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Imperial Chemical Industries and Craig Jordan, “the First Tamoxifen Consultant,” 1960s–1990s

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This paper examines the relationship between Imperial Chemical Industries (ICI), the company that discovered tamoxifen, and Dr Craig Jordan, who played a major part in its success as a breast cancer drug, and who worked as a consultant for the company, but without ever being paid a consultancy fee. Instead, ICI funded junior staff working in his laboratory on topics of his choice. They later paid his expenses as an expert witness in patent-litigation cases, as a result of which the US became a major lucrative market for tamoxifen, and ICI’s other anti-cancer drugs. This case study illustrates that, like consultants, drugs play an important part at the boundary between the academic and industrial spheres. However, even if it is blurred, the boundary remains. Owing to the secrecy that often surrounds industrial research, this boundary may lead to a different understanding of what constitutes innovation, and to different narratives with regard to respective contributions.

Introduction

Ever since they started to establish a science base at the beginning of the twentieth century by incorporating research laboratories within factories or building centres dedicated to research, pharmaceutical companies have relied upon academic scientists as consultants to ensure that they would access cutting-edge research and gain a competitive advantage in novel therapeutic fields.¹ As publicly funded research

¹ This has been well studied, in relation to a number of individual companies as well as in a number of different national contexts. See for example V. Quirke, *Collaboration in the Pharmaceutical Industry* (New York/London: Routledge, 2008).

institutions developed over the course of the twentieth century, firms also turned to the scientist-managers running these institutions or advising governments for more general and strategic direction.² More recently, drug companies have enlisted the help of management consultants, many of them with backgrounds in the natural or physical sciences, for guidance in research organisation and governance.³ However, pharmaceutical firms also targeted the gate-keepers of medical opinion to keep abreast of new trends, test their products, and (more often than not) influence medical practice.⁴ With the birth of welfare states, and as drug safety legislation became more demanding in order to protect the wider public from potential drug disasters, the relationship between pharmaceutical firms and medical practitioners working in hospital settings and performing clinical trials acquired even greater prominence.⁵

Partly as a result of this evolution, the literature on the pharmaceutical industry has tended to become split between two strands; the first emphasising the role of academic-industrial relations in fostering biomedical innovation, and the second highlighting the moral dilemmas and ethical compromises which such close connections entail.⁶ It is therefore both timely and useful to examine the relationship from both perspectives – the company and the consultant – and consider the tensions as well as the rewards which it may bring. This is what the present paper intends to do, by focusing on a specific case study: the relationship between Imperial Chemical Industries (ICI), which developed tamoxifen, and Craig Jordan, who not only helped to turn tamoxifen into a life-saving and best-selling breast cancer drug, but went on to lay the foundations for, and develop, other successful SERMs (Selective Estrogen Receptor Modulators). Using a combination of sources – published books and articles, unpublished company research reports, and a history of tamoxifen written by Dora Richardson, the company chemist who synthesised it, as well as personal communications and oral interviews – the paper will explore the contributions and motivations from both sides. It will illustrate how, in the period under study, pharmaceutical innovation was as much the product of the initiatives of individual researchers, both inside and outside the company, as the result of the company

² For a typology in the American context, see J. P. Swann, *Academic Scientists and the Pharmaceutical Industry: Co-operative Research in Twentieth-Century America* (Baltimore: Johns Hopkins University Press, 1988).

³ On the example of the French company Rhône-Poulenc which from the 1970s employed several firms of consultants, including McKinsey and A. D. Little, see V. Quirke, “Standardizing R&D in the Second Half of the Twentieth Century: ICI’s Nolvadex Development Programme in Historical and Comparative Perspective,” in *Harmonizing Drugs: Standards in 20th-Century Pharmaceutical History*, ed. C. Bonah, C. Masutti, A. Rasmussen, and J. Simon (Paris: Glyphe, 2009), 123–50 (on 141). For a more general history of Rhône-Poulenc, see P. Cayez, *Rhône-Poulenc* (Paris: Armand Collin/Masson, 1988).

⁴ On the influence of firms on the prescribing habits of physicians in the US, see J. A. Greene, *Prescribing by Numbers: Drugs and the Definition of Disease* (Baltimore: Johns Hopkins University Press, 2008).

⁵ For an overview of the history of pharmaceutical innovation and the dilemmas of public-private partnerships it involves, see V. Quirke, “Pharmaceutical Innovation in the Public and Private spheres in the Twentieth Century,” in *Healthcare in Public and Private from the Early Modern Period to 2000*, ed. P. J. Weindling (Abingdon/ New York: Routledge, 2015), 160–93.

⁶ J. A. Fisher, *Medical Research for Hire: The Political Economy of Pharmaceutical Clinical Trials* (New Brunswick/ New Jersey/London: Rutgers University Press, 2009); M. A. Rodwin, *Conflicts of Interest and the Future of Medicine: The United States, France and Japan* (Oxford: Oxford University Press, 2011); J. A. Green and E. Seigel Watkins, eds., *Prescribed: Filling, Using, and Abusing the Prescription in Modern America* (Baltimore: Johns Hopkins University Press, 2012).

managers' visions and decisions imposed from above. Moreover, it will show that, like consultants, drugs circulate between the academic and industrial spheres, blurring the boundary between them.⁷

Craig Jordan and ICI

Jordan's initial interest as a school boy was chemistry:

At grammar school, my main passion was for chemistry and, in a moment of insanity, my mother allowed me to set up a lab in my bedroom. I poisoned myself with chlorine gas, set fire to the curtains and killed the grass outside my window. It grew back blue!

I always wanted to be a chemistry technician at ICI Pharmaceuticals, which later became AstraZeneca, near where I lived in Cheshire. But the careers master said that I should go to university because I was an unusual boy and, by that time, I'd set up a lab at school and was teaching chemistry to other pupils in the lunch hour.⁸

Hence, Jordan's first contact with ICI did not occur until later, in 1967, as a summer student in the first year of his BSc in the Department of Pharmacology at Leeds. He came to ICI's pharmaceutical research centre, Alderley Park, to work with Stephen Carter, who was studying cytochalasins at the time as part of a programme of research on Cell Division and Growth.⁹ Carter had just published an article about it in *Nature*, which Jordan came across during his studies.¹⁰ He recalled first meeting with Carter:

I went home to Cheshire, took a bus to Alderley Park and phoned him up from the call box outside the gates. The operator on the ICI switch board connected me and after chatting for a while he said "Next time you are back in Alderley Edge arrange an interview." "Actually, I am here now outside the front gate!" and I was in and I had the summer job.

He had a tough time with me. I was not happy with sitting silently for 30 min at the tea and coffee lab breaks. I went each day to their wonderful library and found a chemical we should consider for testing as an anticancer agent. All a bit much for his group!! Nevertheless, Wallop's (Walpole) group was opposite and we went out to a Chinese restaurant each Friday. Next door was Mike Barrett in charge of beta-blocker research, with a technician who was an ex-girlfriend of mine. Dora (Richardson), in another building had a technician whom I had a crush on at primary school. ALL IN ALL an interesting summer.

⁷ On drugs as "boundary objects," see Quirke, "Pharmaceutical Innovation in the Public and Private Spheres," 181. On boundary objects in science, see S. L. Star and J. R. Griesemer, "Institutional Ecology, 'Translations,' and Boundary Objects: Amateurs and Professionals in Berkeley's Museum of Vertebrate Zoology, 1907–1930," *Social Studies of Science* 19 (1989): 387–420.

⁸ J. Bryan, "Q&A V. Craig Jordan – the Father of Tamoxifen," *The Pharmaceutical Journal* 296, no. 7890 (8 June 2016).

⁹ Cytochalasins are fungal metabolites with the ability to change the morphology of cells, inhibit cell division, and even cause apoptosis (or programmed cell death). This was one approach to the problem of cancer being considered at the time within ICI.

¹⁰ S. B. Carter, "Effects of Cytochalasins on Mammalian Cells," *Nature* 213, no. 5073 (Jan. 21, 1967): 261–64.

Anyway that summer I met everyone who would change my life, and ultimately the world of women's health [...] Mike Barrett became my head of department at Leeds, got me a lectureship. Wallop to examine my PhD thesis and Dora to give me tamoxifen metabolites, that led ultimately to raloxifene and me to discover SERMs.¹¹

The fact that Alderley Park was situated near Jordan's home in Cheshire, and that by the time he went there in 1967 ICI's tamoxifen project was under way, was serendipitous. However, Jordan's first experience of working at Alderley Park would not only – thanks to tamoxifen – “change [his] life, and ultimately the world of women's health,” but also in the long term benefit ICI's Pharmaceutical Division, and the company more widely. The relationship that developed between Jordan and ICI was therefore mutually beneficial, and to understand how and why it evolved into a formal arrangement centred on a particular product, one must go back to the origins of tamoxifen, which lay in the company's dual interest in cancer and contraception.

ICI and cancer research

The company's interest in cancer was related to its wartime activities, and long predated tamoxifen.¹² Arthur Walpole, a biologist who in 1938 had joined the Medicinal Section of ICI's Dyestuffs Division in Blackley, and during the war worked on analgesics, spasmolytics, and hormones, which were known to play a part in certain types of cancer, began researching the topic. So began ICI's lengthy and complex search for an effective anti-cancer agent, which within the company would bring together chemists and biologists working on different projects, statisticians to analyse their results, and outside the company would mobilise hospital clinicians to carry out trials, and academics to carry out research, in a massive collaborative effort that would eventually lead to tamoxifen.

At first, ICI's approach to cancer was largely empirical, involving the synthesis of derivatives of compounds with known anti-tumour properties. One of these was triphenylethylene (TPE), a derivative of the potent anti-oestrogenic diethylstilboestrol (DES), which had a durable, albeit weak anti-oestrogenic action. Walpole's exploratory work with the substance led to the synthesis of various TPE derivatives, including triphenylchloroethylene (registered in 1940 under the name Gynosone).¹³ In 1942, these compounds were supplied for trials in breast cancer to (later Sir) Alexander Haddow of the Chester Beatty Institute (subsequently the Institute of Cancer Research) in London, and to Edith Paterson at the Christie Hospital in Manchester. Although

¹¹ V. C. Jordan, personal email communication to the author (hereafter pers. comm.) (22/09/17).

¹² For histories of ICI, see W. J. Reader, *Imperial Chemical Industries* (Oxford: Oxford University Press, 1970), vol. 1; C. Kennedy, *ICI: The Company that Changed our Lives* (London: Hutchinson, 1986). More specifically on ICI's anti-cancer project, see Quirke, “Standardizing R&D;” see also V. Quirke, “Tamoxifen from Failed Contraceptive Pill to Best-selling Breast Cancer Medicine: A Case-study in Pharmaceutical Innovation,” *Frontiers in Pharmacology* (12 Sept. 2017): 1663–9812.

¹³ D. N. Richardson, “The History of Nolvadex” (AstraZeneca - hereafter AZ - PH27039 B, 13 May 1980). This appeared later in an abridged form as D. N. Richardson, “The History of Nolvadex,” *Drug Design and Delivery* (1988): 1–14.

improvements were only temporary, there was clear evidence that Gynosone in particular caused tumour regression and therefore could be beneficial in the treatment of breast cancer.

Meanwhile, on the other side of the Atlantic, the compounds known as “nitrogen mustards,” which were being studied as part of a chemical warfare research programme, were shown to inhibit the growth of blood and lymph tumours by Goodman and Gilman at Yale University, a discovery often hailed as the beginning of cancer chemotherapy.¹⁴ Despite this wartime work being top-secret, Walpole and Haddow were also able to investigate these compounds, thanks to an Anglo-American agreement to exchange scientific information. Another, parallel, study relating to cancer at ICI involved anti-metabolites under the leadership of F. L. (“Frank”) Rose. Rose, an azo dye chemist who had joined the Dyestuffs Division in 1932, became Research Manager of its Chemistry Department in 1954, whilst remaining involved in bench work. As well as the search for alkylating agents, synthetic oestrogens and anti-metabolites, he encouraged investigations into carcinogenesis. This was an unusual interest for researchers working on cancer chemotherapy at that time,¹⁵ and was linked to ICI’s concerns over exposure to carcinogens in chemical manufacture.¹⁶

ICI did not have a formal cancer research programme until plans were made to build a pharmaceutical research centre at Alderley Park (south of Manchester), which coincided with ICI starting to organise its research in team projects. Cancer became such a project in 1955. It was entitled “Cancer and Viruses: Antibacterials.” Alderley Park opened in 1957, and “Viruses” became a separate project, while “Cancer” merged with a new project to find an oral contraceptive, led by Arthur Walpole. Then, in 1960, the discovery of the natural antiviral substance interferon, which was also being investigated as a treatment for cancer, and ICI’s involvement in its study in collaboration with the Medical Research Council (MRC), led to “Viruses” and “Cancer” coming together again. “Oral Contraception” was therefore split away from “Cancer,” with Walpole working in parallel on both projects. His involvement would ensure that breast cancer remained an important focus for both his teams. It was within this “Oral Contraception” project that tamoxifen, a TPE derivative, was synthesised and subsequently developed, initially as a contraceptive pill.

ICI, oral contraception and the origins of tamoxifen

The first contraceptive pill had been developed in the early 1950s, and in 1956 Walpole wrote a survey entitled “The Technical Possibility of Oral Contraception,” which – as had become customary within ICI by that time – gave an overview of the

¹⁴ These compounds were later understood to work by alkylation – i.e., the transfer of an alkyl group from one molecule to another, in the case of anti-cancer agents attaching it to DNA, thus inhibiting cancer cell division – hence such compounds became known as “alkylating agents.”

¹⁵ C. W. Suckling and B. W. Langley, “Francis Leslie Rose,” *Biographical Memoirs of Fellows of the Royal Society* 36 (1990): 491–524 (on 507–8).

¹⁶ George B. Hill, *Alderley Park Discovered: History, Wildlife, Pharmaceuticals* (Lancaster: Palatine Books, 2016), 188.

field to enable ICI to decide whether it was worth entering.¹⁷ Taking into account both the requirements for contraception and the need to avoid toxic effects, the search for TPEs, alongside investigations of natural and part-synthesised steroids, became the preferred course of action.

The most promising compound to come out of this programme, ICI 33,828 (which like all other compounds had been given a number indicating its place along the sequence of ICI syntheses), was tested in pre-menopausal patients with mammary carcinoma, on the grounds that it might have a therapeutic as well as an anti-fertility effect. Shortly afterwards, in 1962, Mike Harper, an endocrinologist, was invited to join the team. His new series of biological tests produced a clearer picture of the structure-activity relationships of TPEs, and the programme of chemical synthesis was stepped up. The newly synthesised compounds included ICI 46,474 (later known as tamoxifen, brand name Nolvadex), which was made in 1962 by Dora Richardson, a chemist who had joined the Dyestuffs Division in 1943. By a process of fractional crystallisation described as “revolutionary at the time,”¹⁸ she succeeded in separating its *cis* and *trans* isomers, which revealed that the activity resided in the molecule’s main *trans* isomer (ICI 46,474) rather than its minor *cis* isomer (ICI 47,699).¹⁹ Harper therefore selected ICI 46,474 for additional tests and for preliminary toxicity studies.

Soon after, the company lodged patent applications for ICI 46,474 and related compounds. As well as providing basic data on these compounds, Patent GB1013907 covered a number of potential therapeutic uses, including cancer. It read:

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 therefore. They will also have useful hypocholesteraeamic activity.²⁰

ICI 46,474 (1962–1971)

The early phase of the “Oral Contraception” programme shaped tamoxifen and its future. The compounds developed within this programme were designed to act as contraceptive pills, yet from the beginning their usefulness in breast cancer was also explored. Walpole’s own research interests resulted in this dual objective, which was sustained thanks to the fruitful collaborations he established outside the company both with endocrinologists and with clinicians working in cancer.

¹⁷ See V. Quirke, “From Evidence to Market: Alfred Spinks’s 1953 Survey of New Fields for Pharmacological Research, and the Origins of ICI’s Cardiovascular Programme,” in *Medicine, the Market and the Mass Media: Producing Health in the C20th*, ed. V. Berridge and K. Loughlin (New York/London: Routledge, 2005), 146–71.

¹⁸ John Patterson, pers. comm. (20/04/09).

¹⁹ G. R. Bedford and D. N. Richardson, “Preparation and Identification of *Cis* and *Trans* Isomers of a Substituted Triphenylethylene,” *Nature* 212 (1966): 733.

²⁰ Quoted in P. Y. Maximov, R. E. McDaniel, and V. C. Jordan, *Tamoxifen: Pioneering Medicine in Breast Cancer* (London: Springer, 2016), 39.

Importantly, it meant a constant preoccupation with side effects, and the low toxicity of tamoxifen relative to its potency would turn out to be one of its crucial advantages over its competitors.²¹

ICI 46,474 had been demonstrated as the most potent and least toxic of all the compounds tested by June 1964. However, in testing the compound in preparation for a submission to the Committee of Safety of Drugs (CSD), the new regulatory body that had been set up in the wake of thalidomide, uncertainty arose as to its mode of action. Because such doubts could best be settled in the clinic, plans were made in 1965 for the first trials. Approval to carry out therapeutic studies of tamoxifen for the treatment of anovulation or menorrhagia (at Aberdeen, Manchester, and the Women's Hospital in Chelsea), and of breast carcinoma in thirty menopausal and post-menopausal women (at the Christie Hospital in Manchester) was obtained in 1969 from the CSD's successor, the Committee for the Safety of Medicines (CSM).

The preliminary reports received from Aberdeen and London helped to cast further light on the drug's mechanism of action, showing that tamoxifen was capable of inducing ovulation at higher dose levels, while at lower doses it tended to have an anti-oestrogenic effect. As to the Christie breast cancer trial, although two of the women complained about hot flushes (which was taken as evidence of its anti-oestrogen effect), no toxicity was observed and the drug appeared to be well tolerated.

In her unpublished history of tamoxifen, Richardson wrote of the team's excitement as the first trial results arrived. She described the news of the birth of a child to a woman who had been infertile for twelve years as a "boost to morale."²² The team were also encouraged by the breast cancer trial, even though its results were not received with universal enthusiasm at ICI: Walpole and his colleagues were told that they were supposed to be looking for a contraceptive pill, not an anti-cancer agent! At a Development Department meeting on 28 August 1970, sales estimates and quantities of bulk drug were set at only two kg for initial stocks. Richardson concluded from these figures that the Department obviously envisaged treating only "dead people."²³ Although her conclusion reflected the hopelessness of the condition as it was viewed at that time, on the basis of the positive clinical results, the CSM granted the company permission to prolong the trials and extend them to other centres. By the end of 1970, sixty patients had been admitted to the Christie breast cancer trial, and of the forty women on the trial for more than ten weeks, all had shown measurable and marked tumour regression. The clinicians carrying out the trial reported how impressed they were with the low incidence and trivial nature of any side-effects, especially compared with other agents, which were often either toxic, or – in the case of breast cancer – tended to have masculinising effects, and in some instances were so intolerable that patients had been withdrawn from treatment.²⁴

²¹ Quirke, "Tamoxifen from Failed Contraceptive Pill."

²² Richardson, "The History of Nolvadex," AZ, PH27039 B.

²³ *Ibid.*

²⁴ Norethisterone was a drug with such androgenic effects.

In return, the trials provided clinical material for laboratory studies of tamoxifen. By then, the oestrogen receptor had been isolated and identified by Jack Gorski in the US, in what has been described as the “first molecular characterisation of a steroid hormone receptor.”²⁵ Consequently, Walpole and his team were able to devise a receptor protein-binding assay method, which showed tamoxifen to be a competitive inhibitor of oestrogen in certain species and organs.²⁶ These results suggested that, like other anti-oestrogens, tamoxifen had a kind of agonist/antagonist pharmacological action with which ICI researchers had become familiar in their work on the beta-blockers.²⁷ It helped to cast further light on the physiological processes at a molecular level, and made tamoxifen a particularly useful research tool for investigations of hormone-dependent tumours.²⁸

Given confidence by the clinical and laboratory studies carried out so far, Walpole’s team began planning trials in contraception, and the Nolvadex Development Programme was drawn up. This was an important stepping-stone in the drug’s transformation from quasi-orphan to blockbuster drug, yet owing to uncertainties in the drug’s potential market, it was nearly stopped.

The Nolvadex Development Programme (1971)

The “Development Programme” was an organisational innovation which standardised and codified the R&D process at ICI. ICI’s first Development Programme had been created in 1964 for the beta-blocker propranolol.²⁹ The Nolvadex Development Programme followed seven years later, describing the work done up to June 1971, assessing the drug’s potential market, and making plans for future work. Three important considerations were taken into account. First and foremost were tamoxifen’s possible clinical uses, based on the results of trials received to date, including the treatment of oestrogen-dependent mammary carcinoma. Second, the drug’s position in North America was under question, following Ayerst’s rejection of ICI’s offer of tamoxifen for the American market, and the Food and Drug Administration (FDA)’s likely negative attitude towards its use in breast cancer.³⁰ Third, the commercial situation indicated that a number of treatments of hormone-dependent breast cancers were already in existence, each of which commanded almost equal

²⁵ “In Memoriam: Jack Gorski (1931–2006),” *Endocrine Reviews* 27, no. 7 (1 December 2006): 707–8.

²⁶ Walpole et al., AZ CPR 101/17B *Endocrinology and Fertility* (25 June 1970).

²⁷ V. Quirke, “Putting Theory into Practice: James Black, Receptor Theory, and the Development of the Beta-blockers at ICI,” *Medical History* 50 (2006): 69–92. Tamoxifen is now classed as a Selective Estrogen Receptor Modulator (SERM) after the American spelling for oestrogen, meaning that it activates oestrogen receptors in some tissues, while blocking them in others.

²⁸ V. C. Jordan, M. M. Collins, L. Rowsby, and G. Prestwich, “A Monohydroxylated Metabolite of Tamoxifen with Potent Antioestrogenic Activity,” *The Journal of Endocrinology* 75 (1972): 289–98.

²⁹ V. Quirke, “Thalidomide, Drug Safety Regulation and the British Pharmaceutical Industry: The Case of Imperial Chemical Industries,” in *Making Drugs: Ways of Regulating between Factory, Office, Consulting Room and Court*, ed. J.-P. Gaudillière and V. Hess (Basingstoke: Palgrave Macmillan, 2012), 151–80.

³⁰ This negative attitude may have been due to a 1971 report which suggested that there was a link between DES and a rare form of vaginal cancer, and was promptly followed by an FDA bulletin warning against the use of DES. Food and Drug Administration, “Certain Estrogens for Oral or Parenteral Use. Drugs for Human Use; Drug Efficacy Study Implementation,” *Federal Register* 36, no. 217 (1971): 21537–38.

shares of the market. Nevertheless, tamoxifen had two advantages in relation to breast cancer, on which its market position would ultimately depend: its unique mode of action in being an oestrogen-antagonist without androgenic properties; and very low incidence of side effects compared with other treatments.

As well as further trials in anovulatory infertility (in Aberdeen, Oxford, London, and Dublin), and in breast cancer (Manchester, Glasgow, and London), the Nolvadex Development Programme included contraceptive trials to be carried out in Sweden. These trials led to the finding that, contrary to what might be expected from the laboratory studies in rats, even at low doses, tamoxifen stimulated rather than suppressed ovulation, and therefore would not work as a contraceptive pill in women! The market for a fertility drug was small, like the market for an anti-cancer drug, partly due to the poor prognosis associated with the disease. Despite growing clinical evidence of the usefulness of tamoxifen in breast cancer, the very low sales estimates produced by the Marketing Department suggested that it was never going to cover R&D costs and bring an appropriate return to the company. ICI's Main Board therefore made the decision to close down the Programme, but tamoxifen's champion inside the company, Walpole, threatened to resign. As a result of this announcement, despondency spread through the entire research department. Moreover, when informed of the company's decision, one clinician said that, in view of the encouraging trial results, ICI could not *morally* withdraw the drug.³¹ By then, the breast cancer trials had led to a number of publications, which sparked worldwide interest in tamoxifen. Under such pressure, and in order to preserve the good image of the company, ICI reversed its decision, Walpole remained, and the project was saved.

In February 1973 ICI therefore applied for a product licence, which was granted a few months later, and in October of that year tamoxifen was launched in the UK for both anovulatory infertility and the palliative treatment of breast cancer. Although there continued to be crossovers between the two projects, the rest of this paper will focus on breast cancer, and Jordan's role in relation to it. It will show how tamoxifen was transformed from a research object and palliative therapy for advanced breast cancer, into a diagnostic and predictive tool, an adjuvant chemo-endocrine treatment first in post-menopausal, then also in pre-menopausal women with early breast cancer, and eventually into the first chemopreventative for cancer.

Craig Jordan, ICI and tamoxifen: from palliative care to adjuvant therapy (1972–1975)

ICI's tamoxifen project inspired the topic of Jordan's PhD, funded by a MRC scholarship and entitled "A Study of the Oestrogenic and Antioestrogenic Activities of Some Substituted Triphenylethylenes and Triphenylethanes." Walpole examined

³¹ Richardson, "The History of Nolvadex," AZ, PH27039 B; see also V. C. Jordan, "Tamoxifen: A most Mlikely Pioneering Medicine," *Nature Reviews Drug Discovery* 2 (2003): 205–13.

his thesis in 1972, despite the University's disapproval of a scientist from industry examining a university doctorate, and Jordan was awarded his PhD in Pharmacology in 1973. Thanks to Barrett, now at Leeds University, he was immediately offered a lectureship in Pharmacology. However, at the time, young British scientists were often encouraged to travel to America to complete fellowships before resuming their academic posts back in the UK (referred to as "BTA" – been to America).³² On Jordan's behalf, Walpole therefore phoned his former colleague Harper, now at the Worcester Foundation for Experimental Biology (Massachusetts), best known for the development of the combined oral contraceptive pill, and as a result Jordan took a leave of absence and set off for the US, returning to the UK in 1974.

It was at the Foundation that his formal relationship with ICI began – to be more precise its newly acquired subsidiary Stuart Pharmaceuticals, where he was introduced by Walpole to Lois Trench. Jordan described her as "a woman with a Master's degree looking after the loser drug (all of ICI medicines in clinical studies had male physicians doing the *real* work ...)." ³³ Luckily, she agreed to fund his research. Thus Jordan became ICI's "First Tamoxifen Consultant," with the role of developing laboratory studies "to guide how best to use tamoxifen in clinical trials" and of talking to clinical trial groups in the US, such as the Eastern Cooperative Oncology Group (ECOG).³⁴ While at the Foundation, Jordan acquired knowledge and techniques that would prove most useful both to him, and to ICI: he not only studied with Elwood Jensen, the "father of the field of hormone action,"³⁵ but also with W. L. McGuire, who developed a method for predicting responses to hormone therapy using tamoxifen.³⁶

Jordan would continue to receive grants from ICI (and then AstraZeneca, formed by the merger of ICI's spun-off pharmaceutical division, Zeneca, and the Swedish drug company Astra) through his various appointments, first at Leeds university (1974–1979), then at the university of Wisconsin (1980–1995) – where AstraZeneca provided \$100,000 from Alderley Park to start up his laboratory – and finally at Northwestern University Medical School, Chicago, Illinois (1993–2004). This arrangement lasted until 2002, when he was nominated for an OBE by Dr Barry Furr, then Chief Scientist at AstraZeneca, for "Services to International Breast Cancer Research." He was awarded his OBE soon afterwards. At this point he began working with Eli Lilly on SERMs, a path which ICI chose not to follow, preferring to focus on aromatase inhibitors instead, and his association with the company ceased.³⁷

³² Jordan, "Interaction of V Craig Jordan with staff of ICI Pharmaceuticals, Zeneca and AstraZeneca, 1967–2002" (02/10/18).

³³ Idem, pers. comm. (22/09/17).

³⁴ Idem, "Interaction."

³⁵ D. Moore, "A Conversation with Elwood Jensen," *Annual Review of Physiology* 74 (2012): 1–11; "In Memoriam – William L. McGuire," *Breast Cancer Res and Treatment* 23 (1992): 7–15.

³⁶ Jordan's CV mentions that he studied techniques with both men, whose work was cited in ICI reports. Jordan, "Updated External C.V." (28/03/18).

³⁷ Quirke interview with Jordan (19/06/18).

In a personal communication, Jordan wrote:

During all of these close interactions I was never paid salary or any remuneration from ICI. It was a pure academic investment by ICI in my staff (of my choosing) who received scholarships from me in ICI's name to get their PhD etc. At Leeds my whole group met every 6 months for 4 years with Walpole and Staff at Alderley Park. Their investment in my young talented people, created a sound start to their successful future careers.³⁸

By stressing that he had received no personal remuneration from ICI, Jordan highlighted his and his group's independence from any external influence, in a way that preserved his increasingly public reputation, achieved at first on a transatlantic, and then on a global stage.

Meanwhile, ICI's tamoxifen project continued to progress in Britain and Europe. The growing number of clinical trials suggested to Walpole that tamoxifen could be given to pre-menopausal women with breast cancer to predict whether it would be useful to subject them to more drastic treatments, such as removal of the ovaries. At the same time, he made plans with Dr Jean-Claude Heuson for a trial run by the European Organization for Research and Treatment of Cancer (EORTC, which had been created in 1962). This included oestrogen receptor determinations on biopsies taken from each patient to determine whether there was a correlation between clinical response to the compound and the presence of oestrogen receptors in the tumour tissue.³⁹ Taken together, these observations led to the hope that it would be possible to predict the type of patient likely to respond to treatment with tamoxifen, and develop what became known as "personalized medicine."

However for this to happen, a better laboratory model for tumour inhibition had to be found. The first step was to design a simpler method of receptor analysis, which could be applied routinely on a large scale in this model, before being applied in humans. Walpole's team developed such a method in collaboration with Jordan.⁴⁰ If it proved effective, i.e. if it demonstrated that tamoxifen could bind to the oestrogen receptor in human breast tumours, the team hoped that this method would make it possible to screen patients for the presence of specific oestrogen receptors in biopsy specimens of their tumours and to pre-select for treatment with tamoxifen those in whom such receptors had been found.

Jordan's publication on the subject appeared in 1974:⁴¹ "This was the first report that tamoxifen would prevent rat mammary carcinogenesis and blocked estradiol binding to the human estrogen receptor from breast tumours. The report is the first that started a systematic evaluation of the drug as a breast cancer therapy in America [*sic*]."⁴² The context was ripe for this type of work, and – just like

³⁸ Jordan, pers. comm. (16/09/18).

³⁹ Walpole et al., (AZ CPR 101/26B Fertility, 22 June 1973).

⁴⁰ Walpole et al., (AZ CPR 101/27B Fertility 24 Oct. 1973). See also Maximov, *Tamoxifen*, 40–1.

⁴¹ V. C. Jordan, "Antitumour Activity of the Antioestrogen ICI 46,474 (Tamoxifen) in the Dimethyl Benzanthracene (DMBA)-induced Rat Mammary Carcinoma Model," *J. Steroid Biochem* 5 (1974): 354.

⁴² Jordan, "Updated External C.V."

Jordan – tamoxifen “was in the right place at the right time.”⁴³ Not only had President Nixon signed in 1971 the US National Cancer Act, which enabled medicines to move rapidly from the laboratory into patient care, but in Walpole’s words, “By good fortune, Nolvadex was launched at a time of increased interest in the assessment of the endocrine status in breast cancer.”⁴⁴ Tamoxifen was shown to be highly effective in binding to the oestrogen receptor and, before long, researchers in Europe as well as in the US were using the drug as a tool to “predict the response of breast tumours to hormone therapy.”⁴⁵

Nolvadex was also launched at a time when the value of chemotherapy in cancer was being established with novel drugs tested first alone, then combined, in collaborative multi-centre trials. With drug resistance becoming a growing concern, not only in bacteria, but also in cancer cells, combination therapy was being developed and its modalities refined. Hence, in June 1974, Walpole began planning a trial with two different treatment modalities, supposedly devoid of cross-resistance, and he proposed to alternate their administration on a four-week basis.⁴⁶ This approach was adopted by Heuson at EORTC, alongside another trial in pre-menopausal women.⁴⁷

Such plans and discussions, which were based on a growing number of publications and symposia presenting evidence not only of symptom relief, but also of remissions and survival from breast cancer,⁴⁸ indicate that, both as a research tool and a therapeutic agent, tamoxifen was shifting from palliative care into the realm of therapy. What follows will concentrate on the years 1975–1980, after which ICI’s research reports on tamoxifen and related topics ended. During that period Walpole was mainly involved in the Nolvadex Development Programme, as a consultant himself once he had retired, until his sudden death in 1977. Although his involvement ensured continuity between the research and development phases, Walpole’s gradual disengagement from the research, which can be detected in the reports, meant that the project lacked clear purpose and direction. Months were lost to pressures of competing work inside the company, and aspects of the research were outsourced to external laboratories, the most important of which was Jordan’s. Nevertheless, in that time, the foundations were laid for the next phase in tamoxifen’s trajectory, from adjuvant therapy to the first chemopreventative remedy for cancer.

1975–1980: the final years of ICI’s tamoxifen project

The period 1975–1980 was therefore a fruitful time for both Jordan and tamoxifen. By then Jordan had resumed his lectureship at Leeds, where he established a

⁴³ Patterson, pers. comm. (20/04/09).

⁴⁴ E. V. Jensen et al., “Estrogen Receptors and Breast Cancer Response in Cancer Therapy,” in *Prediction of Response in Cancer Therapy*, ed. T. C. Hall (Washington, DC: US Govt Printing Office, 1971), 55–70.

⁴⁵ Walpole et al., (AZ CPR 101/32B Fertility 27 June 1975). One of these researchers was W. L. McGuire.

⁴⁶ Walpole (AZ CPR 101/28B Fertility 14 June 1974).

⁴⁷ Walpole (AZ CPR 101/32B Fertility 27 June 1975).

⁴⁸ Bonadonna et al., “Cytotoxic Chemotherapy for Mammary Cancer,” *Symposium*, Padova, 8 Apr. 1974, cited in Walpole (AZ CPR 101/28B Fertility 16 June 1974).

“Tamoxifen Team,” which was funded by an equipment grant from the Yorkshire Cancer Research Campaign, as well as a Joint Research Scheme between Leeds and ICI Pharmaceuticals with Jordan and Walpole as Principal Investigators.⁴⁹ The latter provided money in the form of ICI Scholarships for lab members and rats for the experiments. The part played by Dr. Roy Cotton, the clinical researcher responsible for coordinating the tamoxifen studies at ICI, was especially important, as he arranged all the interaction between Jordan’s group and ICI. Jordan described it thus:

Dr Roy Cotton [...] was told not to spend too much time on the drug as it was NOT expected to succeed. He was the innovator who sent hundreds of rats each week for my research at Leeds by ICI chauffeured cars. Without that I could not come out with the strategy of Long Term adjuvant tamoxifen therapy and Chemoprevention, both FDA approved and used worldwide.⁵⁰

Twice a year, Jordan’s team went over to Alderley Park to present their findings. They reported that: tamoxifen could prevent rat mammary carcinoma; longer adjuvant tamoxifen therapy was better than shorter (1–2 years) adjuvant tamoxifen therapy; and only patients with oestrogen-receptor positive tumours would benefit from tamoxifen therapy. Jordan agreed to defer publication on one of their key findings, the metabolic activation of tamoxifen to 4-hydroxytamoxifen (which is 100 times more effective than tamoxifen at blocking the oestrogen receptor) while the company set out to patent all of tamoxifen’s metabolites. Jordan was not invited to be a co-patent holder. He later reflected: “I was not interested in anything but medical progress. For me getting tamoxifen on the market in America was dear to my heart. That’s what I was doing – creating a plan to save women’s lives.”⁵¹

Nevertheless, those years laid the foundations for Jordan’s future work on SERMs. During that time, Jordan wrote about thirty scientific papers. His first paper establishing the new strategy of long term adjuvant tamoxifen treatment was published in conference proceedings following a Symposium at King’s College, Cambridge 28–29 September 1977.⁵² Among the participants were: Craig Jordan; Michael Baum, later to lead the Nolvadex Adjuvant Trial Organization (NATO), the first trial to show a survival advantage for patients taking tamoxifen; and Helen Stewart, who led the Scottish Trial of five years of adjuvant tamoxifen *vs* no treatment, with tamoxifen treatment upon first relapse.

Although neither the Scottish Trial nor the NATO publications mentioned the laboratory studies from Jordan’s laboratory, which may have led to an underestimation of his contribution to this phase in the history of tamoxifen, Jordan’s role was beginning to be recognised in other ways, including by the company itself. In 1978, on the occasion celebrating the Queen’s Award for Technological

⁴⁹ Maximov et al., *Tamoxifen*, Ch. 3; Jordan, “Interaction.”

⁵⁰ Jordan, pers. comm. (16/09/18).

⁵¹ Jordan, pers. comm. (22/09/17).

⁵² V. C. Jordan, “Use of the DMBA-induced Rat Mammary Carcinoma System for the Evaluation of Tamoxifen as a Potential Adjuvant Therapy,” *Reviews on Endocrine-related Cancer* (1978, Oct. Suppl.): 49–55.

Achievement for Tamoxifen, he was the only invitee not to be an employee of ICI. This was the first in a long list of honours and awards Jordan would receive for his work, which became crucial to the survival of tamoxifen after 1980, when Stephen Carter left the company, having taken early retirement, and the project on cell growth was terminated. Thus when tamoxifen was bringing in sizeable profits for the company and Zoladex (for prostate cancer) was in the pipeline, ICI had no longer a cancer research programme, a situation that lasted until 2006, when Alderley Park became the Global Lead Centre for AstraZeneca's cancer research.

Jordan, tamoxifen, and beyond – 1980–2000

Thanks to tamoxifen, ICI were able to tap into a global cancer research network connected in Europe through the EORTC, and in the US through the National Cancer Institute (NCI). By then, the company had already submitted an Investigational New Drug (IND) application to the FDA. It was followed in 1976 by a New Drug Application (NDA) to the FDA's Oncological Drugs Advisory Committee, in which John Patterson, a member of ICI's Clinical Research Department (formerly of the Medical Department), made a detailed and convincing case for the use of tamoxifen in breast cancer, based in part on the basic research carried out by Jordan's lab.⁵³ Although ICI's application for a US patent for tamoxifen had originally been rejected, thanks to the unrelenting efforts of ICI patent attorney Peter Slatcher,⁵⁴ in 1985 the American court of appeals finally granted ICI the patent rights for tamoxifen in the USA, thereby starting the seventeen-year patent cover there, paradoxically at a time when patent rights were coming to an end in other countries.⁵⁵

And there was another way in which Jordan, who in 1980 moved to Wisconsin where he became Assistant Professor of Human Oncology and Pharmacology, played an important part:

As I was considered an expert about the origins on the actual strategic decision to develop tamoxifen as a targeted therapy to treat and prevent breast cancer, ICI's law firm sought my services to aid them (by then Zeneca) defend their patents in the US in the late 80s. This was a Judge decision alone trial for three weeks. AZ won and the Judge ruled in their favour based, as he stated in his written decision, on my evidence by name. I was paid for my time as an expert witness in the Smalkin case in Baltimore. I was an advisor to their law firm at a subsequent case in Boston. Again this was won. Overall this saved the AZ multibillion market in the US, which was being reinvested to develop Casodex, Faslodex, Zoladex and Arimidex. This one drug tamoxifen created the funds and future of AZ as the Cancer Company it is today [...] Tamoxifen has a full patent life in the rest of the world but none in the US until 1985 when they obtained

⁵³ Richardson, "The History of Nolvadex," AZ, PH27039 B.

⁵⁴ Hill, *Alderley Park*, 197.

⁵⁵ Maximov et al., *Tamoxifen*, 40.

a full patent life in the country who embraced tamoxifen but there drug was not patented until then – no other companies cared as chemotherapy [using cytotoxic drugs] was king and would cure ALL cancers.⁵⁶

Tamoxifen's entry into the American market contributed to rising worldwide sales: although ICI's Marketing Department had only expected it to make £100,000 p.a. in 1970, by 1974 figures on the home market alone amounted to £140,000, overtaking one of ICI's well established drugs Mysoline (for epilepsy). By 1976, sales figures were equivalent to those for the anaesthetic Fluothane, the first drug to put ICI's Pharmaceutical Division "in the black," and for over-the-counter drugs such as the antiseptic Savlon. As the expiry date for their tamoxifen patents was drawing near, in 1979 ICI obtained a four-year extension for their UK patent, on the basis of "the nature and merits of the invention in relation to the public," as well as "the profits made by the patentee."⁵⁷ By 1980, it was making £30 million for the firm.⁵⁸ Nevertheless, even as late as September 1982, at the annual portfolio review attended by the managers of the Biology Department (Dr. J. D. Fitzgerald) and Chemistry (Dr. R. Clarkson), the manager of the Marketing Department, who also attended the meeting, commented that "there was no market for cancer."⁵⁹ ICI's Marketing Department were not alone in under-estimating the market for anti-cancer drugs: if tamoxifen had not been "stolen" by American companies while it remained unprotected by patents, it was partly because they did not believe in its usefulness either.⁶⁰ The fate of tamoxifen therefore rested on the qualities of the drug itself, and the interest it generated not only among researchers both inside and outside the company, but also – as I have argued elsewhere – among patients and the wider public.⁶¹

A series of trials throughout the 1990s and 2000s helped to establish its reputation further, despite the newly discovered link between tamoxifen and endometrial cancer.⁶² The trials included the Breast Cancer Prevention Trial NSABP-P1 (BCPT), with the aim of establishing whether five years of tamoxifen would reduce the incidence of invasive breast cancer in women identified as being at high risk of the disease. It started in 1993 and lasted five years, with Jordan as member of the Recruitment, Promotion and Compliance Committee for the duration of the trial. This was followed by another trial, comparing tamoxifen with a second generation SERM, raloxifene, code-named STAR, of which he was Scientific Chairman between 2001 and 2008.⁶³

⁵⁶ Jordan, pers. comm. (16/09/18). Unfortunately, because the information was commercially sensitive and ICI won the cases, access to the documents produced in court is not possible.

⁵⁷ UK 1949 Patents Act, Section 23. http://www.legislation.gov.uk/ukpga/1949/87/pdfs/ukpga_19490087_en.pdf (accessed 15 June 2017). I thank Dr. Michael Jewess for pointing out this section to me.

⁵⁸ Richardson, "The History of Nolvadex," AZ, PH27039 B.

⁵⁹ Dr J.D. Fitzgerald, pers. comm. (01/11/13).

⁶⁰ Maximov et al., *Tamoxifen*, 40.

⁶¹ Quirke, "Tamoxifen from Failed Contraceptive Pill."

⁶² V. J. Assikis and V. C. Jordan, "A Realistic Assessment of the Association between Tamoxifen and Endometrial Cancer," *Endocrine-Related Cancer* 2 (1995): 235–41.

⁶³ D. L. Wickerham, "Tamoxifen Versus Raloxifene in the Prevention of Breast Cancer," *European Journal of Cancer* 38, Suppl 6 (2002): S20–1.

Jordan summarised his contribution thus:

I was instrumental in the discovery process for raloxifene and published the strategy for SERMs first.⁶⁴ Eli Lilly EVENTUALLY moved on that idea and confirmed my early results. They embraced me as the chair of a committee to evaluate breast cancer incidence in their osteoporosis trial with raloxifene. I could choose my own committee which I did. All great success with again a block buster drug (ie a billion \$ in sales annually, like tamoxifen in the US after its patent was awarded in 1985). Delighted they followed my lead and embraced SERMs. I got elected to the National Academy of Sciences (2009) and Medicine (2017) [...] was elected on the first round to the Fellowship of the Academy of Medical Sciences (2009).⁶⁵

By then, in part as a result of the awards and recognition he received, Jordan had also become a key source of information on and major contributor to the history of tamoxifen: he has been the subject of and/or produced at least 15 biographical accounts, including a tribute to Arthur Walpole,⁶⁶ and is the author of numerous review and retrospective chapters and articles on tamoxifen and SERMs more generally.

Jordan's contribution was acknowledged by AstraZeneca, in a Program of Historical Milestones Celebrating its 25 years as a "cancer" company, at San Antonio, Texas, in 2003:

Two clinical Awards and two chemist Awards were presented [...] Wakeling and Jordan received the chemist prize. Wakeling, an AstraZeneca employee, is credited with the discovery and development of Faslodex as the first pure antiestrogen for the treatment of breast cancer. Jordan provided the translational research to justify the use of tamoxifen as a long term adjuvant therapy and as the first chemopreventative agent to reduce the risk of breast cancer in high risk women.⁶⁷

His citation was as "internationally recognized for his research that has resulted in ground-breaking treatment of breast cancer."⁶⁸

Conclusion

Jordan has received wide recognition as "the father of tamoxifen."⁶⁹ However, his role as "the First Tamoxifen Consultant" has largely remained invisible, as has the fact that tamoxifen also had a "mother." Dora Richardson carried out the synthesis of tamoxifen, and of several of its metabolites, thus helping to pave the way for

⁶⁴ V. C. Jordan, E. Phelps, and J.U. Lindgren, "Effects of Antiestrogens on Bone in Castrated and Intact Female Rats," *Breast Cancer Research and Treatment* 10 (1987): 31–5. This publication, which described the –paradoxical– protective effect of tamoxifen on bone, has been acknowledged by others as having "revolutionized the way we have come to think of nuclear receptor functioning." C. P. Miller, "SERMs: Evolutionary Chemistry, Revolutionary Biology," *Current Pharmaceutical Design* 8, no. 23 (2002): 2089–111

⁶⁵ Jordan, pers. comm. (17/09/18).

⁶⁶ V. C. Jordan, "The Development of Tamoxifen for Breast Cancer Therapy: A Tribute to the Late Arthur L. Walpole," *Breast Cancer Res. Treat.* 11, no. 3 (1988): 197–209.

⁶⁷ Jordan, "Documentary evidence" (04/05/19).

⁶⁸ Ibid.

⁶⁹ Bryan, "Q&A."

subsequent SERMs. Although she has numerous scientific papers and at least a couple of patents to her name, far less is known about her than Jordan,⁷⁰ in part because she was not an academic and never left the company, but also perhaps because she was a woman in the very male-dominated world of industrial chemistry.⁷¹ Her history of tamoxifen was mainly for internal consumption, drawing upon her experience as participant in a forty-year programme of industrial research involving a multitude of external collaborators, and in 1980, when she wrote her account, Jordan was one amongst many. Although by then tamoxifen was already showing success as breast cancer adjuvant therapy, she did not have the same hindsight as Jordan, whose historical contributions tracing tamoxifen's journey to blockbuster drug and the very first chemopreventative medicine for cancer would come thirty years later.

This time-lag may explain some of the gaps or discrepancies between the two accounts, which only had partial knowledge of the other side's influence and contribution, and which this paper has attempted to combine and reconcile. It also may have led to a different understanding and appreciation of what constitutes the important phases in the innovation process: on the one hand, to an industrial chemist, the long and painstaking investment in scientific and technical, as well as the organisational effort, that underpins the discovery of a new drug; on the other, to an academic pharmacologist, the strategic thinking and planning, as well as the dogged determination, required for it to succeed in the medical marketplace.

When I interviewed Jordan in June 2018, I asked him why he thought little mention was made of his name in Richardson's account as well as in ICI's internal reports. He replied that companies are highly internal organisations.⁷² Considering the long history of ICI working closely with external collaborators, whether university academics or hospital clinicians, incorporating their knowledge and know-how into internal research programmes, and often citing the relevant literature, I am not convinced this is entirely true.⁷³ Nevertheless, there seemed to be an underestimation of each other's roles, in part due to the veil of secrecy that is present at the boundary between the two spheres, which has the effect of maintaining rather than dissolving that boundary, and to their different perspectives – with one side more interested in academic reputation, and perhaps less in financial reward than the other.

⁷⁰ Dora Nellie Richardson was born in Wimbledon in 1919. Apparently she “had decided on her life's work when seeing people working in hospital laboratories, while visiting her dying grandmother in London's Cancer Hospital.” Hill, *Alderley Park*, 190. She obtained a BSc in chemistry from University College, London in 1941, started work at ICI in 1943 on synthetic anti-malarials, and obtained her PhD (presumably also from UCL) on a related topic in 1953. She worked at ICI until she retired, and died in Stockport, Ches., in 1998. I thank Gerrylynn Roberts and Geoff and Marelene Rayner-Canham for making some of these details available to me. For more on women chemists see Rayner-Canham, *Chemistry was their Life: Pioneer British Women Chemists, 1880–1949* (London: Imperial College Press, 2008).

⁷¹ When she synthesized tamoxifen, in 1962, she was paid 80% of the salary of her male colleagues. Hill, *Alderley Park*, 195.

⁷² Quirke interview with Jordan.

⁷³ See for instance G. K. Roberts, “Dealing with Issues at the Academic-Industrial Interface in Inter-War Britain: University College London and Imperial Chemical Industries,” *Science and Public Policy* 24, no. 1 (1997): 29–35.

When I informed Jordan that I intended to use his interview for a paper on his contribution to the tamoxifen story, more specifically his role as consultant to ICI, he stressed: “I received unrestricted grants from ICI in America and Leeds. I used this to fund the salaries (Technicians, scholarships and PhD salaries) for my group. I had no financial contact, and autonomy to do as I wanted in research.”⁷⁴ Yet he referred to himself as “the First Tamoxifen Consultant.”⁷⁵ This shows the flexibility of the term, which is contingent on time and place, and, more specifically perhaps, the industrial sector to which it is applied. In the pharmaceutical industry, it has often led to moral dilemmas and compromises, heightened after the Second World War when a discourse of “pure science” developed and commercial profits from research were increasingly frowned upon.⁷⁶ Hence stressing one’s moral and financial independence from drug companies is not uncommon, and I have encountered it elsewhere.

The question remains of how typical the relationship between ICI and Jordan was. Although it was not unusual for firms to employ consultants and outsource their research to external bodies by the 1970s–1980s,⁷⁷ the academic credentials of ICI’s staff, many of whom could move almost seamlessly between the realms of industry and academia, or would receive academic recognition such as Fellowships of the Royal Society, was quite exceptional. As to Jordan, how exceptional he was in terms of the extent to which tamoxifen’s success depended on him might best be answered by reflecting on the specific nature of cancer research in the period during which he collaborated with ICI. In a field at that time dominated by cytotoxic chemotherapy, but also marred with uncertainty, and dependent on external (governmental and charitable) sources of funding,⁷⁸ firms may have felt an even greater need to rely on consultants to enhance their image as research institutions, as well as to provide them with scientific knowledge and technical expertise. Jordan undoubtedly brought ICI all of these, and in return benefited from the problems and products provided by the company. Tamoxifen was an outstanding product, the first of its kind, and functioned both as a research tool and a therapy. Like Jordan, it circulated across the boundary between academia and industry. Such “boundary objects,” and the fields or sectors among which they circulate, also need to be taken into account in histories of consultancy.

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⁷⁴ Jordan, pers. comm. (17/09/19).

⁷⁵ Jordan, “Interaction.”

⁷⁶ Quirke, *Collaboration*; see also R. Bud’s comment piece in this special issue.

⁷⁷ J. Mercelis, G. Galvez-Behar, and A. Guagnini, “Commercializing Science: Nineteenth and Twentieth-century Academic Scientists as Consultants, Patentees and Entrepreneurs,” *History and Technology* 33, no. 1 (2017): 4–22 (on 6–7).

⁷⁸ R. Bud, “Strategy in American Cancer Research after World War II: A Case Study,” *Social Studies of Science* 8 (1978): 425–59.

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