–4,500</td>
<td>1960</td>
<td>25</td>
<td>Acute psychotic episodes</td>
</tr>
<tr>
<td>Clomiphene</td>
<td>100–300</td>
<td>1964–1974</td>
<td>34</td>
<td>Fear of cataracts</td>
</tr>
<tr>
<td>Nafoxidine</td>
<td>180–240</td>
<td>1976</td>
<td>31</td>
<td>Cataracts, ichthyosis, photophobia</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>20–40</td>
<td>1971–1973</td>
<td>31</td>
<td>Transient thrombocytopenia&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>“The particular advantage of this drug is the low incidence of troublesome side effects” [16]. “Side effects were usually trivial” [17]
Triparanol was an orally active lipid-lowering agent developed by the Merrell Company during the 1960s [30]. Unfortunately, acute cataract formation was noted in young women treated with triparanol [31] and this ultimately led to the withdrawal of the medicine. The toxicity was linked to the accumulation of desmosterol as a consequence of the inhibition of cholesterol biosynthesis [32] (Fig. 2.3).

The punitive legal issues surrounding the withdrawal of triparanol forced the Merrell Company to avoid long-term treatments with any agents known to, or thought to, cause increases in the circulating levels of desmosterol. Triparanol [33], ethamoxytriphetol, and clomiphene [14] were all tested as treatments for breast cancer, but their potential to harm through cataract formation forced the Merrell Company to abandon work in the treatment of breast cancer. The administration of clomiphene for a few
days to induce ovulation was considered safe compared with the years of therapy necessary for breast cancer treatment.

Arthur Walpole, as head of the Fertility Control Program at ICI Pharmaceuticals Division Alderley Park, was already interested in the pharmacology of nonsteroidal estrogens and was asked to find a safer nonsteroidal antiestrogen in the early 1960s. Dora Richardson was the synthetic organic chemist for the program (Fig. 2.4) and a young reproductive endocrinologist Michael J. K. Harper conducted the antifertility studies in the rat model (Fig. 2.4). The discovery of ICI 46,474 with reduced concerns about desmosterol accumulation was an advance.

From the time that tamoxifen was first available in clinical practice (1973) until the late 1980s, there were remarkably few concerns about the toxicity of tamoxifen, because the side effects from chemotherapy, by contrast, were so severe. Only with the extended use of tamoxifen as an adjuvant therapy in node-negative women, and the proposed use of tamoxifen as a chemopreventive, was there a return to an evaluation of the toxicity of tamoxifen, both by laboratory studies and by the analysis of randomized clinical trials. Despite the fact that tamoxifen was considered safe for long-term adjuvant therapy in women with breast cancer, analysis of the prevention trials organized and run by the National Surgical Adjuvant Bowel and Breast Project (NSABP) would demonstrate a small increase in cataracts and cataract operations for women without disease taking tamoxifen to reduce breast cancer incidence [34, 35].

![Diagram](image)

**Fig. 2.3** The inhibition of cholesterol biosynthesis by triparanol, clomiphene, tamoxifen, and the chlorinated derivative of tamoxifen toremifene (see Chap. 3, Fig. 3.7)
ICI 46,474 was first synthesized by Dr. Dora Richardson at ICI Ltd., Pharmaceuticals Division (Fig. 2.4), and was shown to be an antifertility agent in rodents \[4, 5\]. Dr. Michael Harper (Fig. 2.4)\[3\] made the discovery that the geometric isomers of substituted triphenylethylenes have opposing biological properties: the *cis* isomer ICI 47,699 is an estrogen, whereas the *trans* isomer ICI 46,474 has antiestrogenic activity. Thus the structure of the drug can program the cells for estrogenic or antiestrogenic properties \[36–38\]. Another observation made by Harper and Walpole was that ICI 46,474 exhibits species specificity; in short-term tests, the compound is an estrogen in the mouse and an antiestrogen in the rat \[3, 4\]. The triphenylethylene derivative blocks the binding of $[^{3}H]$estradiol to ERs derived from both rat and mouse target tissues \[39–42\], but no completely satisfactory subcellular mechanism for the species difference of ICI 46,474 has yet been established. In fact, the situation is probably more complex than may at first be appreciated. The long-term administration of tamoxifen to ovariectomized mice results in an initial estrogen-like effect in the vagina \[40\] and the uterus \[43\], but as treatment progresses both the uterus and vagina become refractory to the effects of exogenous estrogen, and ICI 46,474 becomes a complete antiestrogen in the vagina.

Preliminary clinical studies with ICI 46,474 to treat advanced breast cancer in postmenopausal women were conducted by Mary Cole and coworkers \[16\] at the Christie Hospital in Manchester. The confirmation that ICI 46,474 could be used successfully as palliative in advanced disease but produces few side effects \[17, 44\] acted as a catalyst to encourage the study of the mode of action of the drug in animal tumor models. Indeed the conversation between the laboratory and the clinic became the hallmark for the successful development of tamoxifen.

Animal studies were first started in 1973 at the Worcester Foundation for Experimental Biology Shrewsbury, Massachusetts \[45–50\]. The dimethylbenzanthracene (DMBA)-induced rat mammary carcinoma model, originally described a

*Fig. 2.4* (Left) Dora Richardson was a co-patent holder for ICI 46,474 and the organic chemist responsible for the synthesis of triphenylethylenes at ICI Pharmaceuticals. This photograph was taken on the occasion of her retirement in 1979. (Right) Mike Harper who discovered the opposing biological activities of the *cis* and *trans* isomers of substituted triphenylethylenes
decade earlier by the Nobel Laureate Professor Charles Huggins [51], was used to study the efficacy and mode of action of ICI 46,474 under controlled laboratory conditions. The model was considered to be state of the art, because no other hormone-dependent models were then available for study. Rob Nicholson, then a graduate student at the Tenovus Institute for Cancer Research in Cardiff, Wales, also selected the DMBA-induced rat mammary carcinoma model for this study of the antitumor actions of ICI 46,474 and related compounds [52]. These parallel research ventures fully described the antitumor activity of the antiestrogen in vivo [41, 48–50, 53, 54] at a time when the efficacy of tamoxifen was being established widely in breast cancer clinical trials [55].

ICI 46,474 to Tamoxifen

In 1973, Nolvadex, the ICI brand of tamoxifen (as its citrate salt), was approved for the treatment of breast cancer by the Committee on the Safety of Medicines in the United Kingdom. Similar approval was given in the United States for the treatment of advanced disease in postmenopausal women by the Food and Drug Administration on 30 December 1977. Nolvadex was available in more than 110 countries as the first-line endocrine therapy for the treatment of breast cancer [1]. To mark this achievement, ICI Pharmaceutical Division was presented with the Queen’s Award for Technological Achievement by the Lord Lieutenant of Cheshire, Viscount Leverhulme, on 6 July 1978. The remarkable success of tamoxifen encouraged a closer examination of its pharmacology with a view to further development and wider applications.

The metabolism of tamoxifen in animals and patients was first described by Fromson and coworkers [56, 57]. The major metabolic route to be described was hydroxylation to form 4-hydroxytamoxifen, which was subsequently shown to have high binding affinity for the estrogen receptor and to be a potent antiestrogen in its own right [58] with antitumor properties in the DMBA model [59]. Indeed it is an advantage for the tamoxifen to be metabolically activated to 4-hydroxytamoxifen [60], but this is not a prerequisite for antiestrogen action. The metabolite was subsequently shown to localize in target tissues after the administration of radioactive tamoxifen to rats [61]. Originally, 4-hydroxytamoxifen was believed to be the major metabolite in patients [57], but Hugh Adam [62] at ICI Pharmaceutical Division demonstrated that N-desmethyltamoxifen is the principal metabolite found in patients. There is usually a blood level ratio of 2:1 for N-desmethyltamoxifen that has twice the plasma half-life of tamoxifen (14 days vs. 7 days) [63]. The ubiquitous use of tamoxifen resulted in the publication of numerous methods to estimate tamoxifen and its metabolites in serum (reviewed in [64]). The metabolites that have been identified in patients are shown in Fig. 2.5. The minor metabolites, metabolite Y [65], metabolite Z [66], and 4-hydroxy-N-desmethyltamoxifen [67], all contribute to the antitumor actions of tamoxifen, because they are all antiestrogens which inhibit the binding of estradiol to the ER. The metabolism of tamoxifen will be considered in more detail in Chap. 3.

The next significant advance came with the availability of hormone-dependent human breast cancer cells to study antitumor mechanisms in the laboratory.
Fig. 2.5 The scheme of tamoxifen metabolism and the structures of its metabolites
Marc Lippman [68] was the first to describe the ability of tamoxifen to inhibit the growth of MCF-7 ER-positive breast cancer cells [69] in culture and to demonstrate that the addition of estrogen could reverse the action of tamoxifen. Nearly a decade later, Kent Osborne [70] and Rob Sutherland [71] independently described the blockade by tamoxifen of breast cancer cells at the G1 phase of the cell cycle.

Studies with the heterotransplantation of MCF-7 cells into athymic mice demonstrated that, unlike estradiol, tamoxifen does not support the growth of tumors [72]. Tamoxifen [73] and its metabolites [74] will block estrogen-stimulated tumor growth. However, very high circulatory levels (2,300 pg/ml) of estradiol in a low-tamoxifen environment (40 ng/ml) can partly reverse the inhibitory actions of tamoxifen for MCF-7 tumor growth [75]. Overall, these studies of the reversibility of tamoxifen action could have implications for its extended adjuvant use in premenopausal women.

These significant biological advances propelled tamoxifen forward to become the only nonsteroidal estrogen antagonist that would become the “gold standard” for the endocrine therapy of breast cancer for two decades. But none of this seemed possible in the 1970s when ICI Pharmaceutical Division was chauffeuring thousands of rats from Alderley Park to Leeds University. This investment in independent academic research would convert an orphan drug to be multibillion GBP blockbuster that saved millions of women’s lives [76]. What is amazing is that the early work occurred without patent protection, but that changed.

## Patenting Problems

Adequate patent protection is required to develop an innovation in a timely manner. In 1962, ICI Pharmaceuticals Division filed a broad patent in the United Kingdom (UK) (Application number GB19620034989 19620913). The application 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.”

This was published in 1965 as UK Patent GB1013907, which described the innovation that different geometric isomers of substituted triphenylethylenes had either estrogenic or antiestrogenic properties [3]. Indeed, this observation was significant, because when scientists at Merrell subsequently described the biological activity of the separated isomers of their drug clomiphene, they inadvertently reversed the naming [77]. This was subsequently rectified [78].

Although tamoxifen was approved for the treatment of advanced breast cancer in postmenopausal women in 1977 in the United States (the year before ICI Pharmaceuticals Division received the Queen’s Award for Technological Achievement in the UK), the patent situation was unclear. ICI Pharmaceuticals Division was repeatedly denied patent protection in the United States until the 1980s because of the perceived primacy of the earlier Merrell patents and because no advance (i.e., a safer, more
specific drug) was recognized by the patent office in the United States. In other words, the clinical development advanced steadily for more than a decade in the United States without the assurance of exclusivity. This situation also illustrates how unlikely the usefulness of tamoxifen was considered to be by the medical advisors to the pharmaceutical industry in general. No other company chose to “steal” tamoxifen. Remarkably, when tamoxifen was hailed as the adjuvant endocrine treatment of choice for breast cancer by the National Cancer Institute in 1984 [79], the patent application, initially denied in 1984, was awarded through the court of appeals in 1985. This was granted with precedence to the patent dating back to 1965! So, at a time when worldwide patent protection was being lost, the patent protecting tamoxifen started a 17-year life in the United States. The unique and unusual legal situation did not go uncontested by generic companies, but AstraZeneca (as the ICI Pharmaceuticals Division is now called) rightly retained patent protection for their pioneering product, most notably, from Smallkin’s decision in Baltimore, 1996 (Zeneca, Ltd. vs. Novopharm, Ltd.Civil Action No S95-163 United States District Court, D. Maryland, Northern Division, 14 March 1996).

**Conclusion**

The unprecedented advance of tamoxifen from the first unsure steps seems unbelievable but actually occurred. This situation was dependent on the correct, prepared individuals being at the right place at the right time to advance a pioneering medicine that saves lives.

**Postscript.** In September 1972, at the time of the examination of my Ph.D. thesis by Dr. Arthur Walpole, I was unaware that the research director at ICI Pharmaceutical Division had ordered the termination of the clinical development of tamoxifen. This was a financial decision based on non-profitability. My understanding is that all of the clinical research on tamoxifen (then ICI 46,474) had been reviewed in March 1972 at a symposium at Alderley Park [24].

The termination of tamoxifen’s development toward registration and clinical use had resulted in Walpole requesting early retirement. Scientists at ICI Pharmaceutical Division did none of the laboratory work on tamoxifen as an antitumor agent; that was outsourced to me for a decade. But how did that happen?

I had already been recruited to the faculty as a lecturer in Pharmacology at Leeds, but first I was required to spend a couple of years in the United States to obtain my BTA (Been to America, a colloquial acronym as a prestigious research qualification). It had been arranged that I would go to the Worcester Foundation for Experimental Biology (the home of the oral contraceptive) to work with Mike Harper, who had left ICI Pharmaceutical Division some years earlier and now headed an Agency for International Development Program, to create a once a month contraceptive based on prostaglandins (the new research fashion!). I remember my conversation with Mike Harper on the telephone as I stood in the corridor on the phone in the old Medical School in Leeds. He asked three questions: “Could you start in September
“Would $12,000 a year be acceptable?” and “Would you work on prostaglandins?” “Yes, yes, yes,” I replied and headed off to the library to find out what prostaglandins were!

Walpole, my committee, and I met for my examination in the Department of Pharmacology at the Leeds University in early September 1972. This had become a matter of urgency as I had to complete the examination, drive to Southampton to board the QEII, and then travel from New York to Worcester, MA, to be a visiting scientist for 2 years at the Worcester Foundation for Experimental Biology.

When I arrived to the Worcester Foundation in September 1972—incidentally not knowing anything about prostaglandins—I discovered that Mike Harper had accepted a job with the World Health Organization in Geneva. My new boss Ed Klaiber said: “Next week give me a plan of research you propose to complete here in the next two years” and “You can do anything you like as long as some of it includes prostaglandins.” Armed with a brand new Ph.D. in “failed contraceptives” (a topic not designed to equip me for a research career!), I immediately found myself as an independent investigator and planned my work on prostaglandins. However, my new circumstances would also allow me to explore my passion—to develop a drug to treat breast cancer.

A phone call to Walpole started the process of turning ICI 46,474 into tamoxifen, the gold standard for the endocrine treatment of breast cancer for the next 30 years. Walpole informed me that ICI Pharmaceuticals Division had just acquired Stuart Pharmaceuticals in Wilmington, Delaware, and they had created a new company ICI Americas. Lois Trench, the drug monitor for tamoxifen, would be the individual involved in the investment in my laboratory at the Worcester Foundation with an unrestricted research grant to determine how best to use tamoxifen in the clinic. But how to start? I was a pharmacologist with experience in “failed contraceptive” not a cancer research scientist. It seems that the way forward depends upon a clear plan, enthusiasm, and who you meet.

The National Cancer Act was passed in 1971 in the United States and the “war on cancer” began. The president of the Worcester Foundation Mahlon Hoagland realized that the research resources of the foundation in reproductive endocrinology could be steered toward endocrine-dependent cancers with the right advisor on the Scientific Advisory Board. Dr. Elwood Jensen, director of the Ben May Laboratory for Cancer Research at the University of Chicago, was a pioneer in the identification of the ER in estrogen target tissues in the rat and the application of this knowledge for the identification of estrogen-dependent breast tumors in women with metastatic breast cancer. The absence of ER in the tumor meant that there was no possibility of a response to endocrine ablation. Jensen spent a couple of days at the foundation in late 1972 and we spent time together going over my thesis work. I told him of my plans for tamoxifen and he generously agreed to have his staff (or rather Silvia Smith) teach me techniques of ER analysis and most importantly his colleague Dr. Gene DeSombre to teach me the dimethylbenzanthracene (DMBA)-induced rat mammary carcinoma model. My visit to Chicago to learn the techniques was a dream come true!
Lois Trench arranged for me to receive a small collection of deep-frozen breast tumors so we started the program of translational research with the aid of Suzanne Koerner, a superb technician. Lois insisted I became a consultant to ICI Americas to encourage clinicians in oncology groups to study tamoxifen in clinical trial. I lectured to the members of the Eastern Cooperative Oncology Group Breast Committee at their meetings in Miami and Jasper National Park in 1974. Too many adventures there to fit in the limited space here, I am afraid! Lois, then sponsored me to present the first study on tamoxifen as a preventive of mammary cancer in rats at the International Steroid Hormone Congress in Mexico City in September 1974 [45] (more adventures with my boss Ed Klaiber in Acapulco).

The idea of publishing my emerging data for the treatment and prevention of breast cancer did not occur immediately. Nobody in the scientific or clinical community really cared about the development of another (more expensive) endocrine therapy of limited effectiveness. However, that perspective was to change. Eliahu Caspi called me to his office one day in July 1974 and announced he had been charged with the responsibility of evaluating my CV and bibliography to explore the possibility of me staying at the foundation as a staff member and not returning to Leeds University. He was rather frightening as an individual and stared at me across his desk. He reiterated that he had been told to interview me and evaluate my CV. He then said: “but you haven’t got one as you have not published anything.” After a stunned silence from me, I replied: “but I haven’t discovered anything,” to which he then gave me the best advice I had received about developing an academic career up to that point. “Tell them the story so far; each paper can be written within about 2 weeks and create a theme of interlocking research papers.” I have followed his advice ever since.

I would like to recount an unanticipated honor that occurred by chance in 2002. At the commencement of the University of Massachusetts Medical School at the Mechanics Hall in Worcester in 2001, I was delivering my acceptance speech for an honorary Doctor of Science degree and told my Eliahu Caspi story about publication—emphasizing that if you don’t publish, it never happened. A year later I was asked to deliver the inaugural Eliahu Caspi Memorial Lecture at the Worcester Foundation. It was then that I learned of the remarkable background of Dr. Caspi and had the pleasure of spending time with his accomplished family. As a young man in Poland, Caspi had survived a Russian prison camp, escaped to the emerging Israel, joined the Haganah (early Israeli Defense Forces), and then came to America to complete his Ph.D. at Clark University in Worcester. He then joined the Worcester Foundation having a distinguished career in glucocorticoid metabolism and synthesis until his death in May 2001.

References


References
55. Tamoxifen Workshop (1976) Proceedings of the annual spring meeting of the primary breast cancer therapy group, Key Biscayne, p 1409: 66

References 45
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