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http://pharmaceutical-microbiology.imedpub.com/no-new-thing-under-the-sun--on-claims-to-the-discovery-of-penicillin-prior-to-1928.pdf

PUBLISHER

iMedPub

VERSION

VoR (Version of Record)

PUBLISHER STATEMENT

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LICENCE

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REPOSITORY RECORD

Shama, Gilbert. 2017. “No New Thing Under the Sun (?): On Claims to the Discovery of Penicillin Prior to 1928”. figshare. https://hdl.handle.net/2134/24706.

Short Communication

iMedPub Journals
http://www.imedpub.com

Journal of Pharmaceutical Microbiology

2017
Vol. 3 No. 1: 5

No New Thing under the Sun (?): On Claims to the Discovery of Penicillin prior to 1928

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Citation: Shama G. No New Thing under the Sun (?): On Claims to the Discovery of Penicillin prior to 1928. J Pharm Microbiol. 2017, 3:1.

Abstract

Since penicillin came to be developed as an anti-bacterial chemotherapeutic agent during the Second World War numerous challenges to the status of Alexander Fleming as its discoverer have appeared both in print and in other formats. These assertions are examined here from the perspective of current views on *Penicillium* systematics and the wide array of secondary metabolites produced by this particular genus. The tendency to seek to credit a single individual for having made a particular discovery distorts the way by which discoveries are generally made. Alexander Fleming's crucial contribution is here set in context against both earlier observations of microbial antagonism and the long-standing and culturally widespread practice of employing a variety of mouldy substrates to treat infections.

Keywords: Penicillin; Alexander Fleming; Discoveries in Science

Received: March 10, 2017; **Accepted:** March 21, 2017; **Published:** March 25, 2017

Introduction

Ask a class of schoolchildren "Who discovered penicillin?" and the spontaneous response will invariably be "Alexander Fleming!" (I should add that this is not a contrived dramatic entrée to what follows; I have actually posed this question on a number of occasions to schoolchildren and it has never failed to elicit this response). However, there are those who claim that what children have been taught – and indeed are still being taught – about penicillin is incorrect, and that it was in fact discovered long before Fleming noticed the lytic action of a contaminating mould belonging to the genus *Penicillium* on staphylococci sometime in the late summer of 1928.

These avant la lettre claims are not centred on one individual; there are in fact a clutch of scientists that have been credited as being the "true" discoverers of penicillin by their various advocates. The earliest challenge to Fleming's status as discoverer that I have come across appeared in an article published in 1944 [1] at the height of media interest in the mass production of penicillin. The author, Jules Brunel a botanist, appears at first to propose André Gratia and Sara Dath as the true discoverers for work they conducted in 1925, and which he claimed bore a "striking parallelism" to the work of Fleming, but later in his paper appears to credit Adriano Sturli for observations that he published in 1908. Numerous other supposed precursors to Fleming also receive mention in what comes across as a polemic, punctuated with a number of exclamation marks, and published to set the record straight. Appearing shortly after Brunel's claim is that of Maddren [2] who credits the polymath John Tyndall with having made an "early observation of penicillin" in 1875. Starting in 1949 a number of claims have accrued around the French military doctor Ernest Duchesne who published his doctoral thesis in 1897 [3]. Some of these claims appear to be tainted by chauvinistic motives but this is nowhere more obviously the case than in assertions emanating from the former Soviet Union during the Cold War. In an essay on Russian scientific claims published in 1950 [4], Boltz stated that "aggressive nationalism and scientific truths make strange bedfellows" and he then went on to refute claims that Russian scientists had discovered penicillin eighty years prior to the publication of his essay, and also that they had invented the radio and the aeroplane. In 1953 The Guardian newspaper reported that the Russian Academy of Medical Science had decided to publish the works of Alexei Gerasimovitch Polotebnov in order to prove that he had discovered penicillin in 1872 [5]. More recently, Dumont [6] champions the case of the New York surgeon Frederick S. Dennis based on an article that Dennis had published in 1885. Whilst in his widely acclaimed book, Bad Medicine, David Wootton seeks to credit both Joseph Lister – for observations made in late 1871/early 1872 - and Ernest Duchesne who he claims, independently discovered penicillin and took it "somewhat further than Fleming did" [7]. In an earlier paper, Zuck [8] had argued that Lister had been motivated in his investigations by the work of Burdon Sanderson conducted in 1871.

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In what follows I want to evaluate such claims based on the current status of *Penicillium* systematics along with findings relating to the metabolites produced by species belonging to this genus – essentially the same approach which I used to refute the claims made specifically relating to Ernest Duchesne [9].

What Alexander Fleming observed on that now famous petri dish in 1928 constitutes an example of microbial antagonism. He was certainly not the first to observe this phenomenon. In fact, even attributing the discovery of microbial antagonism to a single individual is not possible. I contend that it comes under the category of a "simultaneous discovery" a term which the philosopher of science, Thomas Kuhn, most famously applied to the emergence of the principle of the conservation of energy [10]. Simultaneous discovery may be defined as a number of scientists working independently of one another and announcing identical, or similar, discoveries within a few years of each other. Since Kuhn's pioneering work there have been a number of other examples of simultaneous discoveries put forward including the periodic table [11]. Kuhn himself baulked at the prospect of identifying all those involved in formulating the principle of energy conservation, and similarly it is not my intention here to list all those pioneers of microbial antagonism, as attempting to do so would exceed my limited knowledge of foreign languages. Notwithstanding, the phenomenon began to be investigated in the 1870s. A subset of those involved includes Thomas Huxley (1870) Robert Burdon Sanderson (1871), William Roberts (1874) and John Tyndall (1875). What factor(s) might have motivated them? Whilst it is no simple matter to attempt to recreate the zeitgeist under which these men conducted their investigations, it is surely significant that they all postdate the publication in 1859 of On the Origin of Species by Means of Natural Selection by Charles Darwin. What was under investigation was nothing less than the "the struggle for life," but applied to micro-organisms rather than to members of the Animal Kingdom. One can even discern oblique references to Darwin in work published in 1877 by Pasteur and Joubert on bacterial antagonism of the anthrax bacillus: "among inferior organisms [i.e. micro-organisms] more so than in the higher animals and plants life prevents life [la vie empêche la vie]" [12]. The first French edition of Darwin's momentous work appeared in 1862 [9] and Darwin's phrase "struggle for life" came to be translated as "concurrence vitale," and the term soon gained wide circulation. It appears in the title of Ernest Duchesne's thesis mentioned above.

In the 1870s fungal systematics was at a very rudimentary phase. Arthur Henrici, a mycologist, writing in 1930 complained of the tendency in the earlier literature, and even at the time of writing, to assign all "green forms" to the species *Penicillium glaucum*, and that this designation had been used so indiscriminately that it had become worthless [13]. Later, Raper & Thom [14] pointed out that these assignments were being made in the absence of an adequate description of the species. According to the most recent taxonomic assessments there are 354 species within the genus *Penicillium* only 8 of which produce penicillin [15]

Turning now to the nature of metabolites produced by members of this genus; penicillin itself is of course a secondary metabolite. These are compounds which confer advantages to the organism producing them but which are not indispensable to them as are primary metabolites. A recent estimate puts the number of secondary metabolites elaborated by the genus *Penicillium* as 1338 [16]. A good proportion of these display antibacterial properties, but included amongst them are compounds that are toxic and referred to as "mycotoxins" and could simply not serve as antibiotics.

The fact that Fleming was not the first to observe microbial antagonism does not in any way constitute evidence that any of the studies referred to above, even if they were conducted with species of *Penicillium*, involved that specific chemical entity which we refer to as "penicillin." Indeed, the statistics presented above concerning the number of species of *Penicillium* now known to exist along with the vast number of secondary metabolites they elaborate would render the possibility that a particular environmental isolate belonging to the genus *Penicillium*, and routinely classified as *Penicillium glaucum*, actually produced penicillin as vanishingly small. In the interests of balance it should be added that not all historical reviews of early observations of microbial antagonism involving penicillia contain claims regarding penicillin which cannot be substantiated. With reference to the Austrian surgeon Theodor Billroth, Majno and Joris [17] show that between 1868 and 1873 he worked with cultures of bacteria and moulds and conclude that he "may have been the first to observe an inhibitory effect of *Penicillium* on bacteria" they then go on to qualify this statement by adding "we cannot be sure that the strain of *Penicillium* that he observed truly produced penicillin" - an infinitely more sober and realistic assessment than any of those cited above.

In his book Fabulous Science [18], the author, John Waller, defines his objective as seeking to separate fact from fiction in accepted accounts of scientific discoveries. In a chapter on penicillin entitled "Fleming's Dirty Dishes," Waller has recourse to that celebrated quotation of Shakespeare's concerning the ways by which a person attains greatness; viz. "some are born great, some achieve greatness, and some have greatness thrust upon them," but finds it necessary to create another category to cover the case of Alexander Fleming, i.e. those who, "having let greatness slip through their fingers, snatch it back from those who have a better claim" (!). Difficulties arise when attempting to credit a single individual with a discovery as this distorts the way in which discoveries actually take place. Discoveries tend to be processes rather than isolated single events. Perhaps the first realistic assessment to appear in print of the stages by which penicillin came to be bestowed upon humanity is provided in a letter written by Professor Robert Robinson of Oxford University to The Times of London in September, 1942 [19]. An item on penicillin had appeared a few days earlier, and Robinson, whilst acknowledging that Fleming had indeed discovered penicillin, pointed out that it was Howard Florey and his co-workers who had "separated therapeutic penicillin" and demonstrated its clinical value.

To return to Alexander Fleming; he witnessed an example of microbial antagonism - in Kuhn's term the "that" [20]. He formed an idea that the mould was producing "a simple substance" [21] that was diffusing through the agar and causing the lysis of

growing colonies of *Staphylococcus aureus* the "what" as Kuhn referred to it. He took steps to preserve his culture, and asked a mycologist to identify it for him. Fleming tried, but failed, to extract the penicillin from the mould broth. Moreover, he made the mould freely available to those that asked him for it. In a letter written during the war he stated that he had sent out "a very large number of cultures" [22]. When Florey and his group decided to begin their investigation of microbial antagonism a decade later with penicillin at the Sir William Dunn School of Pathology in Oxford, they were able to acquire a culture from a colleague, Margaret Campbell-Renton, at the Dunn School who had been culturing the strain for her own work on bacteriophages. The strain had been sent to Oxford by Fleming himself. It was Fleming's strain which Florey and his co-worker Norman Heatley took to the USDA laboratories in Peoria, Illinois and from which the first batches of penicillin for therapeutic use were made. No cultures of the penicillia used by the earliest investigators of microbial antagonism have come down to us, and it is therefore not possible to establish whether any of them actually produced penicillin. My argument is founded on the low probability that penicillin was involved, but by the same token, it cannot be proven with absolute certainty.

It is pertinent to enquire when the process of discovery might have been initiated. However, it turns out not to be possible to assign a specific date. Until very recently the earliest evidence for the use of moulds for therapeutic purposes was thought to be contained in the so-called "Ebers Papyrus" which dates back to circa 1500 BC and wherein mention is made of the application of "rotted cereals" for the treatment of diseases of the skin [23]. However, newly published work [24] on the analysis of the dental calculus of a 48, 000 year old specimen of *Homo neanderthalensis* from Spain has revealed the presence of the DNA of *Penicillium* in this individual who suffered from a severe dental abscess inviting speculation that substrates on which mould was growing might have been deliberately consumed for their medicinal properties. Whether the origin of using moulds therapeutically dates back to our hominin relatives or to pharaonic times cannot be determined with certitude. However, one thing is certain, and that is that the practice was passed down through time: there are numerous references in the literature to folk medicines comprising mouldy starch-containing substrates – typically bread – being applied to cure skin infections. The fact that such practices became both culturally widespread and persisted over time would suggest that they were efficacious to some extent, or in certain circumstances. An interesting series of letters appeared in The Sunday Times newspaper under the heading of "Gypsies''Penicillin'" in 1958 in which various folk remedies were described [25]. These included the application of the following mouldy substrates; wheat straw, cheese and leather to the infected part. It is relevant to draw attention here to the findings of Wainwright [26] who documents an example from as late as 1929 (the year in which Fleming's paper on penicillin appeared) in which a young girl suffering from the skin infection, impetigo, was successfully cured of her condition by the application - on the recommendation of a physician - of a starch paste that had been allowed to become mouldy to the affected region. Alexander Fleming may or may not have had knowledge of such practices. Notwithstanding, it seems highly probable that Fleming had an awareness of the phenomenon of microbial antagonism: Leonard Colebrook, a close associate of his at St Mary's Hospital, had published an article on bacterial antagonism involving *Meningococcus* in 1915 [27].

Whilst I disagree with Waller's comments (quoted above) as to how Alexander Fleming achieved greatness, I would like to take this opportunity to "re-mould" some of the terms he uses rather as a potter might re-model a clay pot that showed no signs of its ultimately being able to hold water… What Fleming did when he noticed that most common of occurrences - a contaminated petri dish - was not to let it "slip through his fingers"; rather the knowledge he had accrued over the years both in his work and by "playing with microbes" led him to "snatch it back" from the tray of Lysol in which it had been standing, as a result of which he earned that portion of greatness which was rightly his due for the part he played in the process by which that highly effective chemotherapeutic agent – penicillin - came to be bequeathed to humanity.

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