The potential impact of synthetic animal protein on livestock production: the new “war against agriculture”?

Abstract

The rise of organic chemistry in the 1800s quickly lead to the realisation that products previously derived from plants and animals could be derived synthetically from alternative organic sources. Although it slowly became clear that there were limitations to this technology, the goal of producing animal protein synthetically has remained a tantalising prospect for scientists, with new hopes being rekindled throughout the years as new knowledge emerged or technologies developed. The demonstration of synthetic meat (also termed *in vitro meat*) in 2013 revived this dream and, with the refinement of protein synthesis technologies, 31 start-ups are now working to become the first company to market synthetic animal protein. The potentially transformative nature of this technology make it essential to understand its potential to disrupt conventional agriculture at an early stage. This paper addresses this issue by examining historical substitutions that have lead to the decline or even decimation of agricultural industries, namely: alizarin (madder), indigotin (indigo) and vanillin (vanilla). Following an outlining of the historical cases themselves, it identifies substitution product complexity, ease of synthesis, compatibility with industrial processes, and contamination of the natural product as four key issues that affect the substitution transition. Analysis of the specific synthetic animal protein case suggests that, while there are many additional issues that could affect any transition, three aspects are key: development of transferrable technologies in the medical sector, potential environmental advantages, and a lack of consumer resistance to its “unnatural” nature. Finally, the paper argues that rather than a complete substitution (e.g. alizarin & indigo) a furcated market (e.g. vanillin) with various classes of protein production is likely to emerge – within which industrial livestock production will struggle to compete against cheap synthetic alternatives.

1. Introduction

Predictions of the demise of conventional agriculture have been part of the scientific and industrial discourse since rapid advances in organic chemistry in the 1800s lead to the realisation that products from plants and animals could be produced synthetically from alternative organic sources. Described by anon (1882) in the Journal of Science as the "war against agriculture", the successful synthesis of dyes, medicines, and perfumes lead to the belief – if not absolute conviction – that one day the more complex foods and fibres would also be chemically synthesised. In 1894 Professor Berthelot, then touted as "one of the greatest living men in science" predicted a future for food that would "pass the limits of human belief" with animal agriculture ceasing as people dined instead on meat "manufactured direct from their elements" and milk that will "approach natural milk, in meeting the demands and desires of the public" (Dam, 1894, 303, 310). Dam suggests:

> "the clear evidence of the present leads quite logically to the conclusion that at some more or less distant period in the future, synthetic chemistry *will destroy all the great agricultural industries*, and put to new uses the grain fields and cattle ranges of to-day." (p304 – emphasis added)

While others at the time concurred with this prediction (e.g. Atwater, 1892) later, as scientific understanding of biology and organic chemistry evolved, its limitations were realised and a new synthetic process was suggested – the use of microorganisms as miniature factories to manufacture proteins (Forbes, 1926; Churchill, 1932). In the article, "50 years hence" Winston Churchill noted

> "Microbes, which at present convert the nitrogen of the air into the proteins by which animals live, will be fostered and made to work under controlled conditions, just as yeast is now. New strains of microbes will be developed and made to do a great deal of our chemistry for us." (p397)

In the post-WWII "productivist" era (see Lowe et al., 1993) it seemed technological and structural advances in conventional agriculture alone would prove sufficient to meet future consumption needs, but as progress faltered and capabilities in genetic engineering (GE) grew a radically different future vision began to emerge – one where the world moved "from farming to biotechnology" (Goodman et al., 1987). The arrival of GE promised to limitlessly extend the ability of conventional agriculture by altering the genetic code of plants and animals such that environmental constraints would no longer present an obstacle to agricultural production.

However, progress in the biotechnology revolution has been patchy. Although globally GE plant production has been steadily increasing and now covers 190 million hectares (ISAAA, 2017), environmental and health concerns combined with a fear of “Frankenfoods” have meant that, while many countries accept and produce GE varieties of food, the public remains sceptical about their safety and desirability. Within the European Union market access for GE products remains heavily restricted while consumer sentiment against the use of biotechnology in food production is high.

This may be about to change. In 2013 Mark Post from Maastricht University publicly presented the world’s first lab grown burger (Mosa Meat, 2018). Little more than a gimmick at the time and costing a reported €250,000, the burger captured the imagination of both the press (Chiles, 2013) and a number of ethically concerned scientists researching the biosynthesis of protein in the medical sector. Less than 5 years later 19 synthetic protein start-ups have been announced (five in 2018 alone) and have attracted substantial amounts of seed funding. These companies aim to have biosynthesised animal protein in commercial production by the early 2020s or sooner (see Section 3). With the failure of previous “revolutionary” technological food futures it is necessary to be sceptical of this seemingly miraculous technology. Nevertheless, its potentially transformative implications have already lead many to conclude that we need to prepare for the arrival of biosynthesised animal protein – whether by developing an appropriate regulatory framework (National Academies of Science, 2017), understanding the environmental footprint of the technology (Mattick et al., 2015), or assessing the economic impact on affected agricultural sectors (Beef & Lamb NZ, 2018).

However, with commercial products yet to arrive on the market we have very little information on which to base an analysis of any transition. In these situations, researchers have often turned to historical analyses. For example, Goodman et al. (1987) explored the possible transition to a bioeconomy by basing their analysis both on technological developments in GE and assessments of historical transitions to explore substitutionism and appropriationism in the agricultural industry. Similarly, Geels (2009) employed his widely used multi-level perspective (MLP) to investigate the socio-technical transition from mixed farming to intensive pig husbandry between 1930 and 1980.

This study adopts a similar approach. To understand the issues involved in a biosynthetic protein transition three substitution transitions where chemical synthesis successfully substituted for a natural farmed product are explored. These are: alizarin and the madder industry, indigotin and the indigo industry, and vanillin and the vanilla industry. By combining these case studies with analysis of current synthetic protein technology the paper explores how a synthetic protein transition could develop, factors that are important in its development and how they are likely to influence the transition. The paper is divided into six sections. Following the introduction in section one, section two briefly outlines an existing framework for exploring agricultural biotechnical transition. Section three details the progress of and challenges facing the cellular agriculture start-ups and establishes the current early-stage conditions of the synthetic animal protein industry. Section four presents an historical analysis of the three case studies of agricultural substitution. Section five discusses future transition, first looking at lessons that can be drawn from the case studies, then presenting the case for a synthetic protein transition based on a combination of case study lessons and analysis of drivers of the protein transition. Finally, section six concludes by discussing the possible future of livestock production under a transition scenario.

2 Goodman, Buttel and biotechnological transition in agriculture.

Currently the most commonly used framework for examining transitions within agriculture or food systems is the MLP on regime change developed by Geels (2004; 2009; 2011; Geels et al. 2016). This approach has been highly influential in understanding how settled regimes of practice are disrupted and re-configured (e.g. his aforementioned analysis of the transition to industrial pork production). This article, however, employs an earlier framework developed by Goodman et al. (1987) which accounts for both the kinds of transition that Geels observed inside specific systems and sub-systems, as well as the total substitution of one system by another.

Writing from within the political economy approach of neo-Marxist inflected theories of agricultural change, Goodman et al. (1987) broke with the prevailing orthodoxy by rejecting the idea that major shifts in agricultural systems could be entirely explained by causal arguments derived from structural features of capitalism. Instead, they sought to understand specific historical cases of change in agriculture by balancing major structural economic causes with other causalities stemming from the materialities and biophysical properties of food and fibre products, as well as dramatic new technological innovations arising from new biotechnologies. In doing so, they identified two broad categories of transition. The first – *appropriationism* – involved changing dynamics, relationships and technologies that took specific elements of agricultural production and farming systems and replaced them with industrial systems, inputs or practices. While these could be quite significant changes, they nevertheless retained the overall framework of farming systems. The idea of appropriationism closely prefigured the later insights of Geels about changing agricultural regimes. The key difference was the parallel notion of *substitutionism*, where they posited the potential for new industrial and scientific applications to create entirely new platforms of industrial production which would simply eradicate the need for existing farming systems in particular product sectors. Their case studies of substitutionism painted dramatic pictures of massive, disruptive change through the establishment of entire new bioeconomies which threatened the existence of whole sectors of agricultural production.

However, their contention that biotechnology would revolutionise agriculture received strong criticism at the time. In particular, Buttel (1989), while observing that many social scientists at the time believed new technologies were going to "greatly change the social organization of all societies around the world over the next two or so decades" (p247) believed that while information technologies may meet the criteria of a revolutionary change in a neo-Schumpeterian sense, the "imagery of biotechnology as a first-order, epoch-making causal force in social change may be misleading" (p250). Buttel concurred with Goodman and colleagues' argument that the main application of biotechnology would be to cheapen or improve existing products – but contended the impact would be evolutionary rather than revolutionary. Substitution of biotechnology in agriculture, he argued, occurs mainly in the substitution of new processes and materials for conventional methods, while appropriationist applications simply reflected continuity with the past. To be truly revolutionary, he believed, a technology should meet three criteria: it should have wide public acceptance, it should be applicable over a wide sphere of production and thus "create large new categories of consumer and producer goods" (p251), and it should apply to ascendant economic sectors, or sectors that were likely to be so in the future.

While Goodman et al's (1987) book was highly influential in the discussion of the potential (both in appropriation and substitution) of new genetic technologies and practices in agriculture, scholarly attention to their framework waned as discussion moved elsewhere. Now, in the context of protein substitutes, their framework takes on renewed significance. The following cases follow the organising logic of Goodman and colleagues' original analysis – seeking to understand major shifts in economy and practice in collaboration with dramatic changes in scientific practice, novel technologies, and cultural responses to new protein sources while retaining a sense of the potential scope of the capacity of new proteins to perform dramatic acts of substitution in farming worlds.

3 The beginnings of a synthetic animal protein revolution?

Goodman et al’s (1987) prediction for the development of a bioeconomy, as with the predictions before it, proved a product of its time. While gene manipulation technology has continued to evolve, public concerns for the health and environmental risks associated with the technologies means that their revolutionary GE-based vision did not initially deliver major substitutions in agricultural systems, but rather provided a set of very specific appropriations – such as creating close relationships between particular cropping systems and specific herbicides, or introducing discrete genetic techniques to accelerate innovation in crop and stock breeding. However, hopes for a biotechnology revolution have moved from GE towards conducting agriculture at the cellular level, in particular through two “early stage” technologies involving yeast derived molecules and animal cell cultures (National Academies of Sciences, 2017). As a basis for later discussions, this section outlines the development of these technologies, and presents an analysis of the start-up synthetic animal protein companies as of late-2018.

3.1 The origins of protein/meat substitutes

Knowledge of the different components of food and their influence on human physiology advanced considerably during the 1800s. Observations of the presence or absence of animal protein in the diet lead researchers to conclude that, for those engaged in hard physical work, the inclusion of meat resulted in the workforce suffering less exhaustion and illness (Yeo, 1890). At the same time, however, there was both concern that too much animal protein was not healthy (particularly for the “sedentary man”) and that poorer classes of people such as agricultural labourers needed to make better use of other forms of vegetable protein such as peas and beans (Thompson, 1885). The last decade of the 1800s saw the emergence of the first commercial meat substitute for Western diets (having been observed centuries before in Asia) in the form of the nut-based “Nuttose” in 1896 (Shurtleff & Aoyagi, 2014). Two decades later meat shortages associated with WWI lead governments to promote what were termed “meat substitutes” in the form of cheese, milk, fish, poultry, eggs and legumes (Hunt & Attwater, 1917; Johnson, 1918). Enthusiasm for these products continued after the war and prompted the search for ever more inventive means of substituting meat. Wesson (1930), for example, advocated the use of ground residue from cotton oil manufacture mixed with vegetable shortening and water to produce what he termed "Wessona" – a high protein product that simulated meat for use in products such as sausages and meatloaf.

Early attempts to synthesise edible food protein from non-edible materials via a yeast medium emerged as a result of the shortage of protein during WWII. At this time considerable effort was placed on research into the use of sugar from a variety of sources including sugarcane production (Pyke, 1970), "wood sugars" (Peterson et al., 1945) and citrus waste (Nolte et al., 1943) to grow yeasts with a high protein content predominantly for use as animal fodder. However, despite the frequent use of waste materials the cost of the final product was substantially higher than that of other vegetable proteins – such as soy – making it commercially marginal at best (Peterson et al., 1945). In the 1960s the discovery of abundant oil resources combined with its relatively low price lead oil producers Esso and BP to experiment with the possibility of using oil to produce fodder proteins, but again the price of petroleum-based protein was substantially higher than that of vegetable proteins (Pyke, 1970).

In recent decades a growing trend towards lower meat consumption in European and American diets (Wild et al., 2014; MacInnis & Hodson, 2017) has emerged as a result of concern for human health, animal welfare, and the environment (Vinnnari & Tapio, 2009). At the same time technologies for the production of meat-like products have improved. In particular, the development of high moisture cooking technologies in the early 1990s enabled plant proteins to develop distinctive meat-like fibrous structures (Wild et al., 2014) – increasing the textural resemblance to meat. The 2010s saw the release of burgers that "bleed" (the Beyond Burger and Impossible Burger) to mimic the sensation of consuming real meat by increasing the succulence of the product. These improvements alongside changes in dietary preference have contributed to considerable market growth. Plant-based meat substitutes are expected to achieve a compound annual growth rate (CAGR) of 7.7% from 2018 to 2025 (Allied Analytics LLP, 2018). In contrast, while animal protein production still dwarfs substitutes in terms of total market value, the OECD/FAO predict that global annual per capita meat consumption in the coming decade (2018-2027) will increase by 1.15% – down from 1.89% in the previous decade (OECD/FAO, 2018). It is within this enabling environment of combined technological development and a positive market outlook for plant-based protein substitutes that the potential for taking the next step – the move to biosynthesised animal proteins – has emerged. This development is based on two production processes.

3.2 A tale of two processes: the science behind animal protein synthesis

Numerous publications are available detailing the science behind animal protein synthesis (see, for example, Kadim et al., 2015; Sharma et al., 2015; Bhat et al., 2014, 2017). Here the two main processes are briefly summarised.

3.2.1 The culturing of animal tissues

Cultured meat involves growing tissue (not simply muscle tissue, but potentially also fat, blood vessels, bone, and connective tissue) within an enclosed environment using cells obtained from a 'donor' animal and fed nutrients via a growth medium or "serum". Fifteen start-up companies are currently working on developing a variety of animal products including beef, poultry, pork, tuna and salmon using this process. Although generating considerable media hype and promising products within the next few years, these companies appear to be still in the research and development stage as they attempt to overcome three main technical obstacles. Firstly, the main growth serum used (foetal bovine serum – FBS) is both expensive and undesirable. FBS is extracted from the blood of fetal calves when pregnant cows are slaughtered by "puncturing the beating heart of the unanaesthetised foetus using large diameter needles" (Rauch et al., 2011, 305). While commercial alternatives exist, these are also costly meaning that the development of a viable cultured meat product is contingent on developing a cost-effective serum or alternative production process (Chen & Zhang, 2015). Secondly, the process must mimic the muscle cell development of the animal as muscle cells require exercise-simulation for the myotubes to grow, align into myofibers and prevent atrophy. This has lead researchers to experiment on both electrical and mechanical stimulation (Catts & Zurr, 2014; Bhat et al., 2017). Thirdly, production upscaling is a fundamental limitation. Currently the collection and processing of FBS is targeted at the medical market which generally requires only sufficient serum for the production of proteins at an experimental level. In addition, while strips of muscle fibre sufficient for constructing demonstration products can be produced, current bioreactors are not large enough for the mass production of cultured meat (Kadim et al., 2015). Consequently, the production of cultured meat in volumes that would threaten conventional agriculture is not yet possible.

3.2.2 The fermentation of animal proteins

The second process used in the production of synthetic animal proteins is fermentation. Fermentation involves the use of single celled organisms such as yeast and bacteria to convert a raw material (e.g. sugar) into a desired substance (e.g. a protein). The potential of this technology has recently been significantly boosted by developments in metabolic pathway engineering and the advancement of fermentation production that have enabled DNA within cells to be edited to contain optimal metabolic pathways technologies (Chotani et al., 2000). Unlike cell culturing technology which has yet to be fully commercialised, fermentation technology is already employed in the commercial scale biosynthesis of substitute products – for example, in the production of synthetic "natural" vanilla (Gallage & Møller, 2018), biofuels that meet existing petrochemical standards (Shaw et al., 2016) or commercial amino acids such as insulin, glutamate and lysine for industrial use in the medical sector (Becker & Whittman, 2015). However, despite the widespread commercial use of fermentation technologies, production of edible proteins is again limited by the lack of bioreactor capacity. For example, while Solvay's new biorefinery for vanillin can produce 60 tonnes of Rhovanil®Natural per year – a considerable proportion of the natural vanillin market – global ruminant protein production has been estimated globally at 36,355 Mt/year (Mottet et al., 2017). Chen & Zhang (2015) suggest that production could be enhanced by the development of multiple-product bio-refineries where edible protein is only one product of a refinery that can produce, for example, animal feed (low quality protein), bulk enzymes, biofuels, and biochemicals.

3.3 Cellular agriculture start-ups

Startup Year	Company	Location	Product	Process	In production	Funding raised
2011	JUST	San Francisco	Poultry, foie gras, wagyu beef	Cell culture	2019	$310 million (a)
2011	Modern Meadow	New Jersey	Leather (collagen)	Fermentation	2019	$53 million
2013	Mosa Meats	Netherlands	Minced beef	Cell culture	2021	$7.5 million
2014	Clara Foods	San Francisco	Egg whites	Fermentation	Not given	$3.5 million
2014	Perfect Day	Cork	Milk and milk products	Fermentation	2019	$34.7 Million
2015	Memphis Meats	San Francisco	Beef, chicken, duck	Cell culture	2021	$22 million
2015	SuperMeat	Tel Aviv	minced chicken	Cell culture	Not given	$4.2 million (b)
2015	Integriculture	Tokyo	Foie gras	Cell culture	2020	$2.7 million
2015	Geltor	San Francisco	Collagen and gelatine	Fermentation	2020	$23 million
2015	Bond pet foods	Colorado	Pet food	Cell culture	2019	Seeking funding
2016	Vitro Labs	San Francisco	Biofur (3D printed) and leather	Cell culture	Not given	Unknown
2016	Wild Type	San Francisco	Salmon (initially)	Cell culture	Not given	$3.5 million
2016	Appleton Meats	Vancouver	Beef (ground)	Cell culture	Not given	Unknown
2016	Because Animals	Philadelphia	Pet food	Cell culture	Not given	Unknown
2017	Finless foods	San Francisco	Bluefin Tuna	Cell culture	2019	$3.5 million
2017	Aleph Farms	Israel	Beef (3D printed)	Cell culture	2019	$1.8 million (b)
2017	Wild Earth	San Francisco	Pet food (mouse cells for cats)	Cell culture	2019	$5 million
2017	Higher Steaks	London	Pork	Cell culture	2021	$15 000
2017	Future Meat Technologies	Jerusalem	Chicken	Cell culture	2020	$2.2 million (b)
2017	Blue Naulu	San Diego	Fish	Cell culture	2024	$4.5 million
2017	Biofood systems	Haifa (Israel)	Beef	Cell culture	Not given	Unknown
2018	Mission Barns	Delaware	Kosher bacon	Cell culture	Not given	$3.5 million
2018	New Age Meats	San Francisco	Pork (muscle & fat cells)	Cell culture	2023-2028	$250 000
2018	Meatable	Netherlands	Meat (minced)	Cell culture	Not given	$3.5 million
2018	Fork & Goode	Singapore	Pork	Cell culture	Not given	Unknown
2018	Kiran meats	San Francisco	Meat snacks (not yet specified)	Cell culture	Not given	Unknown
2018	Biofood systems	Israel	Beef	Cell culture	Not given	Unknown
2018	Shiok Meats	Singapore	Shrimp	Cell culture	2021	Unknown
2018	Avant Meats	Hong Kong	Fish	Cell culture	2021	Unknown
2018	Cubiq Foods	Barcelona	Fat (for flavour and Omega3)	Cell culture	2021	$13.6 million
2019	Motif Ingredients	Boston	Protein (dairy, egg, meat)	Fermentation	Not given	$90 million

Table 1 lists the 31 artificial animal protein start-ups as of early-2019[1]. Although there are a very limited number of start-ups involved and the funding, in general, is at seed level only, many of the backers are significant players in the food or technology sectors. Among other venture capital investments, Evonik (the largest speciality chemical company in the world) has invested in Modern Meadow, Sergey Bin (cofounder of Google) in Mosa Meat, Gary Hirshberg (CEO of Stonyfield Farm – the USA's second highest producer of organic yoghurt) in Clara foods, Cargill (one of the world's largest meat suppliers) in Memphis Meats, Tyson Foods (one of the USA's biggest chicken marketers) has invested in Memphis Meats, Temasek (a Singaporean sovereign wealth fund that has already funded the "Impossible Burger") has invested in Perfect Day milk, the PHW Group (the 3rd largest poultry producer in Europe) in Supermeat, Hiroaki Kitano (CEO of Sony Computer Science Laboratories) in Japanese company Integriculture, and the Strauss Group (one of Israel's largest food product manufacturers) in Aleph farms.

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[1] Note that Milburn (2018) suggests the The Real Vegan Cheese Project is also trying to develop dairy products via fermentation. However, the project is an "imaginary avatar" for a team of "biohackers" with, as yet, no intention to create a physical presence (Willbanks, 2017).

The general pattern is one of large food, technology and chemical companies (or individuals) investing in start-ups of relevance to their existing interests to provide “a bit of a hedge for them and … an ability to get close to that culture that they lack” (Polansek, 2016; also see Dance, 2017). In addition to private investors, both the Singaporean and Chinese governments have shown interest in artificial protein manufacture – in the case of Singapore through sovereign wealth fund investments and, in the case of China, through an agreement to purchase US$300m of cultured meat from Israeli companies (Roberts, 2017).

Although the majority of start-ups are developing cell cultured proteins, four are researching fermentation technologies to develop non-meat proteins (i.e. collagen, egg whites, milk and gelatine). These companies appear to be currently closer to production – with most predicting products in the market by 2018 or 2019[2]. In part, this is because it uses tested “decades-old fermentation technology” (Dance, 2017) and is boosted by a dramatic reduction in the cost and availability of gene technology (e.g. Perfect Foods were able to purchase the cow genome and splice genes for producing milk proteins into yeast, while Geltor inserted purchased collagen genes into microbes).

One of the key concerns for the start-ups is overcoming the technological issues raised in Section 3.2. Claims of advances have been made. For example, Integriculture recently patented an FBS free environment (Culnet) which reportedly will reduce the cost of the culture medium by up to one 10,000th and allow a 200g burger to be produced for $2 by 2026 (Integriculture, 2018) while Memphis Meats and JUST also assert they have developed a plant-based FBS replacement (Cosgrove, 2017). While it is possible that these and other companies have developed new technologies but are simply keeping the details confidential – noted by Reynolds (2018) and Stephens et al. (2018) as a common practice in synthetic protein start-ups – the problem of scaling up production remains common to all. Some plan to negate this issue by using existing infrastructure, thus potentially having a greater and more immediate impact (e.g. Perfect Day – Watson, 2017).

Despite reported progress, claims to have a commercial product available by 2018 or 2019 seem overly-optimistic for three main reasons. First, the reported levels of investment in the

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[2] Geltor, while aiming for a release date of 2020, has already produced sufficient collagen to send samples to potential customers (Dance, 2017).

companies is insufficient to enable the development of commercial production facilities – although the levels of capital raised are large for start-up companies (Dance, 2017). Second, research has thus far not focused on the manufacturing processes required to produce synthetic protein commercially. In observing this, the directors of startup New Age Meats recently stated that, in fact, synthetic animal protein is 5 to 10 years away while some companies are "announcing ambitious timelines and making promises that are very aggressive" and could "fool people into thinking clean meat is around the corner" (Watson, 2018). A third issue that may delay the introduction of both cultured and fermented proteins is the current breakneck speed of advances in the biotech sector. A recent report by the US National Academies of Sciences (2017, 172) expresses concern that the profusion of biotechnology products will "overwhelm the U.S. regulatory system" in the next 5-10 years.

In general, the analysis of start-ups suggests an industry in its very early stages of development with only 19 companies in existence – three quarters of which have been formed within the last four years. Many of the plethora of optimistic articles on the development of artificial proteins have been written about the same small handful of companies, meaning that the "industry" has gained a far greater media presence than a commercial one. However, the acknowledged difficulties in bringing these technologies to fruition should not be taken to mean that biosynthesised protein will not eventually threaten conventional agriculture, only that we are at the very beginning of that process. What might a transition look like? The next sections examine three historical substitution transitions – alizarin, indigo, and vanilla – to explore how substitution transitions occur and, on the basis of an analysis of these transitions, assess how an alternative protein transition could take shape.

4. Three substitution transitions – an historical analysis

To understand the potential impact of biosynthesised animal protein on contemporary agricultural systems this section investigates three historical transitions in detail – alizarin, indigotin, and vanillin. Alizarin represents a case where the synthetic production of an identical chemical lead to the rapid decimation of a once thriving agricultural sector (madder production). Indigotin represents a similar case, but follows a different pathway due to issues with the development of a commercially viable manufacturing process and the upscaling of production. Finally, vanillin represents an attempt to synthesise a food product (albeit a flavouring) where complex substitution was required – i.e. synthesising a natural taste rather than simply a colour. Vanillin is also one of the first food products to be commercially produced by biosynthesis.

The cases were explored largely using original historical documents. Recently digitised open-source literature is now freely available from a number of sources (e.g. Google Books, the Internet Archive, the Hathi Trust) and coverage can be relatively comprehensive. A recent study by Burton & Riley (2018) found that in the case of agricultural literature from 1700 to 1799, 86% of publications listed in Louden's (1839) "Bibliography of British Agriculture" were freely available online. Sources used here include trade and scientific journals (e.g. American Druggist, Chemical News and Journal of Industrial Science), popular scientific journals (e.g. Popular Science News, Scientific American), and books and information pamphlets written at the time (e.g. Meldola, 1891 – "Coal and what we get from it"). Sources from the early 20th Century are, in most cases copyrighted and therefore not available from the free on-line libraries. In this case, academic literature searches including JSTOR and Scopus were employed to locate relevant documents – again, relying on original sources as far as possible. Later sources were located using standard academic literature searches.

The analysis looks at the process of substitution including: the development of the technology, society and industry's views on the technology during the transition (e.g. acceptability of the product, industry response to discovery), and the impact of substitution on the affected agricultural sector.

4.1 Artificial alizarin and madder – the rapid death of a major industry

The substitution of alizarin was both the first of the major chemical substitutions of the late 1800s and the worst case scenario – used by many authors subsequently to illustrate how bad substitution could be for existing agriculture. Natural alizarin was obtained by processing the root of the madder plant – which, as an expensive and technical process, made it a highly lucrative industry (anon, 1875). At least six colouring dyes were extracted from madder, including alizarin (intense red), purpurin (red), and rubiacin (orange) – with alizarin being the most important of these (Meldola, 1891). What made madder so valuable was not only its ability to produce a colour-fast dye, but also the huge variety of different shades of red that could be obtained depending on the species and environmental conditions in which the root was grown.

With different regions producing different colours and shades, madder production in Europe at the time of the arrival of artificial alizarin was both widespread and produced at everything from a peasant to an industrial scale (Schot, 1992).

Alizarin synthesis resulted from an extended period of exploration in organic chemistry in the first half of the 19th Century. In 1868 German chemists Gräbe and Liebermann discovered that anthracene (coal tar) could be made from alizarin, and, shortly after had managed to reverse the process to produce alizarin from anthracene (Perkin, 1876; Meldola, 1891). When patented on 25th June 1869 by Gräbe, Liebermann and Caro (the original 1868 process could not be used for manufacturing purposes – Schorlemmer, 1894), the manufacture of alizarin was extremely costly, but by the mid-1870s with refinement and upscaling, artificial alizarin was a major competitor to the natural product.

Initially it was received sceptically. In addition to involving a costly manufacturing process making it more expensive than natural alizarin, considerable doubts were raised concerning the quality of the dye. Some early reports claimed that artificial alizarin was not colour fast (e.g. Christie, 1870). Others objected to the product on the basis that pure alizarin would not be able to replicate the colour varieties present in natural madder (Perkin, 1870)[3]. Even after these doubts had been quelled, the hope remained that natural and artificial alizarin production could exist side-by-side as the aniline dyes were seen as constituting “entirely new products, differing in composition and properties from the old colouring-matters” (Perkin, 1876, 323). Consequently, Versmann (1874, 423) contended that artificial alizarin “might not necessarily kill the natural product altogether”, but simply boost dye consumption.

However, soon concern became widespread in the madder industry. In May 1873 Brandt (1873) observed that the Agricultural Society of Vaucluse was “alarmed by the progress in the manufacture of artificial alizarin” and had set out to inform itself of the threat it posed to madder. At that time Brandt reported that successful trials of alizarin had been held but that problems with the red dyes meant that derivatives of madder were still preferable for a number of processes. However, by the mid-1870s – a mere 6 years after the discovery of artificial alizarin – it was widely acknowledged that the writing was on the wall for the madder industry

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[3] Even at that point processes had been developed for the production of oranges and blues from anthracene, albeit initially at an exorbitant cost.

(e.g. anon, 1874, anon, 1875). Analysis at the time did not place blame entirely on the new technology, but also on complacency that had developed after decades of high profits. Versmann (1874, 423) for example, wrote

> "No doubt the madder growers will have to struggle hard in competition, and of this they seem aware already. Only the other day the Agricultural Society at Avignon inquired of the Industrial Society at Mulhausen what they had to fear from artificial alizarine. The answer was, that to successfully compete, they must improve their product."

In particular, as farmers were being paid by weight, too much emphasis in breeding had gone into increasing the proportion of wood in the root rather than the proportion of dye. Over the period where madder had become extremely profitable the industry had failed to develop new methods (preferring to retain traditional approaches), failed to experiment with manures, and depleted the quality of the soils (anon, 1874). To make matters worse, in the early-1870s chemists developed a new chemical *anthrapurpurin* which produced reds brighter than alizarin or ordinary purpurin as well as a purer product that meant dying products was easier. Aniline dyes proved to be not equal to natural products, but better than them (Perkin, 1876).

The impact was decimating to the madder industry. By 1876 the introduction of commercial alizarin had already reduced the price of madder by half such that Perkin (1876, 323) observed the cultivation of madder roots was "unremunerative" and "it is to be expected that madder growing will soon be a thing of the past" and by 1891 the cultivation of madder was "practically extinct" (Meldola, 1891). In the madder producing region around Baku (Russia) an anonymous author wrote "Huge quantities of madder root are decomposing in the soil, and not thought worth the cost of collection" (anon, 1886, 850). However, the consequences on the overall economy were not all negative. Versmann (1874) observed that the demise of madder would free up thousands of acres for food production which, for the farmers, might prove more profitable. The discovery of artificial alizarin also provided a huge financial boost to the German synthetic dye industry and lead to the establishment of three of the chemical/pharmaceutical giants of today – Baeyer, BASF (Badische *Analin* Soda Fabrik), and Agfa (Aktien Gesellschaft Für *Anilin*fabrikation) (Welham, 1963).

4.2 Indigo – a different transition pathway

Inspired and funded by the success of alizarin, chemists proceeded to work on other dyes – one of which was the important red/blue dye, indigo. The indigo plant (Indigofera sp.) is a leguminous species that grows in warm climates. Around the time of its peak, indigo was commercially grown in India, Africa, Java, China, Japan, Central America, and Brazil with India being by far the largest producer (Perkin, 1900). As with madder, the natural dyes extracted from the indigo root varied depending on the environment in which it was grown – with varieties of Bengal indigo, for example, ranging from ‘superfine blue’ to ‘good red’ with shades of violet in between. In total, Hayes (1873) listed 43 varieties (defined by differing shades and qualities) of Bengal indigo that could be distinguished by “skilful connoisseurs”. Indigo was widely used in the dying of fabrics in the 1800s and had proven extremely profitable for both private companies and the government of India (Delta, 1861).

The development of artificial indigo began with the demonstration in 1869 of the creation of indol by Baeyer & Emmerling and was followed, six years later, by the discovery of a process by which indol could be converted to indigo (Schorlemmer, 1894). However, unlike alizarin, there was no rapid transition to commercial production as scientists struggled to find a simpler and cheaper means of synthesis. Thus while the first patents for the manufacture of indigo (rather ‘indigotin’ – a substance almost identical to indigo – Asiaticus, 1912) were filed in 1880 by Baeyer (Meldola, 1891), the price at which indigo could be synthetically produced in the early years could not rival that of the natural product (Meldola, 1891; Asiaticus, 1912).

This failure lead to what was later seen as an astounding level of complacency amongst the natural indigo producers. Asiaticus (1912) reported that the planters of indigo responded by laughing at “the idea that some German crank could produce indigotin to compete with the natural dye” and thus made little attempt to improve the system of cultivation or manufacture. Some were aware of the imminent danger. In an address published in the Trade Magazine “American Druggist” Allen (1888, 24) observed that what happened with the “entire abandonment” of the madder industry “any month could happen to the culture of indigo” and that, despite artificial indigo being more expensive than natural indigo, it had nevertheless already found “limited application” as a result of its convenience (also see Perkin, 1900). Failure to heed the lesson from madder meant the industry was unprepared when German chemists perfected the manufacturing process in 1896[4]. Artificial indigo was released in earnest on the market in 1898, causing the price of the natural product to crash. Not only was it cheaper than natural indigo but it was superior in terms of its purity and consistency – containing 90% indigotin while natural indigo ranged from 20% to 90% (Adams, 1926; Perkin, 1900). This lead to the rapid decline of natural indigo production (Asiaticus, 1912).

However, the natural indigo industry was not finished. Synthetic indigo production was initially dominated by the German chemical giants. Thus, the outbreak of WWI saw much of the world cut off from its main supply of indigotin and lead to a temporary revival of the natural indigo industry. Reviving the industry, however, proved problematic. Indigo was no longer being cultivated, factories and machinery had fallen into disrepair, and the industry lacked qualified supervisors (Perkin, 2015). Nevertheless, whereas in the five years prior to the war an average of 220,000 acres of indigo had been planted, by 1916-17 this figure had risen to 756,450 acres – a major increase but significantly less than the 1895 figure of 1.7 million acres (Reed, 1992). The production of natural indigo continued after the war while restrictions on coal and raw materials were in place but gradually declined once restrictions were lifted and the production of artificial dyes resumed (Atkins, 1921).

4.3 Vanillin – from natural to chemical to biosynthetic production

Natural vanillin is produced by members of the orchid species with *Vanilla planifolia* – a climbing orchid indigenous to Central and South America – being the most important commercial species (Gallage & Møller , 2018). It was initially used for "imparting an agreeable flavour to chocolate" although it was also believed to have medicinal qualities (Willich, 1804). By the mid-19th Century, vanilla was in widespread use by "cooks and confectioners for flavouring" and the market for natural vanilla considerable (Anon, 1849, 709). Producing vanilla was, however, challenging. Natural pollinators were geographically limited to regions where the plant was indigenous and, consequently, it was only with the discovery of a reliable means of hand pollination in 1841 that plantations were able to spread across the tropics and sub-tropics (Gallage & Møller , 2018). While this enabled vanilla to extend outside of its natural

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[4] Roscoe (1891, 128) refers to the potential of the new process developed in 1891 noting "who can tell that a recent new process for its manufacture may not prove fatal to the indigo planter?"

range, it also made production an extremely expensive business and vanilla a much sought after, limited and therefore valuable commodity.

The rarity and price of natural vanilla also made it a target for organic chemists. Vanillin was isolated as the main flavour constituent in 1858 by Theodore Nicolas Gobley and by the mid-1870s Tiemann & Haarmann (1874) had discovered a means of producing artificial vanillin from coniferin – a glucoside easily obtained from the bark of coniferous trees. Having immediately secured patents for production a manufacturing plant was established and by 1876 was producing “large quantities of this curious artificial flavouring” (E.J.H., 1876). Continued work by Tiemann & Haarmann over the next decade resulted in a gradual improvement of their product to the point that some believed it was “fully equal in aroma to the natural vanillin contained in vanilla beans” (Castle, 1888, 229).

Unlike alizarin the initial price difference between natural and artificial vanilla was relatively small (Simmonds, 1877). However, there were some non-monetary advantages to the artificial product. In particular, purified vanilla essence was frequently adulterated with Tonka essence (an inferior natural vanilla) leading the product to be of notoriously unreliable quality (J.H.S., 1876), while adulteration with other foreign substances occasionally resulted in poisonings (F.L.P., 1874). Further, supply issues and periodic scarcity caused major swings in price which lead producers to rush the preparation of the vanilla pods (which require a lengthy curing time) and dump large quantities of substandard product on the market (anon, 1896). Natural vanilla also had an inedible woody fibre that had to be disposed of prior to use (J.H.S., 1876; anon, 1881) and seeds that appeared as unwanted black spots in baking (anon, 1896).

Initial reports hailed the introduction of synthetic vanillin as “another grand, synthetical discovery” (E.J.H., 1876) and lead to a “panic” amongst the growers of vanilla (Simmonds, 1877). However, this concern did not last for long as the public displayed the “usual opposition and prejudice” (H., 1876) to artificial flavours which was reportedly normal for products of synthetic chemistry until the it was “convinced that it is identical with the natural product” (anon, 1881, 147). Thus, instead of declining after the introduction of artificial vanilla, the market for the natural product flourished (e.g. anon, 1882), leading commentators of the time to label artificial vanilla as a failure. For example, Bernays (1883, 196) noted:

> "The discovery was at the time the subject of much writing and talking, and had temporarily a discomforting effect upon vanilla-growers, and interfered with the progress of the industry. *The invention, however, died a natural death, and is heard of no more*." (emphasis added)

A writer in the American Druggist (anon, 1888, 229) observed similarly that:

> "At one time it was supposed that artificial vanillin would ruin the vanilla industry and trade, just as artificial alizarin has practically ruined the madder industry. But, curiously enough, this has not been the case."

This optimistic view, however, was not shared by chemists and industrialists. Schimmel & Co. (1892, 52) observed that people "in a position to view the increasing extension of the manufacture of this preparation" observed the manufacturing processes were developing "slowly but with certainty" and, as a result, they were in little doubt that vanilla production would be increasingly undermined by vanillin. By the mid-1890s reports were emerging that chocolate and confectionary manufacturers had turned to artificial vanillin – threatening both the natural product from Reunion and Mauritius and the European market as a whole (Thorpe, 1893; Dam, 1894). Artificial vanillin now had several producers in Europe, was steadily declining in price (anon, 1896) and had gone from being of "little importance" to being a "proven a commercial success" (Gerard, 1896). However, it was not replacing natural vanilla, but rather creating a new market and broadening vanilla's use and appeal. As noted in the American Druggist (anon, 1888, 229), in the face of the growth of the artificial product

> "Vanilla holds its own extremely well. In fact, there is much more vanilla grown and sold at the present time than before vanillin was known as a commercial product. And yet, the latter is also consumed in constantly increasing quantities."

Artificial vanillin had a major impact not on the production of vanilla but on the predicted growth in production which, following the arrival of the artificial product, had "not reached the limits which were expected" (Simmonds, 1877). For some producers the effects appear to have been worse than others. Attempts to establish vanilla production in the Seychelles reportedly failed as a result of a combination of poor harvests, a poor quality product and competition from "this terrible vanillin" (Stanmore et al., 1907, 170).

Despite being subject to considerable price fluctuation, natural vanillin has retained its value. Currently it ranges between US$1,200 and US$4,000 per kilogram, while artificial vanillin falls between $11 and $15 per kilogram (Gallage & Møller, 2018). These two markets remain essentially separate because the complex flavours in natural vanilla cannot be chemically synthesised (Labuda, 2011). With the global supply of natural vanilla stable at around 2,000,000 kgs and yet demand for natural products increasing, the natural vanilla bean market is currently undersupplied. This has created an opening for biosynthetic vanilla (Converti et al., 2010). At US$1000 per kg biosynthetic vanilla is not able to compete in the cheap chemically produced vanillin market, however:

> "Vanillin, obtained by bioengineered microorganisms by transforming a range of different substrates into vanillin, is entitled to the label 'natural vanillin' according to US and European legislation." (Gallage & Møller, 2018, 13)

Consequently, biosynthesised vanilla – which, like the natural product, contains a complex array of aromatic compounds (Gallage & Møller, 2015) – competes in the lucrative natural vanilla market rather than the artificial vanilla market. A number of biosynthesised vanillins are now available including Evolva, which bought biosynthesised vanillin to the market in mid-2014 (https://www.evolva.com/vanillin/), De Monchy Aromatics who manufacture Vanillin Natural (ex-ferulic acid) from turmeric, and Solvay who produce Rhovanil®Natural – which the company contends is "the only natural vanillin product available on the market in line with both European 1334/2008 and US Food and Drug Administration (FDA) 21CFR101.22 regulations regarding natural labelling".

5. Discussion: the future synthetic protein transition.

5.1 Lessons from the past

The above section explored the development of three substitution technologies with differing outcomes – ranging from complete and rapid substitution in the case of alizarin to coexistence as competing but separate products in the case of vanilla and vanillin. From understanding the history of these substitution processes a number of lessons can be drawn.

First, the probability of substitution of a product appears to depend on its complexity. An anonymous contributor to the Journal of Science (anon, 1882) divided organic products into two classes, namely; Class 1 – dyes, medicines, perfumes and so on with "definite chemical compounds" that could be substituted by a "closely analogous product", and Class 2 – complex compounds of acids, fats, glycerides, sugars, and so on (anon, 1882, 389). While the author contended the first class were viable targets for the organic chemists, for the second he contended "artificial production is scarcely conceivable" giving the example of a joint of meat:

> "Suppose we could artificially produce the albumen, the fibrine, the gelatinous matter, the fats, etc., our task would be only beginning. If we present the fibrine in dense masses, instead of in the fibrous state from which it derives its name, and in which it always appears in the flesh of animals, we should have a very indigestible matter to deal with. And how to make it assume this fibrous structure without the aid of the processes present in the living animal is a question of a totally different order, from its mere synthesis as a chemical compound." (anon, 1882, 389 – emphasis added).

In the most simple cases examined here, those of the dye products, the development of the substitutes ultimately lead to the complete replacement of the natural product and the extinction of the industries producing it. Where a dye is concerned, the substitution involves only two qualities that affect the consumer – colour and permanency – and, as Rosenstiehl & Naquet (1875) observed of alizarin, it was often impossible to tell the difference between the artificial and natural products. Where products are complex as is the case for vanilla (or any other complex food products such as butter/margarine) the failure of the substitute to match the complexity of the natural product divides the market into at least two product categories. In the vanilla case the natural product continued to be grown as a result of the premium price it attracted, although it was thought at the time that the growth of the market was seriously compromised by the arrival of the artificial product. With biosynthesised vanilla substitutes now able to produce a complex array of aromatic compounds it remains to see whether this will simply add another product category and trifurcate the vanilla market or result in the demise of agriculturally produced vanilla.

Second, the timeframes of transition vary depending on the difficulties of developing a cost effective synthesis process and, consequently, failure to develop a commercial product in the short term should not be seen as an overall failure. In the case of historical substitutions there is a pattern of initial concern – if not panic (often based on the alizarin comparison) – when the discovery is first announced, but once the process of refining and scaling begins the response is often to dismiss the product as incapable of substitution and a period of complacency sets in. In the meantime, technological development continues until the product is refined and becomes economically competitive – at which point a rapid substitution can occur. Here the main lesson for the contemporary livestock sector is that regardless of the success of the current start-up companies preparations should be made for the arrival of synthetic protein products on the market. Perkin (1900) suggested indigo farmers should have responded to the growing threat of artificial indigo by increasing the yield and quality of the indigo plant and endeavouring to improve the process of manufacture, while madder farmers should have worked on increasing the amount of dye in the product rather than its weight (Versmann, 1874). Failure to do so made substitution even more probable.

Third, the success of the product is not only dependent on the qualities as they relate to consumption (colour, taste, texture, etc.) but also on how compatible it is with the industrial manufacturing process. Perkin (1915) notes, for example, that the colouring of the natural product was preferred by dyers because, it was claimed, other organic substances in the dye made it last longer in the vat, allowed the dyes to penetrate the fabric better and made it more colour-fast in the presence of light. However, manufacturers switched to synthetic indigo regardless because the product was easy to manipulate, came in the form of a “convenient” fine powder or paste, and contained a guaranteed percentage of indigotin. Some advantages were common to all substituted products. All had shorter supply chains, were of a reliable quality, and were less subject to adulteration. Even the inability to match the natural product’s complexity was not a barrier to market success. Chocolate and confectionary manufacturers in the 1890s adopted artificial vanillin in the 1890s once the manufacturing costs had been sufficiently reduced, despite the product remaining inferior to natural vanilla. A similar issue is likely to emerge with artificial animal proteins. If the product comes in a convenient form for manufacturing (e.g. in a minced state for burgers or small goods), is of a more consistent quality, is immune from costly food scares, and/or is cheaper than the natural product, then it may be adopted as an ingredient by industry almost regardless of the extent to which it exactly resembles the natural product.

Fourth, adulteration of the natural product can create an opening for substitution of a non-natural product. In the case of vanilla, frequent adulteration of vanilla essence with other compounds lead to poisonings that created concerns for product quality (F.L.P., 1874) while, at the same time, dramatic price fluctuations lead farmers to hasten the manufacturing process and create an inferior product (anon, 1896). In another substitution not reviewed here, prior to the development of margarine adulteration of butter was widespread – in particular, it often contained "very large quantities of water" (Hassal, 1845, xxiii), was adulterated with substances such as lard, wheat flour, potato starch, arrow-root and turmeric (Horsley, 1861), or was simply badly made (anon, 1877). Although current regulations make the sale of dangerous products unlikely, food scares in the animal protein industry have occurred on a regular basis in the last decades – for example, the BSE crisis in the UK (mid-1990s), the foot and mouth epidemic in the UK (early-2000s), the melamine in milk scandal in China (late-2000s), the substitution of horse meat across the EU (early-2010s), and the contamination of milk products with dicyandiamide (DCD) in New Zealand (early-2010s). Occurrences such as these are likely to enhance the market opportunities for alternative proteins in the future meaning a clean image for the industry is essential.

5.2 And what of the failures?

One criticism that could be levelled at this historical approach is that the study only looks at successful innovations and, as a result, it makes the untestable assumption that the contemporary innovation under examination will likewise be successful. Of the "failed" historical substitutions one of the best cases is the attempt to recreate cane sugar. Towards the end of the 19th Century sucrose had become the holy grail for synthetic chemists. It was believed that any chemist who could synthesise sucrose would earn "a fortune far greater than any previous" (anon, 1884, 36) while historical developments in the madder and indigo industries were seen as indicators that it should be "taken for granted" that eventually such a process would be discovered (Roscoe, 1891, 128). This created panic amongst "the immense interests which are concerned in the present cultivation and manufacture of cane and of beets" (anon, 1887, 307). When, three decades later, Ame Pictet and Hans Vogel (Pictet & Vogel, 1928) finally succeeded in synthesising cane sugar the process was so complex that it was ultimately not possible to make it commercially viable.

Synthesis and direct substitution of sucrose was thus technically a failure. However, in developing knowledge of sugar molecules chemists had opened up the possibility of producing synthetic sweeteners that, it was noted at the time, “might prove to be sweeter than common sugar or safer for the use of diabetics” (anon, 1928, 347). This appears to be the direction substitution took. Instead of replacing sucrose, scientists have developed sweeteners that are many orders of magnitude sweeter than sugar, address sugar related metabolic disorders, have a considerable cost advantage and even have the potential to extend product shelf-life (Bahndorf & Kienle, 2004; Carocho et al., 2017). In recent times, pressure to reduce the obesogenic nature of western diets has contributed to a rapidly developing market in these low calorie sweeteners – demand for which is increasing faster than demand for natural sweeteners (Bahndorf & Kienle, 2004; Sylvetsky & Rother, 2016). It is difficult to ascertain whether the failure to develop synthetic sucrose was because there is no means of commercially producing artificial sugar, or because synthetic chemists simply switched their attention to the more potentially lucrative artificial sweetener production.

5.3 Three key factors suggesting a biosynthetic protein substitution might occur

The lesson from sucrose is that substitutions do not always take expected pathways. Whereas in the late 19th Century scientists expected to be able to develop a means of synthesising and substituting sugar, the result instead was the development of substitutes with valuable additional properties and which lead to a bifurcation of the market. The transition to artificial proteins may likewise not take the route anticipated. Scientists involved in the synthetic protein start-ups today are predicting a positive future with the same apparent level of certainty that was shown in the sugar transition, a transition that never happened. However, each transition is different and, in the case of biosynthetic proteins, there are three key features that suggest a partial or even full transition is simply a matter of time.

5.3.1 The independent development of biosynthesis technologies in the medical sector

In the early work of Goodman et al. (1987) and Buttel (1989) it was recognised that the biotechnologies applied to agriculture had been developed independently of the agricultural sector. It was advances in genetic engineering in the field of medicine that lead to the application of biotechnology to agriculture in the 1980s and, in a similar fashion, it has been the development of cellular and fermentation technologies in the medical and pharmaceutical sectors that has lead us to the brink of a cellular agriculture revolution in the 2010s. The commercial forces driving these medical developments in biosynthesis are considerable. For example, the market for biologics in pharmacology alone (i.e. drugs produced biologically including by biosynthesis) grew from $46 billion in 2002 to $221 billion in 2016 and is expected to exceed $390 billion by 2020 – while the market share for biologically vs chemically synthesised drugs is increasing as a percentage year on year (Crespi-Lofton & Skelton, 2017). This is promoting growth in technologies for bioengineering yeasts for pharmaceutical production with "biopharmaceutical proteins (being) one of the rapid-growing and attractive classes of biomedicine" (Madhavan et al., 2018, 30).

Medical biosynthetic protein products face identical technological challenges to the agricultural biosynthetic protein sector. They need, for example, to replace animal serum to promote cell growth for culturing of human organ stem cells (Tüysüz et al., 2017), larger and increased numbers of bioreactors (Seymour and Ecker, 2017), to replace batch processing with continuous processing (Doig & Jones, 2016), real-time gene sequencing and editing (Shendure et al., 2017), improved 3D printer technologies (Kyle & Whitaker, 2018), artificial intelligence for searching DNA databases (Chakradhar, 2017), cellulose scaffolds for the production of organ like structures (Courtnay et al., 2018), and so on and so on.

Technology transferability between the medical field and the field of cellular agriculture, in fact, goes far beyond the genetic modification technologies transferred between agriculture and the medical sector in the 1980s. Almost every step of the developmental trajectory in the medical realm is a step towards addressing the issues facing biosynthetic animal protein production. This largely disconnects the cost of developing artificial protein alternatives from the likely economic returns from edible protein while, at the same time, means that even if the initial start-ups fail, the development of new transferrable technologies will continue at a rapid pace. At some point in the future, regardless of what happens in the agricultural sector, biosynthesis technology will be cheap enough and advanced enough to be transferred to food production – which it will be able to do with relative ease.

5.3.2 The increasing need for environmentally sustainable food systems

The second issue that makes a biosynthetic protein transition likely is the urgent need to address sustainability issues in the livestock sector. Considerable hype has been built up around the environmental credentials of cellular agriculture by the start-up companies – contributing to the emergence of academic literature concerning its environmental potential (e.g. Tuomisto & de Mattos, 2011; Mattick et al., 2015; Hocquette, 2016; Alexander, 2017). An early life cycle assessment by Tuomisto & de Mattos (2011) suggested that, in comparison to conventionally produced meat in Europe, in biosynthesised meat involves 7-45% lower energy use, 78-96% lower greenhouse gas (GhG) emissions, 99% lower land use, and 82-96% lower water use. Similarly, a preliminary study into the milk protein production process for Perfect Day contended that yeast derived milk would use 24-84% less energy, 77-91% less land, 98% less water and produce 35-65% fewer GhG emissions, than conventional milk (Steer, 2015). That these analyses are marked by wide error margins is not surprising given that the production processes have yet to be developed – however, they suggest that cellular agriculture *could* play an important role in addressing key global issues such as land loss to salinization or sea level rise, population growth, and, critically, climate change.

With products yet to reach the market, this outcome is not certain. Recent assessments have suggested that while land requirements may be lower, laboratory grown meat requires a lot of energy – meaning that new clean energy sources and/or further technological developments are essential (Mattick et al., 2015; Smetana et al., 2015). Similarly, Alexander et al. (2017) using the figures produced by Tuomosto & de Mattos (2011) found that, in terms of land use, cultured meat does not offer significant advantages over the production of poultry or eggs – and conclude that the best solution is to change consumer behaviour. However, while similar arguments can be made for an even more environmentally effective move to a vegetarian diet, our understanding of how to promote dietary change is “still in its infancy” (Garnett, 2011, 530), whereas, as we know from the historical cases, direct substitution can have immediate and dramatic impacts on conventional production systems. If start-ups focus on beef (e.g. Memphis Meats, Aleph Farms) and milk production (e.g. Perfect Day) rapid changes in GhG emissions could be achieved as these products alone account for 35% and 30% of livestock sector emissions respectively (Opio et al., 2013). The mitigating effect of successful commercial development of egg whites (e.g. Clara Foods), poultry (e.g. JUST, Supermeat) or fish (e.g. Finless Foods, Blue Naulu) on the other hand, could be substantially lower.

5.3.3 The public acceptability of cellular agriculture

A number of quantitative studies suggest that the public views cellular meat positively. For example, in a study of 180 consumers in Belgium, Verbeke et al. (2015a) found that only 9% rejected the idea of trying cultured meat, 67% were undecided and 24% were willing to try it. Providing the respondents with information about the environmental benefits resulted in 43% being willing to try it. In the U.S., Wilks & Phillips (2017) found similarly that only around 9% of the sample were unwilling to try cultured meat while 31% were willing to try it. Finally, Slade (2018) using a choice experiment, found that when given the choice of natural burger, a vegetable burger, or a cultured meat burger given the same taste and price, 11% of respondents would prefer the cultured meat burger which, as the authors note, would represent a substantial segment of the burger market. Focus group investigations, on the other hand, have tended to produce much more critical outcomes with Verbeke et al. (2015b) suggesting a deep distrust of the product, and Marcau et al. (2015) finding that respondents anchored their perceptions of cultured meat around the "Frankenfoods" metaphor associated with GE products.

However, quantitative studies do not suggest this equivalence. For example, whereas only 9% of respondents in Wilks & Phillips' (2017) U.S. study rejected the idea of eating cultured meat, a representative sample of U.S. residents found that 45% were "absolutely opposed" to GE foods, i.e. "they agreed that GE should be prohibited no matter the risks and benefits" while a further a further 19% were merely "opposed" (Scott et al., 2016, 315). Further evidence that cultured food will not be received in the same way as GE food can be gleaned from Slade's (2018) study where preference for organic products correlated *positively* with preference for cultured meat but *negatively* with preference for genetically modified foods. This suggests that cultured meat could be viewed as an ethical alternative as opposed to a "Frankenfood". Endorsements that have emerged from the animal welfare groups PETA may promote this view (Fox, 2009).

While attitude studies so far have failed to separate the two methods of protein production there is an important distinction in that, while cellular agriculture can avoid the use of GE, fermentation techniques generally require the use of GE to create bacteria/yeasts. This could lead to a public backlash as occurred in 2014 when Ecover substituted oil made from a genetically engineered algae for palm oil (Johnson, 2017). However, in many other cases the products of GE single celled organisms are already being consumed without obvious concern. For example, five of the top six selling insulin products are now produced by GE organisms (anon, 2016), fermentation-produced chymosin is used in approximately 80-90% of cheese in the US and UK (Jaros & Rohm, 2017), and GE organisms are now used in the production of "natural" vanilla as noted above. In addition the vegetarian "Impossible Burger" uses a genetically modified yeast to produce its blood-like heme and is rapidly expanding its market (Business Wire, 2017) – despite a campaign against its use of GE by environmental groups Friends of the Earth and the ETC Group. Market evidence so far thus suggests the use of genetic engineering in fermented products does not raise the same "Frankenfoods" concerns as direct consumption of GE products.

6. Conclusion – the end of intensive animal production?

How and when it will happen is uncertain, but it is likely that within the next decade a synthetic animal protein product will enter the market and compete against conventional animal protein. The impact of this development on livestock production is, however, somewhat more difficult to assess. Historical analyses of past substitutions undertaken here indicate that industry may go through a number of stages of response – beginning initially with panic as the agricultural sectors come to grips with the notion that they have lost their monopoly on production. What we have witnessed thus far – pre-product release – is more of a mild concern evident in, for example, Beef and Lamb New Zealand (2018) commissioning a report on artificial alternatives to meat (including, but not exclusively, synthetic meats). Next in the cases of indigo and vanilla came a period of complacency where, as a result of the industry being unable to develop a commercially viable production process immediately, the agricultural sector dismissed the notion that synthesis was possible. Observers' analysis of events at the time suggested that industry should have learnt from the alizarin scenario – where total substitution was made over a short period of time – and used the delay in development to improve the natural production process. In all cases the critical point for agriculture came where the price of synthetic production fell below that of producing the natural product which, in combination with the additional product consistency and security of supply, lead to widespread and rapid adoption by major industries.

That point may not be far off for synthetic proteins. In two of the most ambitious cases, Integriculture aims to produce a 200g burger for $2 by 2026 (Integriculture, 2018) while Mosa Meat claim they will produce a burger of unspecified weight for $1 by 2021 (Associated Press, 2018). Whether these predictions are based on the need to encourage investors or represent realistic assessments of the state of development is unclear, but, if accurate, it suggests the real challenge for conventional production may begin in the next decade.

One of the key issues livestock producers will have to deal with at that future point is how to maintain their distinct "naturalness" advantage. At the beginning of the era of chemical synthesis, the public had already expressed a preference for "natural" over synthetic (anon, 1881) and this is still prevalent with consumers today (Román et al., 2017). While the concept of naturalness is a complex one, there is little doubt that biosynthetic protein will be perceived as considerably less natural than farmed protein. Food production processes inherent in synthetics including chemical transformation, enhanced processing, genetic engineering, and the combination of multiple entities, have been found to decrease perceptions of naturalness of food products – with genetic engineering causing the most significant decline (Rozin, 2005; Evans et al., 2010). Producing protein via live animals thus ought to have a significant, potentially even unassailable, advantage over synthetically produced alternatives.

However, animal-based farming systems show strong variability. Large commercial producers and manufacturers in the food sector have, for decades, been making efforts to reduce the importance of nature through the processes of appropriation and substitution discussed above (Murdoch et al., 2000). Practices such as rearing animals in enclosed and controlled conditions, preventative antibiotic use, development of ultra-processed foods (Monteiro et al., 2013), enhanced mechanisation, proteomics in animal welfare (Marco-Ramell et al., 2016), repurposed animal protein in concentrated feed, and so on, are increasingly pushing industrial livestock production towards the "unnatural" end of the naturalness spectrum. From a business perspective, these efforts have been extremely successful but, in the process, agricultural systems have bifurcated into industrial producers competing on the basis of bottom-line profitability, and quality-based production where the naturalness of the product contributes to a higher profit margin (Murdoch & Miele, 1999).

Responding to the threat of cheap biosynthetic protein products by further appropriation and substitution would weaken the key advantage of natural animal proteins while, at the same time, perversely normalising or even "naturalising" the processes used in synthetic production. For example, the use of genetic engineering in livestock would only serve to legitimise a process that is a key component of fermented protein production; the development of new ultra-processed protein products would normalise processes which would appear to have overwhelmingly greater utility for biosynthetic protein producers; and further livestock intensification would mirror the confined/concentrated nature of the industrial processes used in synthetic protein production. If the process of further intensification also leads to an increase in environmental externalities or decrease in animal welfare – both of which are strongly associated with intensive agriculture but not with biosynthetic production – the outcome could serve to further advance the position of biosynthetic protein producers.

If the market for animal protein develops in the same way other transitions of complex substitutions have we could witness the transition to a bifurcated market such as vanillin – with synthetic proteins supplying the mass market while high-end production of real animal protein survives, or even prospers, by producing natural high quality products at a premium. Alternatively, given that the animal protein market is already bifurcated on the basis of naturalness, the result could be a trifurcated market, with industrial animal proteins providing a "real" meat experience for those who cannot afford high-end natural produce. Improvements in the processing of vegetable proteins to animal protein substitutes would further complicate the market as more realistic vegetable facsimiles emerged.

One unknown factor is how the value of animal by-products will affect transition. In addition to edible protein a wide variety of other products are obtained from the slaughtering process and, while some of them are of little value (e.g. offal for the pet food industry), others are critically important for the medical sector (e.g. surgical ligatures, antigens, and testosterone). Although the value of by-products is relatively low compared to the rest of the animal, it has been estimated that a 10% increase in the value of beef by-products leads to a 1% increase in the overall value of the animal (Marti et al, 2011). What effect will synthetic protein production have on this section of the value chain? On one hand, it could lower the value of livestock production further. Already insulin production has moved from an animal by-product to a mostly biosynthesised product while Wild Earth is aiming to produce biosynthetic pet foods to replace those based on offal waste. On the other hand, however, any decline in production of livestock for meat would presumably result in supply issues for the rapidly growing biologics market (noted above), pushing up prices and at least partially compensating for the decline in the value of meat. Synthesising edible animal proteins may thus create a need to synthesise a wide variety of additional medical products and/or lead to the development of a livestock sector with an increased focus on serving medical rather than food needs.

Many other factors could affect – or even prevent entirely – a synthetic animal protein transition. New technologies that may negate the need for animal protein synthesis entirely are already under development. By 2022 Finnish firm Solarfoods expects to begin commercially manufacturing fermentation-derived protein (similar to soy) using CO2 directly from the air. This protein is predicted to have an environmental impact 10 to 100 times lower than meat products or even meat substitutes (Solarfoods, 2018). Potential facilitating factors for a synthetic protein transition include increased political will to address greenhouse gas emissions and increased severity of weather events affecting conventional food supply, while disruptive factors such as new regulatory obstacles, litigation by conventional livestock producers, or financial crises could negatively affect any transition.

As a result, while it is relatively safe to assume products will be on the market within the next decade, the exact nature and timing of any transition is impossible to ascertain. What is presented here is an historically informed analysis in which the lessons from past substitution transitions are the applied to the case of the nascent biosynthetic animal protein industry. The transition processes discussed should not be taken as "predictive" of the final outcome. As the analysis of past substitutions indicated, one of the causes of decline in the agricultural industries was their failure to take action to counter the threat of synthetic production – actions that conventional livestock producers could still take. Further, visions of radically different food futures whether driven by major advances in organic chemistry (e.g. Dam, 1894; Forbes, 1926; Churchill, 1932), gene technology (Goodman, 1987), nanotechnologies (Busch, 2008) or cellular agriculture technologies (Mattick, 2018) are formed when optimism for the new technology is high and understanding of the limitations low. We are in an identical position now. Enthusiasm for cellular agriculture among investors, scientists, cellular agriculture companies, and some animal welfare and environmental organisations is high, despite there being neither a single product on the market nor any accurate environmental impact assessment available. Perhaps cellular agriculture will end up falling short of expectations. On the other hand, perhaps the century old vision of a synthetic food future that would “pass the limits of human belief” is finally becoming reality – albeit one that, in the process of development, has taken more twists and turns than 19th Century chemists could possibly have envisaged.

Acknowledgements

I would like to acknowledge the generous support of the Norwegian Research Council who provided the research funding under the Bionær program (Biosmart Project No. 244608). Special thanks also to Professor Hugh Campbell for very useful discussions and his valuable input into the paper, and for the helpful comments of two anonymous reviewers.

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