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Review

The development of tamoxifen for breast cancer therapy: a tribute to the late Arthur L. Walpole

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Key words: antiestrogen, adjuvant therapy, ICI 46,474, endocrine therapy, tamoxifen

Summary

Tamoxifen, a nonsteroidal antiestrogen, is now the endocrine treatment most widely used in breast cancer, both in the adjuvant and advanced disease settings. Here we will trace the development of tamoxifen for advanced breast cancer in postmenopausal patients, consider the biological basis for the recent successful use of tamoxifen for long-term adjuvant therapy, and discuss the use of tamoxifen in premenopausal patients with advanced disease. In part, this will be a historical review offered as a tribute to the late Dr. Arthur L. Walpole, who must receive the chief credit for the discovery of tamoxifen and its subsequent application as an anticancer agent.

Introduction

Tamoxifen (ICI 46,474; Nolvadex®) (Fig. 1), a nonsteroidal antiestrogen, is the endocrine treatment of choice for advanced breast cancer [1]. Adjuvant therapy with tamoxifen has also proved to be effective [2–4] and at a recent consensus conference sponsored by the National Cancer Institute in Bethesda, tamoxifen was recommended as the adjuvant therapy of choice for postmenopausal node-positive women with a receptor-positive primary tumor [5]. 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 towards 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 anticancer agent must be given to Dr. Arthur L. Walpole, then the head of the fertility control program for Imperial Chemical Industries PLC (ICI) Pharmaceuticals Division. Tamoxifen had been identified as an effective postcoital contraceptive in rats [6–8] and there was a distinct possibility that antiestrogens could be developed as 'morning-after' pills [9]. However, the basic pharmacology and physiology of ovulation and implantation is 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 [10, 11] and so is now marketed in some countries for the induction of ovulation in subfertile women [1].

The dependence of some breast cancers on estrogens had been long recognized [12] and antiestrogens were shown to be effective in its treatment, but the drugs then available were considered to be

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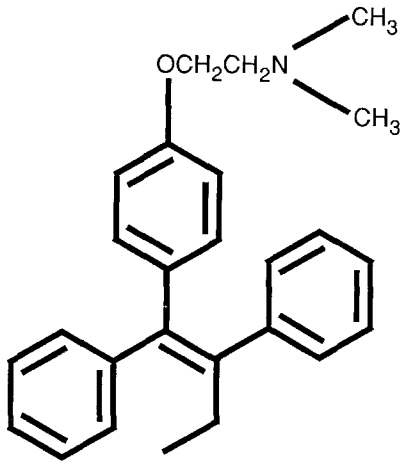


TAMOXIFEN
(ICI 46,474 Nolvadex ®)

Fig. 1. Formula of the triphenylethylene antiestrogen tamoxifen.

too toxic for chronic use [13, 14]. By the end of the 1960s the direct role of estrogen in breast cancer growth was further substantiated with the description of estrogen receptors in breast tumors [15–18]. Consequently, Walpole encouraged the clinical testing of the antiestrogen tamoxifen at the Christie Hospital and Holt Radium Institute in Manchester.

It may seem curious to nominate the head of ICI's fertility control program as the person responsible for advocating breast cancer clinical trials with tamoxifen, but Arthur Walpole had, 20 years earlier, established an excellent reputation for the testing and discovery of cancer chemotherapeutic agents.

In the late 1940s, he was a member of staff at ICI's Dyestuffs Division Biological Laboratory in Wilmslow, Cheshire. This establishment was the fledgling predecessor of the Pharmaceuticals Division Research Laboratories built in 1956–57 at Alderley Park near Macclesfield, Cheshire. Arthur Walpole was asked to establish animal models for the bioassay of potential alkylating agents [19–24] to evaluate compounds as bladder carcinogens [25] and to assess the potential health hazards for workers in the dyestuffs industry [26]. Walpole made the important discovery that trisethyleneimino-S-triazine (M9500) (Fig. 2) was an active anticancer agent in the Walker rat carcinoma 256 [20] and conducted extensive structure-activity relationship studies with many mono and bifunctional compounds. Trisethyleneimino-S-triazine was simultaneously, and independently, shown to be active in other animal cancer models by a team of scientists at the Sloan-Kettering Institute in New York [27, 28]. Clinical testing of the new drug was conducted on both sides of the Atlantic; Karnofsky and Rhoads conducted their study in New York [29] and Edith Paterson conducted clinical trials at the Christie Hospital and Holt Radium Institute in Manchester [30]. Although trisethyleneimino-S-triazine is now only of historical interest, the related compound, hexamethylmelamine (M10, 567) (Fig. 3) was also found to be active by Walpole [23].

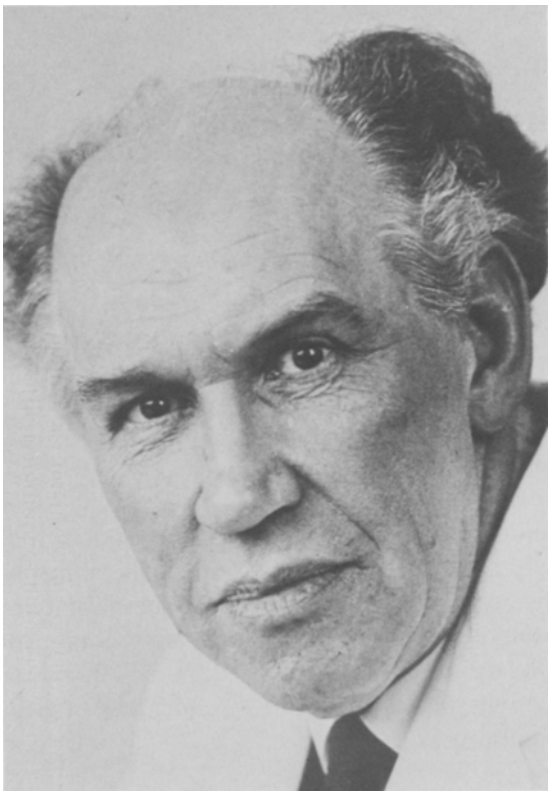
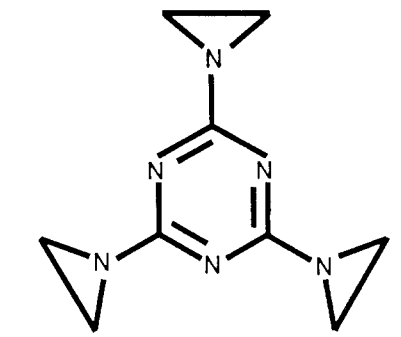
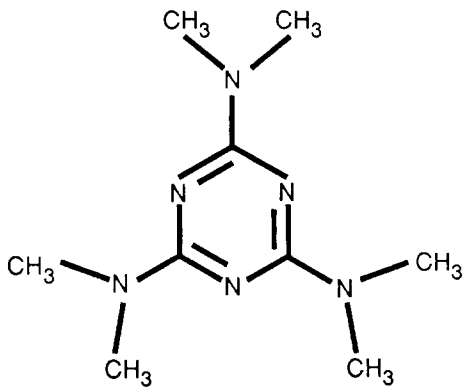


Fig. 2. Dr. Arthur L. Walpole.

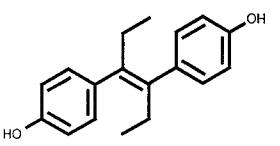


TRIETHYLENEMELAMINE
(M 9500)

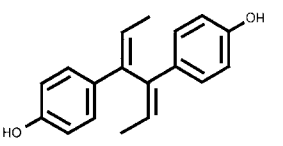


HEXAMETHYLMELAMINE
(M 10,567)

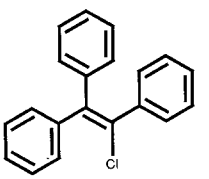
Fig. 3. Formulae of compounds studied by Dr. A.L. Walpole as potential antitumor agents in laboratory models that were subsequently successfully tested in clinical trials.



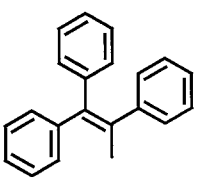
DIETHYLSTILBESTROL



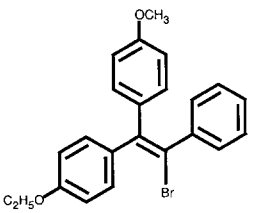
DIENESTROL



TRIPHENYLCHLORETHYLENE



TRIPHENYLMETHYLETHYLENE



M2613

Fig. 4. Formulae of nonsteroidal estrogens used by Dr. A.L. Walpole in clinical studies with Edith Paterson at the Christie Hospital for the treatment of advanced breast cancer. The compounds originally used by Haddow and coworkers (diethylstilbestrol, triphenylchlorethylene, triphenylmethylethylene) are illustrated for comparison.

Hexamethylmelamine* is active in a broad spectrum of tumors, including ovarian carcinoma resistant to other alkylating agents [33]. There is, however, much current interest and debate about the appropriate application of the drug [34, 35]. However, Walpole's interest in alkylating agents and carcinogenesis provides only part of the background which led to his suggestion that tamoxifen should be tested in breast cancer. Walpole was also interested in estrogens and was aware in 1963 that antiestrogens could be used for the treatment of breast cancer.

In 1949, he and Edith Paterson [36] collaborated on a clinical research project to study the effects of therapy with high doses of synthetic estrogens (diethylstilbestrol, dienestrol and M2613) (Fig. 4) in postmenopausal women with advanced breast cancer. Paterson, working with Alexander Haddow, had earlier been the first to show the beneficial effects of high-dose diethylstilbestrol, triphenylmethylethylene and triphenylchlorethylene (made by ICI) in breast cancer [37]. Walpole and Paterson confirmed the earlier findings and also demonstrated that older women were more likely to respond than younger women. The reason for the apparently arbitrary responses was to remain obscure for another decade or two until the era of the estrogen receptor assay [38, 39].

* The clinical evaluation of the pharmacokinetics and metabolism of HMM was conducted at the University of Wisconsin [31, 32].

This article will trace the development of tamoxifen for the treatment of advanced breast cancer in postmenopausal patients and consider the biological basis for the recent successful use of tamoxifen for long-term adjuvant therapy. The contemporary fashion for breast cancer therapy is to evaluate early treatment. Stage I disease accounts for approximately 50% of newly diagnosed breast cancer. Current research on the use of tamoxifen in premenopausal patients with advanced Stage I disease will also be reviewed to point out the potential and the problems with this strategy and to highlight current research interests.

ICI 46,474: The early years

In 1958, Lerner and coworkers [40] described the first nonsteroidal antiestrogen, MER25. The drug was tested in clinical trial in breast cancer but proved to be toxic at the high doses required [41]. A successor compound, clomiphene (also known as MRL 41 or chloramiphene), now known to be a mixture of two geometric isomers with opposing biological activities, was a postcoital contraceptive in rats but was subsequently only developed clinically as a fertility drug [42]. ICI 46,474 was first synthesized by Dr. Dora Richardson at ICI Ltd. Pharmaceuticals Division and was shown to be an antifertility agent in rodents [7, 8]. Arthur Walpole and his colleague, Dr. Michael Harper [6], made the discovery that the geometric isomers of substituted triphenylethylenes had opposing biological properties. The *cis* isomer, ICI 47,699, is an estrogen, whereas the *trans* isomer, ICI 46,474, has antiestrogenic activity. Thus, the structural configuration of the drug can program the cells for estrogenic or antiestrogenic properties [43].

Another novel observation made by Harper and Walpole was that ICI 46,474 exhibits species specificity; the compound is an estrogen in the mouse and an antiestrogen in the rat [6, 7]. The compound blocks the binding of [^{3}H]estradiol to estrogen receptors derived from both rat and mouse target tissues [44], but no completely satisfactory subcellular mechanism for the species differences of ICI 46,474 has yet been offered [45].

Early clinical studies with ICI 46,474 to treat advanced breast cancer, conducted by Mary Cole and her coworkers [46] at the Christie Hospital in Manchester, were followed by several confirmatory reports [47–49]. The confirmation that an antiestrogen could be used to treat breast cancer acted as a catalyst to encourage the study of the mode of action of the drug in animal tumor models. Studies were first started in 1973 at the Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts [50–56]. The DMBA-induced rat mammary carcinoma model, originally described a decade earlier by the Nobel laureate Professor Charles Huggins, 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' as no other hormone-dependent models were then available for study. Rob Nicholson at the Tenovus Institute for Cancer Research in Cardiff, Wales also selected the DMBA-induced rat mammary carcinoma model for his study of the antitumor actions of ICI 46,474 and other compounds [57]. These parallel research ventures fully described the antitumor activity of the antiestrogen *in vivo* [58–61] at a time when the efficacy of tamoxifen was being established widely in breast cancer clinical trials [63].

ICI 46,474 to tamoxifen

In 1973, Nolvadex®, the ICI brand of tamoxifen (as its citrate salt) was approved by the Committee on the Safety of Medicines in the United Kingdom for the treatment of breast cancer. Similar approval was given in the United States of America by the Food and Drug Administration on December 30, 1977. Nolvadex® is now available in more than 110 countries around the world as the first-line endocrine therapy for the treatment of breast cancer [1]. To mark this achievement, ICI Ltd., Pharmaceuticals Division was presented with the Queen's Award for Technological Achievement by the Lord Lieutenant of Cheshire, Viscount Leverhulme, on July 6, 1978.

The remarkable success of the drug encouraged a closer examination of its pharmacology with a

view to further development and wider applications.

The metabolism of tamoxifen in animals and man was first described by Fromson and coworkers [63, 64]. The major metabolic route to be described was hydroxylation to form 4-hydroxytamoxifen (monohydroxytamoxifen) which was subsequently shown to have high binding affinity for the estrogen receptor and be a potent antiestrogen in its own right [65]. Indeed, it is an advantage for tamoxifen to be activated metabolically to 4-hydroxytamoxifen [66], but metabolic activation is not a prerequisite for antiestrogenic action. The metabolite was subsequently shown to localize in target tissues after the administration of radioactive tamoxifen [67].

Originally, 4-hydroxytamoxifen was believed to be the major metabolite in patients [64], but Hugh Adam [68] at ICI Pharmaceuticals 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: tamoxifen in patients maintained on tamoxifen therapy because N-desmethyltamoxifen has twice the biological half-life of tamoxifen (14 days versus 7 days). The ubiquitous use of tamoxifen in recent years has resulted in the publication of a number of methodologies [69–75] to estimate tamoxifen and its metabolites in serum. Two minor metabolites, Metabolite Y [76] and Metabolite Z [77], can also be measured by HPLC.

Tamoxifen and the metabolites which have been identified in patients are all antiestrogens which inhibit estradiol binding to estrogen receptors [76, 77]. The next significant advance came with the availability of hormone-dependent breast cancer cells to study in the laboratory. Marc Lippman [78] was the first to describe the ability of tamoxifen to inhibit the growth of MCF-7 estrogen-receptor positive breast cancer cells [79] in culture and to show that additional estrogen could reverse tamoxifen's action. Nearly a decade later, Kent Osborne [80] and Rob Sutherland [81] independently described the blockade by tamoxifen of breast cancer cells at the G_1 phase of the cell cycle.

Adjuvant tamoxifen: laboratory studies to clinical trials

The initial success of adjuvant monotherapy with L-phenylalanine mustard [82] or combination chemotherapy [83] to delay the recurrence of Stage II breast cancer helped to encourage the investigation of other, perhaps less toxic, therapies. Laboratory studies using the DMBA-induced rat mammary carcinoma model were first used to explore whether tamoxifen would be effective and whether the drug produced a tumoristatic or a tumoricidal effect *in vivo*. Studies *in vitro* had previously indicated that tamoxifen could be a tumoricidal drug [78]. The results from the DMBA studies *in vivo* (first reported at a breast cancer symposium at King's College, Cambridge, in September 1977) demonstrated that a short course of tamoxifen therapy (1 month) given 1 month after the carcino-

Table 1. Adjuvant trials of tamoxifen 'monotherapy' in postmenopausal patients with stage II disease.

Group (ref)	Daily dose tamoxifen (mg)	Duration (years)	Other treatments	Increase DFI	Increase survival	Correlation with receptor status
Nolvadex [3]	20	2	Radiotherapy	Yes	Yes	No
Ludwig [94]	20	1	Prednisone	Yes	No	Yes
Toronto [95]	30	2	Radiotherapy	Yes	No	Yes
Danish [96]	30	2	Radiotherapy	Yes	No	Yes
Swedish [97]	40	2	None	Yes	No	Yes
Christie [98, 99]	20	1	Radiotherapy	Yes	No	Not done
ECOG [100]	20	2	None	Yes	No	Not analyzed
French [101]	40	3	Radiotherapy	Yes	Yes	Yes
Scottish [102]	20	5 or more	Radiotherapy	Yes	Yes	Yes

genic insult only delayed the appearance of mammary tumors: continuous tamoxifen therapy (for 6 months) resulted in 90% of animals remaining tumor-free [84, 85]. Thus, tamoxifen was shown to have a tumoristatic component to its mode of action and indicated that long-term (or indefinite) therapy might be the best strategy for adjuvant treatment. Subsequent laboratory studies using either DMBA-induced rat mammary tumors [86–88], N-nitrosomethylurea (NMU)-induced rat mammary tumors [89, 90] or human breast cancer cell lines inoculated into athymic mice [91–93] have all supported the initial observation. However, most attention has focused on a clinical evaluation of the concept.

Several trials of tamoxifen monotherapy as an adjuvant to mastectomy were initiated towards the end of the 1970s and these are summarized in Table 1. Most early trials selected a one or two-year treatment regimen to determine whether *any* beneficial effects would occur. The NATO (Nolvadex Adjuvant Trial Organization) trial started to accrue patients in November 1977 and analyzed the effects of two years of tamoxifen therapy (10 mg bid) against no treatment. The NATO trial was the first to demonstrate a survival advantage for tamoxifen-treated patients, although all of the studies have shown some effect on disease-free survival.

One controversial aspect of the NATO trial has been the lack of correlation between a beneficial tamoxifen effect and the steroid receptor concentration of the original primary tumor. The result is in marked contrast to the effects observed in the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial, where there are profound effects of tamoxifen plus chemotherapy in estrogen receptor positive postmenopausal women with Stage II disease [103–105] but less effect in estrogen receptor negative patients. Patients with the highest concentrations of estrogen and progesterone receptors do appear to benefit from tamoxifen therapy more frequently than those who have low levels of steroid receptor in the original primary tumor [106].

In both the NATO trial and the NSABP study, there are clear indications that patients benefit only as long as therapy is continued and the results raise the clinical question of how long should therapy be given?

The first pilot clinical study of long-term tamoxifen therapy was initiated at the University of Wisconsin in 1977 by Dr. Douglass C. Tormey. At the time this strategy was being considered, many patients at the University of Wisconsin with Stage II disease had already completed one year of adjuvant therapy with combination chemotherapy and tamoxifen. Based on the laboratory data which showed tamoxifen to be a tumoristatic agent [84], therapy with tamoxifen was continued, initially for five years [107] and subsequently the decision was made to continue the drug indefinitely or until relapse [108]. The results of this study demonstrate the safety [107–110] and potential efficacy of this approach to therapy. Randomized trials are currently underway in the Eastern Cooperative Oncology Group (EST 5181, EST 4181) to test the efficacy of chemotherapy and tamoxifen adjuvant therapy followed by either another four years or indefinite tamoxifen therapy.

The NSABP has recently reported a successful trial of Stage II breast cancer patients who received chemotherapy and tamoxifen for two years or the same regimen followed by an additional year of tamoxifen alone [4]. Three years of tamoxifen is ultimately superior to two years of tamoxifen.

Indeed, Delozier and colleagues [101] have shown, in a small study of tamoxifen monotherapy, that three years of tamoxifen therapy is effective and disease-free survival is prolonged in estrogen receptor-positive patients. However, the most compelling evidence to date that long-term tamoxifen monotherapy has merit as a successful treatment strategy has recently been published by the Scottish Trials Office in Edinburgh. The study compared indefinite tamoxifen therapy (10 mg bid) versus no treatment until relapse. Most patients in the control arm then received tamoxifen upon relapse. There is a clear-cut survival advantage for long-term tamoxifen therapy [102]. It is, therefore, clear that the developing clinical data is providing powerful support for the original suggestion [84–87] that long-term or indefinite adjuvant therapy with tamoxifen is an advantage for patients with Stage II breast cancer.

Premenopausal women and stage I disease

Tamoxifen was initially used in premenopausal women to treat menometrorrhagia [111] and to induce ovulation in infertile women [10, 11]. Subsequent evaluation of the endocrine effects of tamoxifen by Groom and Griffiths [112] revealed an increase in ovarian estrogen production. These findings have bee confirmed by many groups of investigators [109, 113–119]. As a result, there is a general belief that an increase in circulating estrogen may ultimately reverse the antitumor action of tamoxifen because it is a competitive estrogen antagonist, although this is not universally accepted since blood and tissue concentrations of tamoxifen and metabolites are still in considerable excess even over the peak concentrations of estrogens seen in any of these studies [1].

Nevertheless, tamoxifen has been shown to control the growth of Stage IV breast cancer in premenopausal breast cancer patients [114, 120–123] and small clinical trials have demonstrated that tamoxifen and oophorectomy [124, 125] have equivalent efficacy. Adjuvant therapy with tamoxifen for premenopausal women with Stage II disease has also shown efficacy [3, 98, 99, 102], but there are, as yet, no long-term toxicological studies of ovarian pathophysiology and endocrinology.

This is especially important for premenopausal women with Stage I disease who may be treated for many years with tamoxifen. The NSABP is currently conducting a randomized placebo-controlled trial in both pre- and postmenopausal patients to evaluate the effectiveness of tamoxifen as a long-term endocrine therapy in such women. Similarly premenopausal women with Stage I breast cancer have been treated for many years in the Scottish trial [102]. An analysis of the endocrinology of the patients will be extremely important.

At the University of Wisconsin, a clinical study of postmenopausal women with Stage I disease (Study Coordinator, R.R. Love, M.D.), designed to monitor the effects of tamoxifen on bone density, blood lipid profiles and clotting factors has started. Several laboratory/clinical studies [110, 126–130] report that there are no serious complications of tamoxifen therapy with regard to these parameters. However, the future development of tamoxifen as an agent to prevent breast cancer in high-risk patients, which will perhaps involve the lifetime administration of the drug to tens of thousands of women, will depend on successful long-term toxicological evaluations to ensure the continued well-being of the patient.

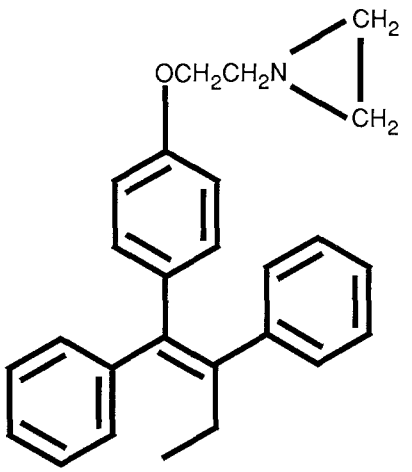
Postscript

Arthur Walpole died suddenly on July 2, 1977. At the time of his death, he had retired from ICI's Pharmaceuticals Division, but he continued to work as a consultant on a joint research scheme between ICI and the Department of Pharmacology at the University of Leeds.

One of the projects with which he was involved was the investigation of alkylating derivatives of steroids and tamoxifen. We tested several compounds with a view to developing a targeted tumoricidal agent, but we met with little success [131]. In contrast, the innovation provided independently by John and Benita Katzenellenbogen to study alkylation of the estrogen receptor by a related compound, tamoxifen aziridine (Fig. 5), proved very successful [132, 133]. Their studies have provided the research community with a valuable new tool for biochemical investigations.

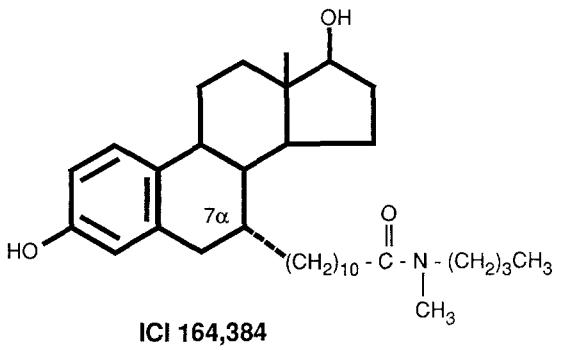
Another series of compounds synthesized in the same joint research scheme by Jean Bowler at ICI, aimed to attach an alkylating moiety to the 7 position of estradiol by a short hydrocarbon chain. Later, following publication by Etienne Baulieu and colleagues [134], who demonstrated that attachment of long hydro-carbon chains to estradiol did not cause a loss of receptor binding activity, Jean Bowler, Brian Tait, Alan Wakeling and others at ICI showed that novel pure antiestrogens could be produced by this means [135] (Fig. 6). A generation of novel pure antiestrogens may, therefore, be developed for future clinical use.

Arthur Walpole's research interests were not confined to studies with antiestrogens. In collaboration with Barry Furr (who is now head of Bioscience I at ICI Pharmaceuticals), Arthur Walpole laid the foundation for the development of novel



TAMOXIFEN AZIRIDINE

Fig. 5. The formula of tamoxifen aziridine.



ICI 164,384

Fig. 6. The formula of a new nonestrogenic steroidal antiestrogen.

inhibitors of androgen and progestin action and the highly potent LHRH agonist, Zoladex [136, 137], which is currently being used so successfully as a once monthly depot formulation to treat prostatic carcinoma [138, 139] and which has clear efficacy in premenopausal patients with breast cancer [140]. The success of tamoxifen as a breast cancer therapy and the inspiration of Arthur Walpole has fostered the development of a whole range of new antihormones as nontoxic and specific antitumor agents which have potential for novel clinical applications. He provided leadership and example for many of us working in the field of antihormonal agents and studying hormone action. The legacy that Arthur Walpole established in the 60s and 70s will continue to provide innovation to the end of the century and will still help to give insights into cancer biology and endocrinology.

Acknowledgements

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