

Merlin Pryce (1902-1976) and Penicillin: An Abiding Mystery

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SUMMARY

In the scientific and medical pantheon few have received more adulation and honour than Sir Alexander Fleming. Even so it is abundantly clear that his triumphant discovery of penicillin owed much to the work of others, especially Florey and Chain, who accomplished the difficult task of taking penicillin from the test tube to patient. This essay does not attempt a detailed re-examination of that discovery. Rather the present study suggests that even the initial observation on that critical day in September 1928 and its subsequent ramifications were even more complex and perplexing than the accepted version. It is likely that Professor Daniel Merlin Pryce, a somewhat unconventional but gifted son of the Welsh mining valleys played an important, quite possibly a crucial, role in that original observation. However one which, except for a very few occasions, he himself sought to downplay, even virtually to deny.

RÉSUMÉ

Dans le panthéon scientifique et médicale, peu sont eux à recevoir tant d'éloges et d'honneur que Sir Alexander Fleming. Il est tout à fait clair, néanmoins, que la découverte triomphante de la pénicilline doit beaucoup aux efforts d'autrui, en particulier de Florey et Chain, qui, eux, ont accompli la tâche difficile de transférer la pénicilline de l'éprouvette au patient. Cette dissertation ne propose d'approfondir l'examen détaillée de cette découverte. L'étude actuelle indique plutôt que même l'observation initiale qui eut lieu ce jour critique de septembre 1928, et ses ramifications, étaient encore plus complexes et embarrassantes que dans la version reconnue. Il est bien probable que le Professeur Daniel Merlin Pryce, fils plutôt non-conformiste mais doué des vallées minières galloises, a joué un rôle important, voire capital, dans cette observation originale, rôle qu'il voulait pour la plupart minimiser, même nier.

THE TRAIL

A hint that Merlin Pryce's contribution to the discovery of penicillin might have been underestimated came in correspondence from Dr J. Hirwain Thomas, a retired consultant from Porthcawl in Wales. He referred to a short article that had appeared in his local Welsh language paper [*Papur Bro*] ~ *Yr Hogwr*, (1) by D. Vivian Thomas titled - "*Penisillin: Y Cysylltiad Cymreig*" - (Penicillin: The Welsh Connection) which claimed that Professor Merlin Pryce's contribution was much more significant than commonly believed.

Through the good offices of Dr Hirwain Thomas a direct approach was made to Mr D. Vivian Thomas and to his mother-in-law, Mrs Hilda Jarman [H.J.] Merlin Pryce's sister. Contact was also established with Professor Pryce's son and two daughters - Ms. Ann (Sian) Pryce [A.P.], Mr Edward Llewellyn Pryce [E.P.], both of London, and Mrs Eira Pryce-Anderson [E.P.-A.],

who lives in Copenhagen. All family members proved exceptionally helpful, submitting long written reports, sending copies of family documents and answering patiently additional telephone questioning.

Jointly they provided a picture of home life and illuminated their father's relationships with notable professional colleagues. The present paper, drawing on this and other documentary evidence is concerned with Daniel Merlin Pryce himself, his scientific and personal relationship with his 'chief' - Sir Alexander Fleming and the initial phase of the penicillin story.

MERLIN PRYCE'S LIFE

Born at Troed-y-Rhiw, Glamorgan, on 17 April 1902 to Rachel and Richard Pryce who kept a local tavern, Merlin was first educated at Merthyr Tydfil County School before moving to Pontypridd Grammar School for Boys. As a seventeen year old he started his pre-clinical

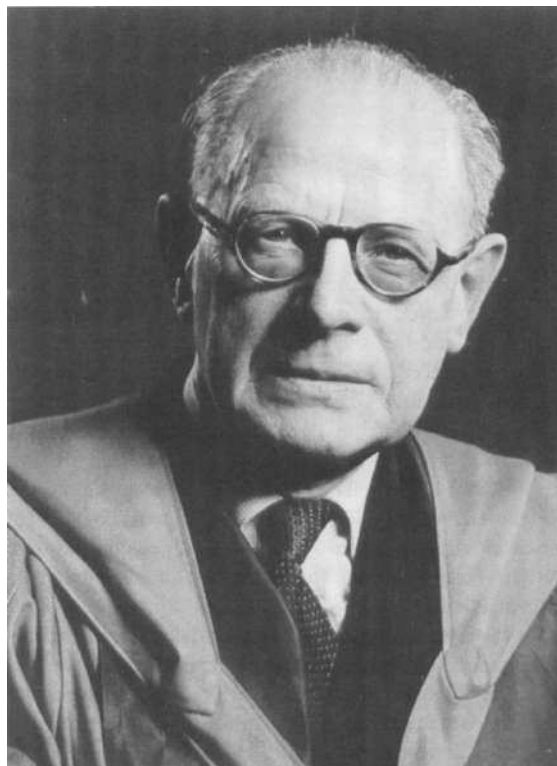
studies at the Welsh National School of Medicine in Cardiff, concluding his initial medical course at St. Mary's Hospital, London in October 1922. He took the Conjoint Diploma in January 1926, and passed the final M.B., B.S. degrees of London University the following November.

Early in the 1920s Merlin and his sister, Hilda, moved to London and were soon followed by their parents who started a small business in Ealing in 1925 where the four members of the family shared the home. In 1927 Dr Pryce was appointed to a Junior Research Scholarship under Alexander Fleming in the Bacteriology Department. According to Hospital Records he was later appointed 'Second Assistant Pathologist' - a 2-year post - under Professor Newcomb on 19 April 1928. He spent three years in the Department of Chemical Pathology, as assistant to Dr Roche Lynch, before being appointed 'First Assistant' in 1933, a post involving teaching duties. He was awarded a M.D. in Pathology from London University in 1935. Throughout the war he was responsible for pathological services in the section of St. Mary's that was transferred to Harefield and Amersham Hospitals but continued teaching. In 1948 he became Reader in Pathology, and six years later, when Professor Newcomb retired, he was appointed to the Chair.

It had been a long and, no doubt, arduous journey from Troed-y-Rhiw to his Professorship, but on his retirement in 1967, Merlin Pryce could look back with quiet satisfaction on forty years of distinguished service to the medical profession as morbid anatomist and to St. Mary's.

Some understanding of Pryce's personal qualities and his home life are essential to understanding his relationship with Fleming and the discovery of penicillin. In the present context, they are more important than his research and publications in pathology.

Pryce was a devoted St. Mary's man from his early student days to his elevation to the Chair in 1954; an event greeted with delight by his colleagues. He does not appear to have initiated any new fundamental research projects although pioneering the use of twin diffraction rings in measuring the size of red corpuscles and a method of growing tubercle bacteria. Rather he shone as an excellent teacher of generations of medical students. His students and colleagues held him in respect and warm affection, recalling his teaching as 'practical and matter of fact', his 'sincerity and integrity' - and his modesty and self-effacement. Retrospectively Pryce's colleagues admit that, in spite of the efficiency and success of his department, 'he had to make the best of accommodation that could only be described as



Professor Merlin Pryce

inadequate'. By nature and conviction he was a co-operator rather than competitor. In his obituary in the *St Mary's Hospital Gazette* (2) his colleague, R.R. Wilcox, pays tribute to 'his larger qualities of warmth, sincerity, tolerance and love of his fellow men - and above all that of his family. Above all he was a brave man.' The tribute concludes by stating that his departed colleague 'seemed to have been a permanent feature on the St Mary's scene, - All salute the passing of one of St Mary's best loved and stalwart sons'. One of his oldest friends and colleagues commented, after knowing him for close on half a century, that 'he brought his Welsh warmth, laughter and kindness, and professional integrity to his chosen place of work, and over the years he was one of those who made it a pleasant place to be in'.

In July 1934, a few months after being appointed First Assistant in the Pathology Department, he married Molly Whelan, who was a constant source of strength and encouragement to him. They had three children, Ann, Edward and Eira. All three are alive and well, and cherish happy memories of their father and mother and a home atmosphere of enquiry and encouragement. They regard their father as 'a great man and think that he deserves better recognition' ... 'Always helpful but he was very modest, rather reticent and perhaps a bit of a dreamer [A.P.], did not conform to the establishment [E.P.] and, by universal agreement, an idealist. Although reticent and modest and deeply committed to his work, he was gregarious rather than a loner [H.J., A.P.]. All stressed that he was never rude or sarcastic at home, or with the students at St Mary's always insisting on the children's need to be truthful while setting them an example himself. He was both humane and humorous

and encouraged his family to enjoy a very wide range of interests.... loved classical music....'Art Galleries and Museums' and 'to the great Italian and French films' [E.R]. His interests extended to learning German, Italian and finally modern Greek.

As a young man he had an ambition to become a geologist and discovered the remains of an Ichthyosaurus [E.R]. This was later translated into an attachment to all forms of natural history, a love of mountains and archaeology and hence possibly his love of rock climbing and museums. He could not bear languid, idle holidays.

Pryce had a long wait for professorial recognition. This tardiness is almost certainly not a reflection on his ability. It has been suggested that Pryce's reticence and shyness, which persisted in spite of his professorial success, was the result of his social background and an awareness of his lack of a public school education compared with most of his counterpart colleagues at St Mary's. On the other hand it could simply have arisen from his desire to attain preferment within St Mary's. There was an influential Masonic Lodge there at that period comprising many consultant staff. Pryce was pressed to join but, although well aware of the advantages, declined to do so.

Of much greater importance in this context might have been his commitment to Communism, probably extending back to his student days in Cardiff, and perhaps even a little earlier. As a youth he could not fail to have been aware of the enormous tension in the south Wales coalfield during that period. His awareness of the impact of deprivation and suffering did not lessen with the passage of time. He welcomed with enthusiasm the advent of the National Health Service, and indeed worked hard to expedite its coming. One may safely assume that most of his consultant colleagues were vehemently opposed and concurred with the stubborn early resistance of the BMA. Nor was his advocacy merely theoretical. In later years, when he needed vascular surgery, he insisted on being a patient in a general ward in St Mary's, and enthusiastically praised the care that he had experienced.

The exercise of staunch humanitarian principles was an abiding feature in the Pryce home. When the home of Alexander Fleming, transiently his former Chief at St Mary's Bacteriology laboratory, was bombed and severely damaged in March 1941, Fleming and his first wife, Sareen, were offered immediately accommodation at the Pryce's home and stayed there several months. Happily Molly and Sareen, both Irish and former nurses, were on excellent terms. During the war Molly undertook activities that brought her in contact with a

number of unmarried mothers. Molly and Merlin took them in and gave them shelter and comfort in their own home during the late stages of pregnancy, and after delivery, received them back, if necessary, for a period of convalescence. In turn they would help with the children. To the consternation of their neighbours, the Pryce's used to invite German prisoners stationed locally to tea. The local condemnation did not deter their conciliatory gestures.

During his last years he suffered much from hypertension and its progressive complications. Although he had retired, he undertook locum duties as hospital pathologist for colleagues in the London area. He zealously maintained his links with St. Mary's and resumed his research on coagulation of the blood.

Daniel Merlin Pryce died on 8th February 1976 and was cremated at Golders Green Crematorium; but his life also was celebrated in a funeral service at a Roman Catholic Church. At that service his close friend for over thirty years, Lord Porritt, formerly Senior Consultant Surgeon at St. Mary's Hospital, and later President of the Royal College of Surgeons of England, paid an eloquent tribute to his colleague.

THE GREAT EVENT

Other young men and women have trodden a similar path to academic recognition overcoming difficulties and disadvantages. However, one event makes Merlin Pryce's story unique; because, as a young doctor he was directly involved in a great discovery - perhaps the greatest discovery, in the history of medicine.

As a junior researcher in Fleming's Department in 1927, he was directed to undertake a special study of the *Staphylococci* - and their variants. Macfarlane (3) emphasises how closely Fleming and Pryce worked together culturing staphylococci from various sources for further study. Pryce's scholarship was a short term rotating appointment; consequently he had to leave the Bacteriology Department between February and April 1928 to gain experience in the Haematology and Pathology Department. Nevertheless both men had become lifelong friends despite the differences in their status and age.

It is at this point that the histories of Pryce, Fleming and Penicillin become intertwined as recorded by Maurois in his 'official' biography (4), as Pryce was present at the crucial moment when Fleming first noticed and then decided to subculture the strange mould.

Pryce annotated his personal copy of the Maurois' biography. Some of the comments are of minor significance, such as changing the word mutants to

variants; substituting 'scalpel' with 'loop'; asserting that 'Flem was one of the *tidiest* of workers and because of this, well able to work efficiently in a small lab even often shared with another (First Todd &).' With regard to 'stifling' in the tiny room [in a previous paragraph], Pryce wrote 'Balls! the door was always open.' Incidentally, the 'window which looked on to Praed Street' which [Fleming] 'would open', and through which the offending mould was said to have drifted, had never been seen open. Other observers claim it was 'because [the window] was inaccessible'. But the window became part of the myth!

More significantly commenting on Fleming's revisiting the work on staphylococci, Pryce wrote in the margin - "This has nothing to do with the resumption of work by Flem. on 0. Flem wished to quote me as saying that the variants were stable. Biggar said that in his paper but I had not set out to verify this and would not commit myself, and would not say yes tho. F repeatedly asked me to. This is when he came over to the blood lab to see me about it. If I had said yes (and it would have been easy to say so) there w'd have been no P'in".

Fleming published the first paper on the penicillium mould in 1929 (5) with only the mildest therapeutic suggestion - 'It may be an efficient antiseptic for application to, or injection into, areas affected by penicillin-sensitive microbes'. It received little attention. The 'discovery of penicillin' - the substance that had destroyed the culture of *staphylococci* growing on the famous mould-infected Petri dish - lay largely dormant for more than a decade, although various scientists sought to purify and exploit the active ingredient without success. In 1940 Howard Florey and Ernst Chain and their colleagues in Oxford successfully addressed the problems of purification and assessing the therapeutic value of their purified penicillin and later its production in adequate quantity and quality. Only then did observation turn into revolution as Fleming himself recognised (6).

The first official biography of Fleming in 1959 was prepared by Andre Maurois at the invitation and with the active support and assistance of Lady Amalia Fleming, his second wife. The book (4), translated from the French by Gerard Hopkins, received international acclaim and attained an enormous circulation although it was clearly evident that the distinguished author was somewhat handicapped by lack of knowledge of bacteriology. It became the original 'authorised' *version* of events.

There followed a vast 'Fleming' bibliography (see refs 6-12.)

Despite all these publications a number of mysteries remain, some personal and some scientific. What was precisely Merlin Pryce's role on the fateful day in September 1928? Indeed, is there convincing evidence to support Vivian Thomas' more ambitious claims for Merlin Pryce? And why did he appear reluctant to take any credit for participating in the crucial discovery?

In order to examine these issues further, we will need to turn in part to the testimony of the Pryce family but also to the correspondence between Merlin Pryce and Professor Ronald Hare in the late 50's and 60's. We will also need to appreciate that, not only was much luck and some serendipity involved in the crucial observation, but also some scientific confusion.

FAMILY TESTIMONY

As already noted, Merlin Pryce's three children - Edward, Ann and Eira [Elizabeth] had been very helpful in presenting a full picture of their father's life. They were born between March 1936 and January 1940, so that they became aware of progress in clinical exploitation of penicillin, which was important institutionally to St Mary's Hospital as well as to the family, as young children. This caveat has to be borne in mind with regard to the timing and reliability of such recollections.

"Penicillin was a natural fact of our lives as we grew up but Father didn't refer to it. Usually his students or colleagues would ask when they came for a meal. So from early on, and I can't say how early but extremely early, we knew something about penicillin." However, there was no expression of satisfaction or pride at all. He just described it as it happened, i.e. an extraordinary event that he noticed ... as it happened — genuinely and sincerely ..."[E.P.-A.]

Unfortunately no early family letters, documents or any written evidence that would provide that so important link to the Petri dish, are extant. It was clear in their view that 'it was [their father's] decision not to accept and receive joint recognition with Fleming.'

Eira Pryce-Anderson recalled that

"my father *never* talked [spontaneously] about his part in penicillin. He was modest ... [However] he [Pryce] told the story, which I can clearly remember, when persuaded. The first time when I was 14 ... and the second time when I was 18. The time of the second occasion was within 7 years of father's retirement from the professorship of pathology. On both occasions (he) told the story exactly the same way—He knew, it seemed, the story by heart.'

There is complete agreement on the warmth of their family's relationship with the renowned 'Flem' and his first wife, Sareen. Later Merlin Pryce's personal copy of the Maurois biography bears a message in Lady Amalia Fleming's hand: To my husband's loyal friend with my affection and all good wishes. Amalia.'

Further family evidence is offered by Mrs Hilda Jarman, Merlin Pryce's sister, on 13 August 1998. She started her story with their joint move to London when her brother began his clinical studies at St Mary's. She remembered Merlin qualifying and securing his first job in the Bacteriology Department under Fleming at the age of 26 or so. She was aware of his desire to study pathology and naturally very proud of his professorship. Then she went on to describe the Petri dish event as she first heard it seventy years ago - and heard it, of course, from Merlin himself on a number of occasions. She stated that Fleming was away on holiday and was due to return. It so happened that a routine tidying up of various bacteriological plates and dishes was necessary. This was normally done by the technical staff - the laboratory assistants - but on this occasion they were involved in some labour tension or difficulty - she ventured, with some hesitation, to call it a 'strike'. As a result the responsibility for clearing or destroying old and used plates fell entirely on 'young Merlin'. During the clearing process Merlin noticed unusual features on one of the plates and preserved it carefully - and destroyed the rest - and personally showed it to Fleming on his return from holiday. Soon afterwards, she suggested, Merlin moved to pathology.

Mrs Jarman went on to say that when Fleming wrote his first paper on penicillin he wanted to include Merlin's name as a significant contributor or possibly co-author. Her brother 'who was always of a retiring nature and a very modest man would not accept the suggestion.' She confirmed that Fleming and Merlin remained life-long friends and recalled that, when the Fleming home was bombed [in March 1941], Fleming and his wife, Sareen, went to live with Merlin and his family at home in Rickmansworth. It can be certain that Merlin and Molly also gave Fleming a great deal of support when Sareen died. She informed me spontaneously that the Fleming Papers were kept at the British Museum [Library] and that they were not available for inspection, and added that sadly Merlin's diaries have been lost. For a lady in her 96th year (1998) her memory was clear and detailed.

Many, although not all, the details of Mrs Jarman's recollections can be confirmed independently.

It is generally agreed that the Petri dish incident occurred on 3 September 1928 - a Monday - the usual

day to return from holiday. Fleming indeed had been away for several weeks at his country house, The Dhoon, Barton Mills, Suffolk, but he made a special journey to St Mary's on that Monday:

'a flying visit to London to assist a surgical colleague with the treatment of an abscess ... It was probably while waiting for his colleague to appear that Fleming took the opportunity to discover penicillin ... Having discovered penicillin without looking for it and narrowly escaping failure to do so. Fleming then returned to his country home to resume his interrupted holiday, and did not start work again until the end of September (but leaving his new assistant Stuart Craddock to carry out some experiments). Even so, it was not until the end of October that an experiment with penicillin was recorded, and late November before serious research can be said to have started' (7).

Mrs Jarman also said that Andre Maurois, when preparing his book - *The Life of Sir Alexander Fleming: The Discoverer of Penicillin* - came to St Mary's Hospital to interview Lady Fleming and Merlin Pryce: probably quite early in 1956. After Maurois left the room, Lady Fleming turned to Merlin, by then Professor of Pathology, and said, according to Mrs Jarman: 'Anyone would think that you had found the mould', in a voice that could be described as 'withering', but Mrs Jarman finally suggested 'a voice that was not at all gracious'. According to Mrs Jarman, Merlin replied: 'but I did'.

THE FLEMING LEGACY

As one might expect, at least one British scientist, Professor Ronald Hare, the eminent bacteriologist on the staff of St Thomas's Hospital, London was seriously considering writing Fleming's life-story. Hare was also a close personal friend of Merlin Pryce. A doctor's son from Durham he was also a student at St Mary's Medical School, graduating M.B., B.S. (London) in 1924 after a distinguished undergraduate career. In common with Fleming, his first post was in the Inoculation Department in 1925 at St Mary's working on puerperal fever. He stayed in that department for four years. Later having obtained a M.D. in 1935 - the same year as Pryce - he took a post in the Connaught Laboratories in Toronto and stayed in Canada for *ten* years. In 1946 he was appointed to the Chair of Bacteriology at St Thomas's Hospital, London where he stayed until his retirement in 1964.

Hare maintained a life-long interest in infection by bacteria - especially the spread of *Staphylococci* in hospitals, and diseases caused by *Streptococci*. While in Canada he set up the first penicillin plant there. Tributes

after his death in March 1986 were paid to 'his incisive mind and his great ability to recognise facets of research likely to be useful and rewarding.' Emphasis was given to 'his dislike of hypocrisy of any kind.' Socially he was noted for his kindness and his 'unquenchable and lively interest in other people.' He was a keen musician and water colourist.

Pryce and Hare spent many holidays together including in the summer of 1928, mountaineering, sleeping in tents, climber's huts and remote farmhouses, with Pryce undertaking the difficult climbs and fell-walking and Hare, it seems, being more concerned with pursuing his primary interest in painting.

Hare possessed all of the attributes necessary to write an authoritative biography of Fleming and there is incontrovertible evidence that he had planned to do so. On 13 February 1956 Pryce wrote to Hare a letter that is recorded in an appendix to this paper (Letter 1) It proves that Ronald Hare was seriously considering writing a biography of Fleming at exactly the time Lady Fleming was pressing Maurois to undertake the responsibility. She visited Maurois in Paris 'to explain very exactly the problems with which [he] should have to deal' and appeared to be indicating the tenor of the biography and ensuring that it accorded with her wishes. As Pryce wrote: 'She wanted anecdotal stuff and not a truly scientific review and assessment. Amalia Fleming must have known Hare - and of his reputation. Pryce was emphatic that Hare was the person to write the biography, because he knew Fleming, was conversant with the complexity of the field and had an ability to write well. Furthermore, Maurois wrote in French while all Fleming's work was recorded in English.

By allowing Maurois access to the Fleming Papers she blocked Hare's desire to prepare the biography. One cannot escape the conclusion that her obstructive tactics were deliberate, born possibly of an element of personal animosity between her and Hare. Nevertheless in 1970 Hare published an important analysis of the penicillin story (7). Twenty-five years later in 1982 when Ronald Hare published his final detailed article (8), the first footnote was again despondent with regard to the Fleming papers at the British Library. The copyright-holder, Lady Fleming, would not grant permission for the documents to be quoted by Hare or even the reproduction of some drawings 'lest it lead to the wrong suspicion that she agreed with the conclusions of the author.' The last section of the footnote reads:

'The editors consider it unfortunate that the facts about a discovery of such importance, made over half a century ago, cannot now be made available for public discussion except from one particular standpoint. Historians of modern medical science, when dealing

with the Fleming Papers should be warned in advance of this hazard'.

THE HARE - PRYCE CORRESPONDENCE

Pryce's letter to Hare of 13 February 1956 revealed that Hare was contemplating a biography of Fleming. The next letter available - dated some four months later - disclosed that Hare had been hard at work, and had submitted a draft for Pryce's assessment on 27th June (letter not included). There is no letter at hand to indicate Pryce's assessment of the first draft of Hare's biography, but on 18 July, 1956, Pryce sent a closely-typed A4 sized script giving a full description of events surrounding the fungus-infected Petri dish (Letter 2) Pryce added a postscript at the top of the page in his own hand: 'Dear R.H. I w'd rather the story went like this. Kindest regards DMR' A curious turn of phase, one which would imply that Pryce had amended Hare's version. No copy of an acknowledgement from Hare has been seen and it appears highly probable that he decided, around this time, to discontinue - or at least postpone - his plan to write Fleming's life-story. The knowledge that Maurois was already at work and that he had the support and 'guidance' of Lady Fleming, to say nothing of access to the Fleming Papers, must have been a strong disincentive.

Interestingly the Maurois description of the Petri dish incident is an obvious paraphrase of Pryce's detailed contribution of 18 July 1956. Hare is unlikely to have passed the document on to a rival, but Pryce could well have co-operated with Maurois if he had received a direct personal request from Lady Fleming, given his unflinching loyalty to his former 'Chief. Thus in all probability Merlin Pryce himself is the source of the 'authorised' version!

Ronald Hare's much more science-orientated 1970 version of events (7) contained a concise, factual and non-adulatory account of Fleming's personality that might well not have pleased Lady Fleming, but Macfarlane accepted in full its accuracy. The preparation of this volume meant a further exchange of several letters during 1967 between Hare and Pryce. It is not clear when the actual writing re-started, but a letter from Pryce to Hare on 23 January 1967 (Letter 3) shows that the work was proceeding steadily. Much of the letter refers to technical matters concerning staphylococci 'going stale', incubation temperatures and 'sealing of Petri dishes' - and with what appears to be a sincere attempt to reconstruct the details of an event that had taken place almost forty years earlier. This correspondence graphically illustrates the original technical problems and the difficulties of reproducing events and some of Pryce's technical misgivings (letters 3 to 9).

Several other illuminating points emerge from this increasingly fraught correspondence. While Merlin Pryce is at pains to protect on all occasions the reputation and standing of Fleming, Hare was focussed on the analysis of microbiological and experimental detail. Pryce was clearly jealous of his own integrity and reputation and sensitive to any implications of personal carelessness. Hare appears impatient and disbelieving of the authorised version and appears to suspect the Pryce is being less than frank. Technical nuances become intertwined with personality and history. Much of Hare's interest centred on the temperature and conditions at which the plates were stored. It is now clear why this exercised him as later work attempting to reproduce the discovery showed this to be critical. To produce the penicillin effect the fungal spores must have germinated and began to release penicillin before the staphylococci began to grow. This in turn implies a very specific temperature regime as fungi grow at lower temperature than bacteria. Hare in his 1970 paper (7) had found from examining the meteorological record for London that nine days in early August in 1928 were indeed cool enough for fungal spore germination and growth and that later in the month the temperature rose enough to allow staphylococcal growth. Sadly after this correspondence it appears that the long friendship between Hare and Pryce, including the shared holiday in summer of 1928, floundered. Apparently for the last few years of his life Pryce never spoke to Hare.

One salient point emerges. Merlin Pryce not only enormously admired Fleming but also regarded Fleming's specific action in re-culturing the mould as **seminal** and **crucial** and that he, 'DMP', would *not* have done that. Implying that he felt disqualified, almost 40 years later, from claiming any glory or praise: positive action being more important than any passive observation!

REVISIONIST IDEAS

When he was appointed Professor of Pathology in 1954 the *Western Mail* on 26.2.54 in its column of 'Our London Letter', perhaps depending more on patriotic pride than on inside information, referred to Pryce's 'brilliant career', and added that he: 'played no small part in the epoch-making discovery of penicillin.' Much more compelling evidence is required if Vivian Thomas' claims are to be given credence.

In his obituary Richard Willcox (2) while emphasising 'an affectionate personal relationship between Fleming and Pryce, notes '—he [Fleming] would question [Pryce] on his investigations of Penicillin - indeed he has been described as acting as a catalyst in its [Penicillin]

evolution.' Another St Mary's man of the same era took a much more robust view. Henry Courtney Mansel Walton was born on 22 January 1909, educated at Charterhouse, Cambridge and St Mary's Hospital and graduated in 1932. He was posted to India with the R.A.M.C. in 1934 where his duties were in the fields of pathology and hygiene, and from 1937 he specialised in pathology. He served in this capacity at home and abroad in the Middle East and Burma before being appointed consultant pathologist to the Swansea Hospital in 1951 where he served until his retirement. He died on 25 May 1988 at the age of 79.

Walton was a man with formidable St Mary's associations. His maternal grandfather, father, uncle, and son were all St Mary's men. Therefore it is highly improbable that he would do anything to diminish the status and standing of his 'hospital' or its role in the discovery of penicillin. Walton appears to have been a man of high personal integrity, founding the first branch of the Samaritans in Wales.

From his letter to Pryce (letter 10) he must have been convinced of the truth of his version of the story otherwise he would have kept a mere suspicion to himself. — 'Most of the doctors in south Wales know, because I tell them frequently that —.' - Certainly he had the experience and the social and medical contacts to be well informed. The tone of the letter is friendly and unequivocal and, as far as can be determined, he had no particular axe to grind. Edward Pryce was with his father when he opened the Walton letter. His comment was a brief and a somewhat forceful "Damn fool" - but he made no denial or further comment. The letter was not destroyed and found later among his papers but never referred to again.

Mr Vivian Thomas' article in the *Yr Hogwr*, (1) contains the following quotation. (Translation by E.W.J.)

'Over twenty years ago my wife and I were guests at the annual dinner of the West Kent Pharmaceutical Society. It was strange because the chairman was a brother of my father-in-law, and the guest speaker was the brother of my mother-in-law, namely Professor D.M. Pryce. In the course of his speech he spoke of that moment in 1928 when he suggested to Alexander Fleming that he should look on a dish where an historical piece of mould had grown. He said that it was possible that Penicillin would never have been discovered if he had not been working with Fleming at the time and that if he [Pryce] had not noticed this particular dish. This growth was the miraculous substance that became such a wonderful remedy.'

This unexpected statement would be of considerable importance if it could be confirmed. No record of the annual dinner can be found in the *Royal Pharmaceutical Society Journal*. However the *Kentish Times* for Friday, 26 November 1965 contained a full account of the dinner held at the Yorkshire Grey Hotel, Eltham Green, on 17 November 1965, when 'Professor Pryce ... proposed the toast of the Pharmaceutical Society of Great Britain'. The report was headed 'A COMPLETE REVOLUTION IN MEDICINE'.

'If it had not been for Professor Pryce, Professor Alexander Fleming might never have discovered penicillin. The speaker told the diners how he had walked into the room where Fleming was working, prompting him to pick up the plate on which that historic piece of mould had formed'. [Then he quoted the actual words used by Pryce in inverted commas] "If I had not walked in at that moment and talked to him, he would never have picked up the plate and there might be no such thing as penicillin."

It was a well-attended dinner and some 170 chemists, hospital pharmacists and their associates were present.

This is the first and perhaps only occasion, when Pryce spoke in such positive terms that, in essence, amounted to a priority claim; contrasting with family evidence of his reluctance to be drawn on the subject and his comments in the Hare-Pryce correspondence.

There remains one other relevant episode. Eira Pryce Anderson relates an experience, "very distressing at the time". Among the large congregation at the Memorial Service held at St Mary's Hospital, was Ronald Hare, in spite of the long years of estrangement. At the beginning of the service he approached Eira who had known him well since childhood. He said, with no pleasantries, 'Today we are remembering the man who was the discoverer of penicillin.' And walked away.

What really happened on the 3rd Sept 1928 is very difficult to disentangle. Richard Willcox's obituary (2) suggested that 'Pryce acted as a catalyst in the evolution of penicillin', which may be an opaque compromise capable of several interpretations. One is that it was Merlin Pryce himself who was the first to observe the phenomenon. Ronald Hare, who was a young research worker on the staff of the same laboratory, though not directly under Fleming, and had spent part of the summer of 1928 with Pryce appears to have formed this opinion. A belief cherished by such a distinguished bacteriologist can scarcely be ignored.

More recently, M. Lawrence Podolsky in his book *Cure out of Chaos* (12) has offered a similar description of the moment of discovery of the plate in Fleming's laboratory. Fleming's own words on the occasion of the

Nobel award are quoted by Podolsky. Fleming disclaimed that he had discovered penicillin: 'as a result of serious study ... and deep thought' and added: 'That would have been untrue and I preferred to tell the truth that penicillin started as a chance observation.' Podolsky goes on to paint a picture of Pryce picking out the crucial plate and, at the second time of asking, Fleming deciding to make the critical subculture.

This account of the discovery of the fungus-infected dish appears to accord with what Pryce himself claimed in his speech to the pharmacists of Kent at Eltham Green in November 1965. Both have provided an extra element of much more personal involvement than the original Maurois or MacFarlane versions. The paragraph in the *Kentish Times* is itself somewhat ambiguously phrased but one implication seems beyond doubt, namely that: 'There might have been no such thing as penicillin' had Pryce not been present in Fleming's laboratory that day. He does not claim to have done anything of a technical nature, but he 'talked' to Fleming, and that 'talk' stimulated his former 'Chief' 'to pick up the plate' - the crucial action that day, not once but twice - Pryce has not claimed to be the discoverer, but asserts that penicillin could not have been discovered without him. Is that meant to be a gentlemanly and cautious plea for recognition of his contribution or just a mild exercise in equivocation? In his letter to Hare on 18 July 1956 Pryce expressed his view that Fleming 'was a great dialectician.' It would appear that the pupil was similarly endowed.

EPILOGUE [GarethWyn Jones]

During his last illness in January 1999 one of my father's great concerns was that the manuscript of his work on the association between Daniel Merlin Pryce and the discovery of penicillin lay unfinished. I undertook to try and complete and edit his work.

My father appeared not to have reached any final analysis of the possible primary event nor the ensuing human drama. Indeed he may not have wished to do so, as no unambiguous resolution can be offered. Perhaps nonetheless this story cannot be left without some final weighing.

Several interpretations can be offered. On one hand Merlin Pryce's role could be seen as simply that of a passive observer who happen to make a social call on his old boss during the latter's fleeting visit to his laboratory during his extended annual holiday. By a remarkable coincidence this call coincided with Fleming's making and acting upon his historic observation thus creating the first 'penicillin culture'. Clearly Hare did not accept this view and is likely to have had a direct knowledge of the event of the summer of 1928.

The reference to Merlin Pryce acting as a catalyst is capable of several interpretations. Possibly, by refusing to accept that the 'Biggar mutants' were stable, he precipitated the discovery of penicillin — although the substance of this argument is vague. It might be construed as a 'negative contribution', his stubbornness simply forcing more plates to be prepared. However this is probably of being more relevant to the review, 'The Staphylococci', a section in *A system of Bacteriology in relation to medicine* published by Fleming in 1929 (13). Alternatively his catalytic role was that of a colleague who drew Fleming's attention ("prompting to him to pick up the plate" according to the report in the *Kentish Times*) to the crucial plate.

This alternative scenario is partly based on Mrs Jarman's testimony and is supported by the evidence in the *Kentish Times*, from Dr Walton and from the reactions of Prof. Hare. This hypothesis would suggest that the primary observation of the crucial plate fell to Pryce, either somewhat casually on Monday the 3rd September in Fleming's presence or, just possibly, prior to that date while he was attending to residual duties in a laboratory he had left several months previously. In either event, it would appear that he specifically drew Fleming's attention to the peculiarities of the infected plate but had not appreciated the crucial necessity of making a sub-culture. It is possible, given the importance of the precise temperature regime in early August of 1928 (vide 7,8) but unprovable, that Pryce in mid/late August had set the plate aside to bring to the attention of his mentor and friend. This interpretation would be strengthened if there were independent evidence of industrial unrest amongst the technicians referred to by Mrs Hilda Jarman.

Given the nature of Fleming's fleeting visit to London on the 3rd of September and the evidence adduced, this latter scenario or some minor variant of it, must be a reasonable possibility, perhaps even a probability.

If a more active, 'catalytic input' is accepted, this raises the question, why did Pryce disavow and minimise his possible role? In 1929 his refusal to include his name in the paper would have seemed a relatively slight, even

trivial, decision. (The evidence for this apparent refusal comes from the family while the Pryce-Hare correspondence only makes clear that he refused authorship of or acknowledgement in, the Staphylococcal review) (13). Certainly neither he nor Fleming could have been aware of the enormous implications of their fortuitous observation. As is clear from the correspondence with Hare, nearly 40 years later Pryce still harboured technical doubts. Also he felt, with characteristic modesty that his role, even if it had covered the primary observation, did not merit inclusion in a paper by an already illustrious senior partner. This correspondence also suggests that Merlin Pryce [and possibly also Fleming] did not fully appreciate the complex and particular microbiology which lay behind the development of the crucial plate. Possibly even in 1929 it was apparent to Merlin Pryce that his career lay in Pathology.

By 1940 and certainly in the post war decades, it would have seemed disloyal to his friend and admired colleague and indeed to St Mary's as an institution, had he sought to claim belatedly some proportion of the glory. Given all the evidence of his personal integrity and high moral standards, such behaviour would have seemed unethical and demeaning. It is not difficult to imagine that he felt that a discrete silence was called for on virtually all occasions. Crucially he clearly believed in his letter to Ronnie Hare [23 Jan 1967] that whatever the precise history of the plate and its interpretation, Fleming actually made the subculture and "DMP would not have subcultured that mould".

It would be a great insult to the memories of Merlin Pryce and Alexander Fleming and indeed my own father if recounting this fascinating story led to an unseemly battle for primacy between protagonists for and against Fleming and Pryce. They remained loyal friends and colleagues throughout their eventful lives. The story does however reveal the complexity and the humanity of scientific and medical discovery and the contributions of unsung and magnanimous individuals.

Correspondence

ALAN POWDITCH, M.C.
HOUSE GOVERNOR

ST. MARY'S HOSPITAL

W.2

TELEPHONE
AMBASSADOR 1280

DEPARTMENT OF PATHOLOGY

13th February, 1956

Dear Hare,

I have, as I told you committed to paper some notes on this incident some time past, and I should be only too pleased to get them for you, The only hitch is Lady Fleming; she has apparently broached Andre Maurois to write this thing and wants some anecdotal stuff to make it interesting. I don't feel happy about that. This man may be capable of writing a nice little book, but I should have thought that the person to write the life of Flem would be yourself; you have known him a long time and I think it is important that the person who writes the biography should be somebody who knew him; and of course not only that, but you have the ability to write. (You may even feel a compulsion to be closer to the facts than A.M.) Meanwhile I shall give a few scrappits to Lady Fleming if I can recollect any, but I don't feel like putting myself in the hands of this polished French writer of English prose.

Yours sincerely,

(D.M.Pryce)

Professor R.Hare,
Department of Bacteriology,
St.Thomas's Hospital Medical School, S.E.I.

LETTER I

ST MARY'S HOSPITAL.

W. PARKES, D.S.O., M.C.
HOUSE GOVERNOR

W. 2

TELEPHONE
PADDINGTON 9051

DEPARTMENT OF PATHOLOGY.

18th July, 1956.

When I worked with F. one of the things he did was to test the bactericidal resistance of the staphylococcal mutants produced by Bigger. Later when F. was asked to write the section on staphylococci he came along one day, and asked if these strains were permanent. Had I said 'yes' I would have been quoted in the article which was what F. wanted to do, "but I said I didn't think I had done enough work on this particular point. 'So F. had to repeat Bigger's work himself — because I had now left the Department. Sometime afterwards I went to see F. and jokingly he chided me for all the work I had caused him. Mutant strains produced by Bigger's technique are so striking, looking more like a mixture of contaminants and nothing like the original culture, that we naturally took to looking at the culture plates as we talked. F. had been doing a lot of work and the lysol tray was piled high with cultures ready to be thrown away. Among the plates we looked at was the famous penicillin plate. Several other plates were contaminated with colonies of yeasts and moulds but we went back to this particular plate because the lysis of the staphylococcal colonies around the mould had attracted F's attention. He took a plate up, looked at it, and after a while said, "That's funny." I don't know what was going through his mind, but, for my own part, I thought that the lysis was due to acids produced by the mould. I had seen staphylococcal colonies slowly autolyse on keeping, and develop daughter colonies, and I had presumed that the lysis in that case was due to acidity. But pandering to the great man I actually said "That's just how you discovered lysozyme." He made no comment, but with automatic hand he took his platinum loop and subcultured the mould into a tube of broth. I remember that he didn't just touch the mould but cut out a piece about 1 mm. diameter which floated on top of the broth. I think it is important that he not only observed, but immediately took action. Many who observe and may even feel the possible importance of an observation, do not take action but just wonder and - forget. And apropos of this occasion there is another incident which happened when I worked with him. Something had gone wrong with one of my cultures, I can't remember what, but I do remember his exhortation and advice to make use of one's mistakes. It was his attitude to life. There is, of course, nothing startlingly original in this, but nevertheless it was the attitude of a man who, if not in wordy argument, at least in his thinking and working was a great dialectician. DMP

LETTER 2

St. Mary's Hospital Medical School
DEPARTMENT OF PATHOLOGY
ST. MARY'S HOSPITAL
LONDON, W.2.
Ambassador 1280

23rd January, 1967

Dear Ronnie,

I was glad to see you at the meeting and sorry not to have had more time to talk. I am writing now because Len Crome said you had spoken to him about my letter. I was a little worried when I wrote to you after reading your typescript that you were belittling Flem too much. I think old Flem was truly great but not happy with his colleagues on account of his different social background. I hope you won't belittle him because even if he was a bit odd this was due as much to his colleagues as to him. I hesitate therefore to say what I think was the real explanation of the appearances on the penicillin plate but anyway here goes:

For some reason one of the things I did with staphylococci was to let them "go stale" (whether at 37° or room temperature I can't remember). Drying was prevented with plasticine sealing of the petrie dishes. After some weeks the colonies gradually lysed and became transparent. Later still, opaque white dots appeared in the lysed colonies which I thought were contaminants but which, of course, we now know would be due to the growth of mutants; I could find only staphylococci when I made films of the white dots - it struck me at the time as very funny for staphylococci to be contaminants of staphylococci. But those were early days (when one spoke of microbic variation and not mutation), and mutant dots (as in McConky coloured colonies) had not been described.

When we looked at the penicillin plate I thought to myself that the translucent appearance of the colonies surrounding the mould was due to an acceleration of the lytic process which I had previously seen with ageing. What actually I said to Flem however was "this is how you discovered lysozyme." He kept mum but took a loop and dug out a bit of the mould and floated it on top of broth. Since you wrote to me - or rather since I saw you at the meeting - I have begun to wonder whether the lysis of the colonies wasn't after all really due to spontaneous lysis of dying cells. As far as I can remember there was very little or no inhibition of growth. The colonies surrounding the mould were as large as those elsewhere but were transparent. It may be that I was right in thinking that the appearances on the plate were due to food exhaustion and/or pH changes, which of course would have been greater in the vicinity of the mould. These possibilities could easily be tested. The plate may have been above the lysol for some days* although this is unlikely. But I think that the contamination with the mould, and certainly its growth, took place after the colonies had attained their ordinary 24-hour size.

But even if the appearances had nothing to do with penicillin they lead to its discovery and that is the important thing. DMP would not have subcultured that mould.

I hope you are well and will write that book about Flem, and that it will present a nice picture of him. He was "the greatest." And let's see you soon.

With best wishes.

Merlin

* which w'd delay evaporation and the lysol fumes might possibly accelerate changes leading to lysis and to greater susceptibility to lysis about the mould.

8 Warwick Square,
London S.W 1
Jan 31, 1967

Dear Merlin

I was very glad to get your letter. The version I sent you six months ago - although it was about the twelfth - was still only a trial trip and the main reason for sending it to you was for your recollections of (a) what part you played in the study of staphylococcal variants before you left for your holiday (b) the actual procedure employed by Fleming in his part of the work because his description in the original paper is so vague as to be almost valueless (for example, did he or did he not incubate at 37°C before leaving the plates on the bench, or did he just leave them, or did he know himself what he had actually done?) (c) the procedures that he went through when making the discovery (for example, was the plate one that had already been seen by him, put on the pile standing high and dry on the lysol bowl and then looked at again when you appeared on the scene, or was the story different from this?)

All these details may not appear to be very important but if you read the enclosed new version you will see why.

In regard to your fear that I may denigrate Fleming you must realize that I am not writing his biography. I am trying to put down on paper exactly what led to the discovery of penicillin, what he did with it when he found it and why he did not proceed further with it when Ridley left.

On all these matters, the official biography is not only worthless but misleading. It does not draw attention to the fact that the discovery of penicillin was an almost fantastic stroke of luck, it knows nothing about the fact that the temperature of Fleming's laboratory was a very important factor in the discovery, or the high probability that the mould came from LaTouche in the lab below. Worst of all, it tries to lay the blame for Fleming's inactivity on Wright who is supposed to have opposed him whereas it was almost certainly the instability of penicillin that defeated him.

Moreover, both Fleming and the Biography do less than justice to the work that Craddock and Ridley did. I do not know why but the two of them made really significant advances which should be put on record. In support of this, I have photostats of Craddock's notebook and Ridley has got his own notebook from Lady Fleming just recently. Practically all of this work seems to have been ignored by Fleming and the Biography. Indeed, they did so much that a few more weeks of work might have anticipated events at Oxford 12 years later.

I now come to the translucent colonies that appear in the neighbourhood of the mould and which you think, as indeed, did Fleming are due to acid or lysis by penicillin. I am very doubtful whether either is the real explanation for the following reasons

- (a) Fully grown colonies of staphylococci are not lysed by penicillin in any quantity.
- (b) Fleming's phenomenon can only be seen if growth of the staphylococci is delayed long enough (3-4 days) to enable the mould to grow and produce penicillin.
- (c) This requires a temperature below 20°C.
- (d) Staphylococci grow slowly at this temperature that even either 3-4 days they may be only colourless ghosts.
- (e) When the mould starts to produce penicillin, these ghosts do not develop further because the organisms are killed.
- (f) More distant colonies that looked the same but not under the influence of penicillin, begin to develop into more normal opaque colonies characteristic of the organism.

All this is explained in the enclosed typescript and I have photographs showing these changes.

On the other hand, the lysis you saw on your plates where penicillin was not involved, may well be a true lysis and quite possibly due to acid. But this is a different story even though the appearance of the colonies may look the same.

I hope I have made myself clear
Yours ever

LETTER 4

St. Mary's Hospital Medical School
DEPARTMENT OF PATHOLOGY
ST. MARY'S HOSPITAL
LONDON, W2.
Ambassador 1280

23rd May, 1967

Dear Ronnie,

Your second manuscript, which I mislaid, was found last night, and after reading the letter I couldn't sleep - even with the help of two Soneryl.

I am very worried about the 'down' you seem to have about Fleming. He was a good sort and I owe my present position more to him than to anybody else. He was disappointed that I didn't publish anything when I worked with him in 1927 and pleasantly surprised when I worked with him during the war and published that paper on tuberculosis. With regard to his scientific status, I regard him as one of the truly great, and I think you'll make a hash of things if you go on as you are.

Re the instability of Penicillin and its concentration: Craddock and Ridley failed to concentrate merely because the freeze drying technique had not then been invented. Raistrick also failed for the same reason, and without this technique Chain himself would have failed. It is silly to say that another fortnight's work would have made all the difference. But what I am worried about most is what you say about me. I did not fail to do what was required by Flem. I was asked to see if the Bigger variants differed bactericidally. Obviously they did but it was impossible to do this accurately because comparable suspensions could not be made, and Flem. was not at all worried about this. What he was concerned about and what he wanted to know when he was asked to write the staphylococcal section in the system of bacteriology was whether the Bigger variants were stable. I had left the department by this time and he came over to the blood lab. especially to see me about this. I was a very prim and proper little scientist at this time and I said I didn't think that serial subculturing had been carried on long enough to be certain. In view of Arkwright's work on microbial variation it must have been obvious to him that they would be stable and he almost begged me to say 'yes.' He merely wanted to do me a good turn and write that "according to Pryce these variants are stable" but I would not. It would take very little effort on his part to show that they were stable and he went away sad, not because of the extra work entailed but because I was so obstinate and wouldn't be helped. If in answer to his question I had uttered the single word 'yes' there would probably be no Penicillin and no modern surgery!

You are also wrong about the plate: the colonies were lysed and almost fully grown. I keep on telling you this. It's no good trying to reproduce the phenomenon until this fact is accepted. And please I beg you don't write anything about my holiday having anything to do with the matter. I had no holiday between jobs as the change over was in February.

Yours sincerely,

D. M. Pryce

Professor R. Hare,
3 Warwick Square,
S.W. 1.

LETTER 5

8 Warwick Square,
London S.W 1
June 4, 1967.

My dear Merlin,

I am sorry I could not go to Elizabeth's private view but Carshalton takes so much out of me that once I am back in Town, I have more or less had it. But I went to see it today and thought it a great success. I particularly liked the water colours.

And now for your letter. I wish you would not persist in thinking I have a down on Fleming. I am merely trying to find out how he discovered penicillin. I don't think he himself knew because Holt tells me that he never succeeded in bringing the phenomenon off again. It can be imitated of course but that is not the same thing.

This is probably because he, like you, persisted in thinking that penicillin can attack fully grown colonies. But you know as well as I do that unless you start with such a colony and actually see it disappear, you cannot, in all truthfulness, say that has been lysed. I don't think either of you ever saw this. What you saw were what you thought were the end results of lysis. My thesis is that you saw colonies that had started to grow and then stopped. I can demonstrate this but I cannot demonstrate the former. Perhaps you can.

Now for your part in the discovery. You complain that I said you had failed Fleming by leaving him. If you will refer to the enclosed photostat of two pages from Mourois' Biography, you will see that this is more or less implied in the statements "Fleming therefore had to work again over the ground already covered by Price" and again, "he reproached Pryce for obliging him to re-do a long job of work". As Mourois must have obtained the information for this bit from you, I naturally thought that you had been studying the variant colonies in the same way as Fleming did and then suddenly stopped and went to Newcomb's department. As Mourois seems to have misrepresented you, I will of course omit all reference to this.

And then the holiday. I am grateful to you for telling me that you went to Newcomb's department in the February and not, as I thought in the July. All reference to the holiday will also have to be omitted. It spoils the story but I am not telling stories. I am trying to get at the truth.

I now want to ask a very important question. If you will look at the paper by Biggar which began it all and which is, I think, Biggar, Boland and O'Meara in the Journal of Bacteriology and Pathology 1927,30,261, you will see that they obtained many of their variant colonies by not incubating the plates but leaving them on the bench. As I suppose you must have been looking for such variants to do your bactericidal tests, is it possible that you did the same thing? After all, when one repeats another man's work one usually uses the same methods. Fleming may also have been doing this, but I have no means of finding out.

I know that all this happened a long time ago but if by chance you can remember whether *or not* this is what you (and possibly Fleming) did with your plates, it throws a flood of light on the discovery. It would take too long to give the reasons for this but I would like to know.

I hope this letter will not cause you too much emotion but you are the one person who can clear up these points.

Yours ever

LETTER 6

St. Mary's Hospital Medical School
DEPARTMENT OF PATHOLOGY
ST MARY'S HOSPITAL
LONDON, W.2.
Ambassador 1280

6th June, 1967

Dear Ronnie,

Once more unto the breach dear friends...!

Nobody believes that Penicillin lyses staphylococci and I do not for one moment believe that the lysis about the mould was due to Penicillin, but lysis of those colonies there most certainly was. Flem and I looked at the plate and I thought to myself that the lysis was due to a change of phi, but what I actually said was "that's how you discovered lysozyme." I was merely pandering to the old boy and I did not think that there was any great discovery at hand. But I'll tell you how a holiday was concerned in the work of the Dublin group. These people made their observations as the result of O'Meara taking a holiday and leaving his broth culture of staphylococcus to cook. The resulting mutations were so extraordinary that O'Meara was accused (I think by Boland) of mucking up his cultures by contaminating them. O'Meara was quite hurt and expostulated that it was impossible. He repeated the procedure and showed how the mutations were produced. When Flem asked me to repeat this work I did exactly what the Dublin people described in their paper - leave the culture to go stale. Flem did exactly the same thing. With regard to the statements quoted from Maurois, the repetition of the work by Flem was merely because I did not utter that word "yes" when asked if the mutations were stable. I would not say that they were because I thought subculturing of the strains would need to be carried further before one could be really sure. I doubt whether Fleming subcultured any further than I did but it should be easy to see whether he did by reading his contribution to the System of Bacteriology. I have just looked at Bigger's paper again and he says most of the strains were stable. Flem wanted me to say yes so that he could put my name in the article he wrote.

I hope this is of some use to you. With regard to the challenge - could I repeat the phenomenon? I am quite sure Ronnie that I could.

Yours sincerely

D. M. Pryce

Professor R. Hare,
13 Warwick Square,
S.W.1.

LETTER 7

8 Warwick Square,
London S.W 1
June 7, 1967.

My dear Merlin,

Thank you for your prompt reply to my letter. I think we had better stop haggling about lysis or otherwise of staphylococcal colonies. It seems to be getting us nowhere.

I am afraid that you have missed the point of my question about the way you and Fleming treated your cultures. I know and everyone else does that the discovery of penicillin depended on a phenomenon seen when a plate had been allowed to go stale as you express it; in other words, left on the bench for a long time. There has never been any doubt about this.

But perusal of the paper by Biggar et al shows that they did not incubate their plates. They merely put them on the bench and left them there. How in the early stage at least, of your and Fleming's work you were trying to confirm the findings of Biggar et al and most people in such a situation do the same thing as the other fellow. What I want to know is whether

(a) you/and/or Fleming incubated your culture plates at 37°C for 24 or 48 hours or so before leaving them on the bench

or

(b) left them on the bench without preliminary incubation as had Biggar et al.

In other words, all I want to know is the history of the first 24 or 48 hours of your plates. No more than that. Can you remember what you did so long ago or have you notebooks that might remind you?

Sorry to be such a nuisance but a lot hangs on it.

Yours ever

St. Mary's Hospital Medical School
DEPARTMENT OF PATHOLOGY
ST MARY'S HOSPITAL
LONDON, W.2.
Ambassador 1280

Professor R. Hare,
13 Warwick Square,
S.W. 1.

9th June, 1967

Dear Ronnie,

Sorry you are so annoyed. Of course we read Bigger's paper and repeated the work exactly as instructed. The Bigger mutations we used were produced by allowing broth cultures to go stale. The Dublin workers showed that mutations occurred whether the broth cultures were kept at incubator temperature or at lower temperatures but we worked at 37°C.

Bigger also investigated the mutation rate in what I think were confluent growths on agar but this was not repeated by us. I was personally interested in the aging of individual colonies and I think I was the first to see mutant daughter colonies* and the first to see Liesegang precipitation halos when the serum agar sometimes used contained antibody. This work, however, had nothing to do with either Flem or Bigger.

In answer to your specific questions:

- a) Our plate cultures were incubated at 37° C for 24 hours before putting them on the bench. This applied to explants from stale broth cultures and to cultures from colonies on agar.
- b) We did not leave any culture plates on the bench before incubating them at 37°C.

The famous penicillin plate was not what one might call a "Bigger plate" but an ordinary plate culture of the original staphylococcus.

Yours sincerely,

D. M. Pryce

Hrl single colony plate cultures kept on the bench.

SWANSEA 54901

BECK LABORATORY,
SWANSEA HOSPITAL

[T. COL H. C. M. WALTON
ii' March' 1971'

SWANSEA 68443

GALLEONS,
HIGHER LANE,
MUMBLES,
SWANSEA

My dear Professor

Discovery of Penicillin

Most of the doctors in South Wales know, because I frequently tell them, that you were the man who noticed the mould growing on the plate in that old laboratory overlooking Praed St.

Before both of us get too old to remember the details of the great moments in history, please can you tell me the words in which you told Fleming that the staphylococci were being inhibited by the penicillium?

My little contribution to the history is sitting with 'Beaky' Rogers in the old club about 1930. He was a member of the Rifle Club, and had developed a pneumococcal conjunctivitis for which Fleming had given him some of the impure fluid in which penicillium had grown. After a day or two of use, Rogers' eye was back to normal.

I hope you & Mrs Pryce keep well. I do not get to St. Mary's often nowadays, but hope to attend the annual meeting of the College of Pathologists next November. I hope I may see you there.

Best wishes,

Yours sincerely

Courteney Walton

Prof. D. M. Pryce,
11 Bromfield Rd.
LONDON W.9.

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Authors

Emyr Wyn Jones MD FRCP Hon LLD was Physician in Charge of the Heart Department of Liverpool Royal Infirmary for many years. He was President of the History of Medicine Society for Wales 1980-1986 and a prominent member of many cultural and medical organisations and societies in Wales. Author of a number of books and articles on aspects of medical history. Dr Wyn Jones died at the age of 91 on January 14th 1999.

R. Gareth Wyn Jones DPhil DSc FiBiol holds a chair in biological science at the University of Wales Bangor.

Acknowledgements

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