THE DEVELOPMENT OF PENICILLIN IN THE NETHERLANDS 1940-1950: THE PIVOTAL ROLE OF NV NEDERLANDSCHE GIST- EN SPIRITUSFABRIEK, DELFT.

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The Development of Penicillin in the Netherlands 1940-1950: The Pivotal Role of NV Nederlandsche Gist- en Spiritusfabriek, Delft.

by

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ABSTRACT

In November 1945 the recovery of Maria Geene in Delft's Bethel Hospital signaled the success of the secret wartime research on penicillin at NV Nederlandsche Gist- en Spiritusfabriek (NG&SF) in Delft, the Netherlands. Fifty years later, Gist-Brocades, of which NG&SF was the forerunner, had become one of the world's largest producers of bulk penicillin. By the year 2005, Gist-Brocades was part of Dutch State Mines and market forces required that all production of penicillin in Delft stop.

While the historiography of the Netherlands during its years of occupation is well documented, little has been recorded of the wartime research with penicillin at NG&SF. Also, little has been documented of NG&SF's determination, at the end of the war, to continue penicillin production, a time when the whole of the Netherlands required reconstruction. By 1950 the continued success of NG&SF was highlighted by the gift of the predicate *Koninklijke* (Royal).

It is known that it was information on the success of Allied penicillin that stimulated the wartime research of NG&SF. This thesis, therefore, begins with a general history of penicillin production in Britain, the United States and Canada. This is offset by the unsuccessful experiences of France, Germany and Japan.

For the Netherlands, Nazi occupation meant that, from May 1940, the whole country was cut off from the outside world. In fact, this occupation occurred three months before Florey and his associates first published on penicillin in *Lancet*. Also, from 1943 there was an Allied embargo on publications regarding penicillin. How, therefore, did knowledge of Allied penicillin reach the Netherlands? Was NG&SF the only Dutch company interested in penicillin? Why were they successful? How, at the end of the war, could NG&SF consider financing such a new venture? It is the remit of this thesis to bring these questions to the fore.

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GLOSSARY AND ABBREVIATIONS

Aankoopvergunning
Permission to buy.

Academisch Ziekenhuis, AZ
University Hospital.

Academische Ziekenhuis Leiden, AZL
Leiden University Hospital.

Acetone
Colourless, flammable liquid with a sweetish smell, used as a solvent.

Ammonium salt of penicillin
Used to produce long-acting Penicillin G. See: Salt.

Amsterdamse Chinine Fabriek, ACF
Amsterdam Quinine Factory.

Aeratiekolven
Aeration flask.

Aerobe
Bacteria able to utilise (respire) oxygen.

Afdeling Antibiotica
Antibiotics Department.

Agar
Gel derived from seaweed and used for growing micro-organisms in the laboratory.

Akademische Ziekenhuis, AZ
University Hospital.

Algemeene toewijzing
General allocation.

Algemeene vergunning
General permit.

Amerikaanschen Voorlichtingsdienst
American Information Service.

Anaerobe
Bacteria able to grow in the absence of oxygen.

Antibiotic
A substance originally produced from a fungus that in small quantities inhibits bacterial growth – originally antibiotics were produced by fungal fermentation although semi- and fully synthetic antibiotics have subsequently been introduced.

Apothekers
Pharmacists.

Arbeidsfront
A workers organisation under the leadership of the NSB modelled on Nazi unions. In 1942 the Nazi occupier disbanded all Dutch Trade Unions and demanded that Trade Unionists become members of the *Arbeidsfront*. The *Arbeidsfront* was led by H.J. Woudenberg. It was disbanded in 1945.

Ariërverklaring
Aryan Declaration.

Artsenkamer
Medical Association

Assessor
Examiner.

Aspergillus
Genus (family) of fungi found, for example, in soil, manure and grains.

Bacinol
The codename given to the antibacterial substance produced at NG&SF – the name is derived from the *Penicillium* used to obtain Bacinol, namely *Penicillium baculatum.*

B-buizen
B-flasks.

Bedrijfs assistenten
Company assistants.

Beta-lactam
The chemical structure central to the penicillin family of molecules.

Bibliotheek
Library.

Binnenlandse Zaken, BZ
Ministry of Internal Affairs.

Bonnen
Vouchers.

Brieven
Letters.

Broad Spectrum Antibiotic
An antibiotic effective against many types of bacteria.

Brocades, Stheeman en Pharmacia, BS&P
Company that developed Expansine. Eventually merged with KNG&SF to create Gist-Brocades.

Buffer
A solution in which the pH is not altered by the addition of acids or alkali.

Buisje
Small flacon.

Butanol
A colourless liquid used as a solvent. Also known as butyl alcohol.

Caprylic alcohol
An anti-foaming agent. Also known as octanoic alcohol.

Centraalbureau voor Schimmelcultures, CBS
National Collection of Fungal Cultures.

Chemisch Technische Dienst, CDT
NG&SF's Chemical Technical Service.

Chloramphenicol
Broad spectrum antibiotic produced by the soil dwelling organism *Streptomyces venezuelae* and active against a wide range of Gram-positive and –negative bacteria. Usefulness limited by toxic side effects.

Clostridium
A genus including anaerobic bacteria, some of which are responsible for diseases such as gas gangrene, botulism and tetanus – plural is *clostridia* and the adjective *clostridial.*

Commissie inzake Antibiotische Geneesmiddelen
Commission for Antibiotic Medicines.

Commissie Blauw
Commission under the leadership Ir. Blauw and Prof. De Boer - charged by the Dutch Government-in-exile with obtaining scientific literature that was not available in occupied Netherlands for distribution in the Netherlands when the war and occupation ended.

Corn Steep Liquor
A by-product of the maize industry that was used to increase yields of penicillin – it was originally applied pragmatically and later discovered to be able to provide building blocks for the penicillin molecule.

Corticosterone
A steroid hormone secreted by the adrenal gland and involved in stress responses and anti-inflammatory activity.

Delfsche Eenheden, DE
Delft Units - the arbitrary unit developed by NG&SF in Delft to measure the strength of early penicillin samples. The unit was defined as the amount of bacteriostatic substance, which just completely suppressed the growth of *Staphylococcus aureus* in 1ml of peptone water at 37°C. One Delft Unit was equivalent to 1/10 Oxford Units.

Delft University of Technology. TUD.

Depocilline
A long acting penicillin product introduced by NG&SF originally intended to be called Retarcilline.

Depot
Scientific term for sustained release preparation.

Department van Handel en Nijverheid, DHV
Department of Trade and Industry.

Deutsche Chemische Gesellschaft
German Chemical Society.

Deutsche-Niederländische Gesellschaft, DNG
German-Dutch Business Association.

Deviezen
Foreign exchange.

Digesta Antibiotica, DA
Antibiotics Digest. An NG&SF Company publication on all matters antibiotic, intended as an information source for medical doctors. The DA was published from 1947 until 1966.

Distributiewet
Distribution Law.

Doctor Ingenieur, Dr. Ir.
Doctor Engineer, a Doctorate coupled with a Degree in Chemical Engineering.

Dolle Dinsdag
Mad Tuesday, 5 September 1944. The day on which reports of an allied breakthrough led to premature celebrations of imminent liberation in the North and West of the Netherlands.

Dutch State Mines BV, DSM
The company that acquired Gist-Brocades.

Economische Zaken, EZ
Ministry of Economic Affairs

Ensinkketel
Ensink fermenter. The fermenter used for the first large-scale production of penicillin at NG&SF.

Erlanmeyers
Conical flasks.

Ether
A volatile liquid with anaesthetic properties used as a solvent.

De Fabrieksbode, FB
NG&SF/KNG&SF/Gist-Brocades/DSM company newspaper normally published every two weeks.

Fermentation
The process whereby organic compounds such as carbohydrates are broken down by microorganisms such as yeast to produce energy, carbon dioxide and by-products. Fermentation can be directed by the choice of organism and conditions to produce substances such as penicillin or alcohol.

Fout
Literally 'at fault'. A term used in Dutch society at the end of the war to determine those who had acted 'incorrectly', for example through collaboration with the occupying forces, during the war years as opposed to those who had been *goed* /'good'.

Freeze Drying
A method of preserving by simultaneously freezing rapidly and drying in a vacuum.

Fungus
Ubiquitous microorganisms that form thread like structures or hyphae. Coloquial name is mould. Used in the cheese, brewing and antibiotic industries.

Gist-Brocades, GB

Gist-Brocades Centraal Archief, GB:CA
Gist-Brocades Central Archive.

Gist-Brocades R&D Archief, GB:R&D
Gist-Brocades Research and Development Archive.

General Practitioner, GP.

Gemeente
Municipal or Local Authority.

Gemeentearchief
Local Authority Archive.

Geneesmiddelenwet
Medicines Act.

Gemeentelijke Geneeskundig en Gezondheidsdienst
Local Authority Health Department.

Gewoon aandeelen
Ordinary shares.

Gezondheidsraad
Health Council.

Gezondheidszorg
Health Care System.

Goed
Literally 'good'. A term used in Dutch society at the end of the war to determine those who had acted 'correctly' during the war years as opposed to those who had been *fout*, 'at fault' / collaborator. Part of the *Zuivering* process.

Graanbeslag
Grain base.

Gram Stain
An empirical method of classifying bacteria by means of staining, washing with alcohol and counterstaining – Gram-positive retain the first stain, Gram-negative retain the counter stain. Penicillin is only active against Gram-positive.

Haemolytic
Destruction (lysis) of red blood cells with release of haemoglobin - commonly seen in tonsillitis or 'strep throat' caused by *Streptococcus pyogenes*.

Handel en Nijverheid
Department of Trade and Industry.

Hectolitre; Hl.
100 litres.

Heilmittel
Cure.

Hodgkins Disease
A malignant disease characterised by progressive enlargement of the lymph nodes, spleen and general lymphoid tissue.

Hongerwinter
The hunger-winter of 1944-1945 when the German occupier prevented foodstuffs and fuel from reaching the towns and cities of the western Dutch provinces.

Hoogedruk-ketelhuis
High-pressure boiler-house.

Hornex
A counter-current system in the form of a carousel; a continuous method for concentrating and purifying the penicillin fluid.

Impeler
A stirring rod.

Ingenieur, Ir.
Chemical Engineer, University Degree.

Ingenieur, Ing.
Engineer (approx. HND level).

Instituut voor Praeventatieve Geneskunde
Institute for Preventative Medicine.

Insulin
The hormone secreted by cells in the pancreas known as Islets of Langerhans - deficiency of insulin leads to diabetes.

In Vitro
Means: ' in a test tube'.

In Vivo
Means: ' in an animal or human'.

Jaarverslagen
Annual Report.

Jenever
Dutch gin.

Kluyver Archive, KA.

Keesings Medisch Archief, KMA
Keesings Medical Archive.

Klinisch-bacteriologisch Laboratorium
Clinical Bacteriological Laboratory.

Kluyver's *kolfje*
Kluyver's flask.

Kolfje
A small flask.

Koninklijk,
Royal.

Koninklijke Bibliotheek, KB
Literally Royal Library; more appropriately the National Library.

Koninklijke Maatschappij tot Bevordering der Geneeskunde, KMBG
Royal Society for the Promotion of Medicine.

Koninklijke Nederlandse Akademie van Wetenschappen, KNAW
Royal Academy of Arts and Sciences.

Koninklijke Nederlandsche Gist- en Spiritusfabriek, KNG&SF
Royal Netherlands Yeast and Spirit Factory.

'Kijk'
Literally 'Look'. A publication from the American Information Department.
This newspaper was published at the end of the war until individual Dutch newspapers of the Dutch press came through the *Zuivering* process, which allowed them to renew their reporting activities.

Leidsche Aparatenfabriek, LAF
Leiden Apparatus Factory.

Leiden Universiteit Medische Centrum, LUMC
Leiden University Medical Centre, successor to AZL.

Leiden Universiteit Pers, LUP
Leiden University Press.

Lymphatic System
A network of vessels in the body carrying lymph, a colourless liquid containing white blood cells, that removes micro-organisms and other debris from tissues.

Lysis
Dissolving of cells or bacteria, adjective is lytic.

Lysozyme
A natural antibiotic found in tissues such as lymph, saliva and tears.

MBT
Medical Brains Trust.

Mededeling
Announcement.

Medisch Front
Medical Front.

Medisch-Wetenschappelijke Dienst
Medical Scientific Service; established by NG&SF to provide the medical profession with information on antibiotics.

Minister van Sociale Zaken,
Minister for Social Affairs.

Ministerie van Binnenlandse Zaken, BZ,
Ministry of the Interior.

Ministerie van Economische Zaken, EZ
Ministry of Economic Affairs.

Mould Juice
Fermentation broth.

Mycelium
The mass of threadlike structures that forms the growing part of a fungus. Plural is mycelia.

Mycology
The study of fungi.

Nationaal Socialistische Beweging, NSB
National Socialist Movement.

Nederlandsche Artsenkamer
Netherlands Medical Association.

Nederlands Instituut voor Oorlogsdocumentatie, NIOD
Netherlands Institute for War Documentation.

Nederlandsche Instituut voor Volksvoeding
National Institute for Nutrition.

Nederlandsche Maatschappij ter Bevordering der Pharmacie, NMP
Dutch Pharmaceutical Society.

Nachrichten für Aussenhandel NfA
A German Trade Journal.

Nederlandsche Gist- en Spiritusfabriek, NG&SF
Netherlands Yeast and Spirit Factory.

Nederlandsche Tijdschrift voor Geneeskunde, NTvG
Dutch Journal of Medicine.

Nieuwe Rotterdamsche Courant, NRC

Noodnumber
Emergency number.

Northern Regional Research Laboratory, NRRL
United States Department of Agriculture Research Laboratory in Peoria, USA.

Onderduiken
To go into hiding.

Ondergedoken
Hidden.

Oestrogen
A steroid hormone belonging to the group of hormones that control the reproductive cycle and the development of secondary sexual characteristics in females. American spelling estrogen.

Oleic acid
A fatty acid commonly used as an anti-foaming agent in the fermentation process.

Osteomyelitis
An acute or chronic bone infection, usually caused by bacteria.

Oxford Unit
The arbitrary unit developed by Norman Heatley at Oxford University to measure the strength of early penicillin samples. The unit, which was later adopted as the international standard, depended on penicillin causing specific zones of inhibition in an agar plate seeded with *Staphylococci*. 10 Oxford Units were equivalent to 1 Delft Unit.

Pancreas
The large gland next to the stomach that secretes digestive enzymes and insulin.

Parenteral
Dosing route other than oral – generally taken to mean by injection when oral dosing is not possible.

Pathogenic
Disease or infection producing.

Penicillin
An antibiotic effective against some important bacterial infections, produced from a fungus.

Penicillinase
An enzyme produced by some bacteria that inactivates the penicillin molecule by cleaving the beta-lactam ring.

Penicillium
The fungal genus that includes the penicillin producing species. Conventional scientific nomenclature customarily writes the genus with a capital initial letter, sometimes abridged to the initial, while the strain is written with small letters. Both are italicised e.g. *Penicillium notatum.* The name of the identifier or isolator of the strain is then added in normal script starting with a capital letter e.g. *P. notatum* Biorge.

Petri Dish
A small glass or plastic dish with a lid into which a layer of feeding material is poured upon which a bacterial culture is grown.

pH
A measure of the acidity of a solution with a value of 7 denoting neutral and lower or higher values denoting acid and alkaline solutions respectively.

Phamaceutisch Weekblad, PW
Pharmaceutical Journal. Published weekly.

Phenylacetic Acid
A chemical compound that provides a building block for the penicillin molecule. American spelling – Fenylacetic.

Physiological Saline
A salt solution of 0.9% sodium chloride in distilled water, which is the same concentration of sodium chloride in blood. Commonly used to dissolve drugs to be injected intravenously.

Prioriteits-aandeelen
Priority shares.

Proef locale
Tasting area.

Proefgistingen
Test fermentations.

Prontosil rubrum
A synthetic red dyestuff produced by Bayer chemists. It was later shown to be broken down in the body and the active substance sulphanilamide produced *in vivo.*

Puerperal sepsis
Fever occurring in the post partum (birth) period usually as a result of infection - also known as Puerperal Fever.

Pyrogenicity
The property of an injected fluid to cause an abnormal increase in temperature due to the presence of pyrogens, frequently large organic molecules.

Radio Oranje
Radio Orange, Dutch radio transmitted from London during World War Two.

Razzia
Unexpected raid.

Reichsapotheekerführer
Leader of German Pharmacists.

Reichsmark
Former German currency.

Reichskommissar
Reich Commissioner.

Reserve voor Vernieuwing
Reserve funds for renovation, Renovation Reserve.

Ridderzaal
Knights Hall in Dutch Houses of Parliament used on State occasions.

Rijksbureau
State Department.

Rijksbureau voor Geneesmiddelen
State Department for Medicines.

Rijksbureau voor Genees- en Verbandmiddelen,
State Department for Medicines and Medical Supplies.

Rijksbureau Voedselvoorziening in Oorlogstijd
State Department for the Supply of Food in Wartime.

Rijksinstituue voor Oorlogsdocumentatie, RIOD
State Institute for War Documentation.
Now NIOD.

Rijks Instituut voor de Volksgezondheid, RIV
State Institute for Public Health.

Rijksinstituut voor Volkesgezondheid en Milieu, RIVM
National Institute for Public Health and the Environment.

Rustrungsbetrieb
Public Service Company.

Sarcoidosis
Non-infectious disease of the lungs, whereby the lungs lose elasticity and, therefore, breathing volume is reduced.

Salt
The product of a reaction between an acid and a base. The acid donates hydrogen, the base accepts it, producing salt and water. For example, the ammonium salt of penicillin was used to produce long-acting Pen G. Penicillin is the acid which reacts with the ammonium base to produce the ammonium salt of penicillin plus water.

SHAEF
Supreme Headquarters Allied Expeditionary Force.

Slavenarbeid
Slave work, forced labour.

Slavenarbeiders
Slave workers, forced to work like slaves.

Sociale Zaken, SZ
Social Affairs.

Staphylococcus
Bacteria from the genus *Staphylococcus* that are round and grow singly or in clumps. Some species are responsible for food poisoning, sore throats and boils. Plural is *Staphylococci* and the adjective *Staphylococcal.*

Streptococcus
Bacteria from the genus *Streptococcus* that grow in long chains. Some cause diseases such as scarlet fever, tonsillitis and rheumatic fever, others are benign, Plural is *Streptococci* and the adjective *Streptococcal.*

Streptomycin
An antibiotic discovered by S.A. Waksman at Rutgers University. It is active against many types of infection including streptococcal infections and tuberculosis.

Submerged Culture
Also known as deep fermentation was initially described in 1933 and is a system whereby fungi are grown in the medium as opposed to on the surface. The great advantage is in increased yield of product.

Sulphonamides
Also known as sulpha (American spelling is sulfa) were the first synthetic antibiotics produced by the German pharmaceutical company I.G. Farben in mid-1930.

Technische Hoogeschool, TH
Literally translates as Technical Highschool but more equivalent to Polytechnic Colleges of the UK; now Delft University of Technology (TUD).

Toegespaste Natuurwetenschappelijk Organisatie, TNO
Organisation for Applied Scientific Research.

Technische Universiteit, TU
Literally translates as Technical University but more University of Technology.

Toewijzingsbonnen,
Allocation vouchers.

Tweede Kamer
Lower Chamber of the Dutch Houses of Parliament.

Tijdschrift voor Artsenkunde, TvA
Journal of Medical Affairs.

Unit
The international unit was the accepted way of expressing the strength of early penicillin samples. As the chemical structure became known and analytical methods became more sophisticated the more conventional milligram was adopted.

Vakgroepen
Trade Associations

Vergunning
State allocation permit.

Verwalter
Supervisor.

Verzuild
Society made up within denominational segregation.

Virus
A microorganism consisting only of a nucleic acid surrounded by a protein coat. Viruses can only develop in other cells and frequently kill them – responsible for a wide range of diseases including the common cold. Insensitive to penicillin.

Vitamin A
Also called retinol is a fat-soluble vitamin essential for growth and resistance to disease – found in liver, cod liver oil and eggs.

Vitamin B
Group of vitamins (known as the Vitamin B Complex) that are water-soluble, essential for good health and include riboflavin, pyridoxine and folic acid.

Vitamin C
Also known as ascorbic acid, is a water-soluble substance found predominantly in citrus fruits, deficiency of which can cause anaemia and scurvy.

Vitamin D
Fat-soluble vitamin essential to the formation of bones the lack of which can lead to rickets – found in butter, eggs and fish and formed in the skin on exposure to sunlight.

Vitamine Gistvlokken
Vitamin Yeast Flakes.

De Vliegende Hollander
The Flying Dutchman; propaganda newspaper dropped over the Netherlands by Allied bombers returning from missions in Germany.

Vrije Universiteit,VU
Literally Free University, Amsterdam, more 'the VU'.

Wederopbouw
Reconstruction.

De Wervelwind
The Whirlwind; monthly propaganda magazine dropped over the Netherlands by Allied bombers returning from missions in Germany.

Wetenschappen
Sciences.

Wet Uitzonderingsgevallen
Exception Law.

Yeast
A unicellular organism used in fermentation in the alcohol and bread industries – yeast and yeast extracts are an excellent source of the B vitamins.

Ziekenfonds
National Health Service.

Ziekenfondsbesluit
Health Service Decree.

Ziekenfondsraad
National Health Service Council.

Ziektransport
Transport of those who were ill.

Zolder
A room in the attic.

Zuivering
The 'purification' process that took place in Dutch society at he end of the war, i.e. the cleaning up process to find those deemed to have been *fout* as opposed to those who had been *goed.*

CONTENTS

Chapter 1

Introduction

In November 1945 Maria Geene, a patient in Delft's Bethel Hospital was successfully treated for an otherwise fatal staphylococcal infection with penicillin produced by the Dutch company NV Nederlandsche Gist- en Spiritusfabriek[1] (NG&SF). The research and production of this penicillin had taken place in Delft, the Netherlands, in spite of wartime occupation by Nazi Germany. By the end of 1946 NG&SF could supply all the penicillin needed by Dutch hospitals; by 1948 they supplied all penicillin requirements for the whole of the Netherlands; and, in 1949 they began exporting penicillin.[2] In 1950 NG&SF was awarded the predicate *Koninklijke* (Royal) by gift of Her Majesty Queen Juliana to mark its eightieth year. This gift also marked the post-war achievement of NG&SF as one of the largest producers of bulk penicillin in the world. A trend that was set to continue as the company evolved under the name Gist-Brocades (GB).[3]

By 1998 Gist-Brocades had become part of Dutch State Mines (DSM). In March 2005, however, market forces deemed that, almost exactly sixty years from the end of the war, all production of penicillin in Delft stop. The quest for cheaper production methods took DSM penicillin to China and India.

The wartime success of research by Howard Florey and Ernst Chain's Oxford Team is well documented, as is the fact that during the war years penicillin production became a national priority in both Britain and the United States of America (US). At the time, however, Ingrid

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[1] My translation: Netherlands Yeast and Spirits Factory.
[2] Gist-Brocades, 'Van Fleming tot Flemoxin Solutab, markante momenten in 60 jaar penicilline', Company publication, 1989, pages not numbered.
[3] In 1967 NV Koninklijke Nederlandsche Gist- en Spiritusfabriek merged with NV Koninklijke Pharmaceutische Fabrieken v/h Brocades Stheeman & Pharmacia to become Gist-Brocades NV.

Pieroth states that from 1943 until January 1946 no publications on the production and chemistry of penicillin were permitted outside the US and Britain.[4] Also, the Netherlands was isolated from any Allied information by Nazi occupation. How, therefore, did information about penicillin reach the Netherlands? How was the development of penicillin at NG&SF possible? How was it kept secret?

Were they the only Dutch company interested in the development of penicillin? If not, why did they succeed where others failed? Moreover, at the end of the war, at a time of *wederopbouw* (reconstruction) and severe financial restriction, how could NG&SF afford to invest in such a new product? How, only five years from the end of the war did NG&SF manage to achieve its worldwide position in the production of bulk penicillin? Little, if anything, has been recorded of how, in the immediate post-war years, under the severe financial restrictions that encompassed Europe, NG&SF managed to lift itself to become a world supplier of penicillin. Ultimately, the remit of this thesis is to research the factors that mark the development of penicillin in the Netherlands and the success of NG&SF.

To begin with, from the history of penicillin we know that it was discovered and named by Alexander Fleming in St Mary's Hospital, London, in 1928. It was, however, the 1940 publications of Florey and Chain with their Oxford group, which showed that penicillin could be injected safely into the bloodstream and cure otherwise fatal systemic bacterial infections that brought penicillin to the fore. This revelation of properties appeared at the time to be almost miraculous and has been described as one of the great turning points in medical history. Indeed the history of penicillin is marked by its reputation as 'the wonder drug', a term first coined

[4] I. Pieroth, 'Penicillin: A Survey from Discovery to Industrial Production', in Kleinkauf, H. and Dohren, H. von, eds, *50 Years of Penicillin Application: History and Trends*, (Czech Republic: PUBLIC, 1980), p.29.

during the Second World War. It was during the war that penicillin was shown to increase considerably the chance of recovery for wounded soldiers and to lessen their suffering.

At the end of the Second World War, the part played by penicillin in the military field was endorsed by Field Marshall Bernard Montgomery's statement that the healing of war wounds had been 'revolutionised by the use of penicillin'.[5] Many men, he said, who would have been permanent invalids, were fit and ready to go back to the line within a month of being wounded. Much of this was due to the use of penicillin by military doctors. 'To sum up', Montgomery continued, 'the doctors were prepared to lay 15 to 1 that once a man got into their hands, whatever his injury, they would save his life and restore him to health'.[6]

The impact of penicillin as a 'wonder drug' is vividly portrayed in the film *The Third Man,* which illustrates the role penicillin had come to play in the medical world by the end of the war, with those in need prepared to pay extortionate black market prices.[7] The influence of this black market also highlights the ongoing post-war scarcity of penicillin for the population at large. Much has been written about the main characters, the factual accuracy of the various claims of the British and American teams, the patent battles that ensued and the way in which penicillin ushered in a new golden era of antibiotic discovery. As such, the story of penicillin remains an iconic narrative.[8]

Hailed as an all-encompassing history of those concerned in the history of penicillin in both Britain and the United States, Gladys Hobby's book *Penicillin. Meeting the Challenge* deals not

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[5] *London Gazette*, Supplement, 3 September 1946, Number 37711, Field Marshall The Viscount Montgomery of Alamein, G.C.B., D.S.O., 'Operations in North-West Europe from 6th June 1944 to 5th May 1945', The War Office, 4 September 1946, pp.4431-4451.
[6] *London Gazette*, p.4451.
[7] Film: *The Third Man*, 1949. Director Carol Reed. Taken from the novella by Graham Greene.
[8] Personal Communication, J. Bennett, 2000.

only with the development of penicillin as a therapeutic agent but also reflects the part she played in that history from its beginnings in the laboratory, through successful clinical trials to the first steps in production.[9] She also highlights the part played by many State institutions, such as the British Committee on Medical Research and the American Office of Scientific Research and Development, working together with other academic institutions and commercial research departments.

Robert Heron agrees that the development of penicillin was one of the outstanding accomplishments of the last century in the field of microbiology. But he also points out that, while the biographies of the principals in the research and development of penicillin convey scientific insight and brilliant research, few relate the organisational and leadership skills that brought this important antibiotic to the world. This effort was not of one person but of many people at all levels in organizations such as universities in Britain and the United States, the Rockefeller Foundation, the Northern Regional Research Laboratory (NRRL) of the United States Department of Agriculture and private industry. In particular, during the war years, the NRRL and American universities continued the development of penicillin to include research into synthetic production; deep culture fermentation; the precursor concept; and, innovations in purification, strain selection and genetic engineering.[10]

For Kevin Brown, Curator of the Alexander Fleming Laboratory Museum in St. Mary's Hospital, London, 'the story of penicillin is one of collaboration between bacteriologists, microbiologists, mycologists, chemists, government agencies, chemical and pharmaceutical companies, the military, civil servants and politicians'. It is also a story of transatlantic cooperation which

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[9] G.L. Hobby, *Penicillin. Meeting the Challenge*, (New Haven and London: Yale University Press, 1985), Foreword, pages not numbered.
[10] R.W. Herion, 'History of Penicillin: A Cooperative Research and Development Effort', *SIM News*, 50, 5, (September/October 2000), p.231.

without the impetus of war would have been unthinkable. The effect of the Second World War overrode commercial rivalries and allowed the transmission of information between two Allied nations, between government bodies and commercial companies, and between competing firms. As such the history of penicillin belongs as much in the history of the Second World War as in the history of medicine.[11]

Consequently, as Hobby, Heron and Brown illustrate, most of the history of penicillin remains based on the experience of penicillin research and development that took place in Britain and the United States during World War Two. In pointing to the wartime experience of other countries, Hobby states that ultimately it was in those countries where microbiology as a science was highly developed – and particularly those with established fermentation technology – that interest in penicillin production was most rapidly aroused. In particular, she cites Austria, France and the Netherlands.[12]

Bearing in mind the failure of Hobby's other named countries, France and Austria, to match the Netherlands as a supplier of penicillin at the end of the war, one of the objects of this thesis will be to reassess the development of Dutch penicillin during the war years. Most questions on the wartime research at NG&SF have been addressed by two publications based on this author's unpublished earlier work.[13] These publications clearly set out the microbiological research and

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[11] K. Brown, 'Penicillin in Peace and War, 1928-1945: An historical overview', Andrew J. Moyer Lecture. Sixtieth Anniversary of North American Involvement in The Development of Penicillin. National Center for Agricultural Utilization Research, Peoria, Illinois, 12 July 2001. Personal Communication Kevin Brown, February 2002.

[12] G.L. Hobby, *Penicillin*, p.202.

[13] M. Burns, 'Codename Bacinol: The Secret Production of Penicillin at the NV Gist- en Spiritusfabriek in Delft, the Netherlands, during the Second World War whilst under Occupation by Nazi Germany', MA Dissertation, Open University, UK, September 2000; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process in Delft, the Netherlands, During World War II Under Nazi Occupation', *Advances in Applied Microbiology*, 51, (2002), pp.185-200; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol. Dutch microbiologists, working in secret during the last months of WWII, developed procedures for making Penicillin', *ASM News*, 69, 1, (2003), pp.25-31.

identify the charismatic influence of François Gerard Waller, NG&SF's Deputy Director in charge of the Delft plant during the war years. They also name the principal NG&SF research workers and highlight the influence of its then advisors, Prof. Albert Jan Kluyver and Dr. Andries Querido.[14]

Kluyver had been Professor of Microbiology at the Technische Hoogeschool, (TH; College of Technology)[15] in Delft since 1921. He was a fermentation expert and his ability in the field of microbiology had earned him a prestigious reputation both in and outside the Netherlands. He had been an advisor to NG&SF on a formal basis since 1933. Indeed, most of the academic staff of NG&SF were graduates in Chemical Engineering from the TH. Most, including F.G. Waller, had studied in Kluyver's department. During the war years his advisorship and close working relationship, which included regular Monday meetings, did not change.

Querido had returned to the Netherlands from the Pasteur Institute in Paris just before the outbreak of war. He had secured a position as a specialist in internal medicine at the Academische Ziekenhuis in Leiden (AZL; Leiden University Hospital).[16] On Kluyver's recommendation Querido had been offered and had accepted a part-time advisorship at NG&SF. During the war years, Querido's Jewish background and his refusal to sign the *ariërverklaring* (Aryan declaration) forced him to move from the AZL to the Nederlands Israëlitisch Ziekenhuis (Dutch Jewish Hospital) in Amsterdam. However, as will be shown, it was this Amsterdam connection that led to the influence of 'chance' in the development of NG&SF's penicillin when Querido met a former Israëlitisch Ziekenhuis colleague in Amsterdam Central Station.

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[14] Dr A. Querido became Professor A. Querido, founder of Dijkzicht Academische Ziekenhuis Rotterdam (Dijkzicht University Hospital Rotterdam).
[15] Literally translates as Technical Highschool but more equivalent to Polytechnic Colleges of the UK; now Delft University of Technology (TUD).
[16] AZL literally translates as Academic Hospital Leiden, more Leiden University Hospital.

Yet, questions surrounding the development of penicillin at NG&SF remain. Did Querido's 'chance' meeting play such a major role? At the same time, consideration has once more to be given to how news of penicillin reached those in Delft. Further, was there really no knowledge of penicillin in the Netherlands during the Second World War? Although cut off from the outside world, was it possible that information on the progress of Allied penicillin got through, not only, to those in Delft, but also, to others? Was there a dissemination of information on penicillin across belligerent countries? If so, what impact did this have on the research and development of penicillin in the Netherlands during the war years and after?

Writing a Preface to the first edition of *Penicillin. Its Practical Application* in 1946, Fleming noted that the object of the book was to tell the practitioner how to use penicillin to best advantage when it became readily available to the whole medical profession. In his Preface to the second edition in 1950 Fleming said that:

> In the three years since the First Edition of this work appeared, penicillin treatment has become more standardized. It is now known with a fair amount of certainty what the drug can do and what it cannot do in the treatment of disease.[17]

Again, open to discussion is the question: What role, if any, did the availability of such information in the early post-war years make to the development of penicillin in the Netherlands and more specifically to NG&SF?

However, as Kevin Brown has illustrated, the development of penicillin in Britain and the United States is as much a story of 'what happened' during the Second World War.[18] For The

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[17] A. Fleming, General Editor, *Penicillin. Its Practical Application*, 2nd ed., (London: Butterworth & Co. Ltd., 1946), Preface.
[18] K. Brown, 'Penicillin in Peace and War', Andrew J. Moyer Lecture, 2001.

Netherlands the same holds true. Accordingly, in order to bring the effects of Nazi occupation on the Netherlands to the fore, this Chapter will introduce some of the available sources. Before continuing with the development of penicillin in the Netherlands between the years 1940-1950, Chapter Two will set the contrast between those in the Netherlands and those outside by relating a general history of penicillin in Britain and the United States. This will expand to include the experience of another successful producer of penicillin, namely Canada, and point to unsuccessful European penicillin producers, Germany and France. Consideration will also be given to American influence in the success of post-war penicillin production in Axis countries such as Germany and Japan. In concluding, Chapter Two will use the archive of the Centraalbureau voor Schimmelcultures (CBS; National Collection of Fungal Cultures), to highlight, not only, a pan European interest in the search for penicillin producing mould cultures, but also, Dutch academic and pharmaceutical interest. Chapter Three addresses the consequences of occupation for Dutch health care and brings into consideration the topic of Dutch penicillin research during the war years. Chapter Four specifically re-introduces the experience of those at NG&SF in the production of penicillin under the name Bacinol. In order to do so NG&SF's research with the strain *Penicillium baculatum* will be expanded and fuller consideration given to the ability of NG&SF staff and the influence of their advisors, Kluyver and Querido. Following liberation, Chapter Five and Six highlight the Dutch post-war desire to reintegrate with the rest of the world, specifically in the arena of scientific research and development. Chapter Seven will return to the experience of NG&SF. In particular, the post-war scale up of penicillin and the difficulties that had to be overcome for mass production will be addressed. Before concluding, Chapter Eight combines the reconstruction of the Dutch Health Service and the considerable part played in that reconstruction by the scale up of penicillin production at NG&SF. Chapter Nine will draw the whole thesis together.

Historiography of the Netherlands 1940-1950.

In considering the historiography surrounding the experience of the Netherlands under occupation during the Second World War a wide variety of sources are available. Of prime importance is the fourteen-volume *Het Koninkrijk der Nederlanden in de Tweede Wereldoorlog* (The Kingdom of the Netherlands in the Second World War) by Louis de Jong.[19] A prolific writer on the history of the Netherlands during the Second World War, de Jong's personal experience lends an authenticity to his writing. During the war he was employed as a journalist in London and wrote for the Dutch radio station, *Radio Oranje* (Radio Orange). He also wrote articles for the *De Vliegende Hollander* (The Flying Dutchman), a propaganda newsletter distributed over the occupied Netherlands by Allied aircraft as they returned from bombing raids over Germany. At the end of the war de Jong became Director of the Rijksinstituut voor Oorlogsdocumentatie (RIOD, State Institute for War Documentation). Founded in 1945, RIOD has since been renamed as the Nederlands Instituut voor Oorlogsdocumentatie, (NIOD, Netherlands Institute for War Documentation). This institution is acknowledged as the prime centre for information and research on the Netherlands during the Second World War.

Publication of *Het Koninkrijk der Nederlanden in de Tweede Wereldoorlog (Het Koninkrijk)* began in 1969 and ended in 1991. Two versions of each volume were printed; one 'scientific' with annotations and sources, the other, with fewer annotations, was directed more to the 'popular' market. Both versions sold well and reflected the renewed interest in the Second World War that surfaced in the Netherlands during the 1960s. Before publication each volume was submitted to supervisory committees and government institutions for approval. Accordingly, as Pieter Lagrou points out, *Het Koninkrijk* comes as close to an official history as can be achieved

[19] L. de Jong, *Het Koninkrijk der Nederlanden in de Tweede Wereldoorlog*, 14 delen, (Delen 1-10: s'Gravenhage, Martinus Nijhoff; Delen 11-12: Leiden, Martinus Nijhoff; Deel 14: 's-Gravenhage, SDU Uitgeverij, 1969-91).

in Western Europe.[20] Moreover, while RIOD became the almost exclusive and certainly the dominant source of war historiography, Louis de Jong became the personification of the history of the war both in writing and on television.[21]

Even so, the publication of the last two volumes of *Het Koninkrijk*, 14a and 14b, both entitled *Reacties* (Reactions), illustrate that de Jong's work prompted differences of opinion over particular wartime events and activities. Accordingly, the aim of Volume 14 was to incorporate the ideas, opinions and analyses of de Jong's contemporaries. Erik Somers and Mark Pier state, in their foreword to the two volumed *Archievengids van de Tweede Wereldoorlog* (Second World War Archive Guide), that rather than marking the 'last word' in the history of the Netherlands from 1940 to 1945, de Jong's last Volume served to open up different insights and questions. This, in turn, highlighted the need for further research regarding the experience of the Netherlands during the Second World War.[22]

In his book *Grijs verleden. Nederland en de Tweede Wereldoorlog* (A Gray Past. The Netherlands and the Second World War) Chris van der Heijden claims that de Jong's views are too black and white. Van der Heijden's premise is that during the occupation, with the exception of a handful heroes and villains, most people just tried to get on with living, to muddle through. Life became a 'no-man's land' filled with *grijs* (gray) areas.[23] He poses the uncomfortable question "Given the same circumstances, what would I have done?"[24]

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[20] P. Lagrou, *The Legacy of Nazi Occupation. Patriotic Memory and National Recovery in Western Europe, 1945-1965*, (Cambridge: Cambridge University Press, 2000), p.73.
[21] P. Lagrou, *The Legacy*, p.303.
[22] E. Somers en M. Pier, *Archievengids van de Tweede Wereldoorlog*, 2 delen, (Zutphen: Rijksinstituut voor Oorlogsdocumentatie p/a Uitgeversmaatsachappij Walburg Pers, 1994), Introduction.
[23] C. van der Heijden, *Grijs verleden. Nederland en de Tweede Wereldoorlog*, (Amsterdam/Antwerp: Olympus, Uitgeverij Contact, 2001), pp.411-412.
[24] C. van der Heijden, *Grijs verleden*, p.15.

From sources available in English, *The Oxford Companion to the Second World War*, consultant editor M.R.D. Foot's introduction cites the Netherlands as a democratic kingdom with nine million people that had never been at war with another state since it was founded in 1815. In 1939 the intention of the Dutch government was to remain neutral. After an unprovoked attack, Germany's *Blitzkrieg* tactics brought with it occupation. Under occupation the professions were Nazified. Leiden University was closed down. In February 1941 strike action was followed by seventeen executions in a country that had no death penalty.[25]

The consequences of occupation for the Netherlands are further explored in the proceedings taken from a conference held at University College, London, on 3, 4 and 5 April 1989, edited by M.R.D. Foot and entitled *Holland at War Against Hitler*. As the Introduction explains, repeated assurances of goodwill had been offered to the Dutch regime by Nazis at every level from Hitler downward. However, like other Nazi promises these proved to be worthless. As dawn broke on Friday, 10 May 1940, the full might of a *Blitzkrieg* fell on the Dutch who were wholly unprepared for it. Queen Wilhelmina felt a sense of personal outrage that Hitler had not respected the neutrality of her country. On the fourth day of fighting she was forced into exile as she sailed from the Hook of Holland on a British destroyer. Her hope was to carry the war on from Zeeland but, as war conditions worsened, she was taken to Harwich instead. Most of her Cabinet followed. The next day Rotterdam encountered a savage attack from the air by the German Air Force. Having reached their limit of resistance against the German military forces, the Dutch armed forces capitulated. The Queen and her Cabinet, however, continued as the official Dutch government, in exile, from London.[26]

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[25] *The Oxford Companion to the Second World War*, Ed., J.C.B. Dear, Cons. Ed., M.R.D. Foot, (Oxford / New York: Oxford University Press, 1995), pp.782-783.

[26] M.R.D. Foot, ed., *Holland at War Against Hitler Anglo-Dutch relations 1940-1945*, (London: Frank Cass Ltd. / Wanders Uitgevers, 1990), p.xvii.

With the Queen and her Cabinet in London, in the short term the Netherlands was rudderless. Heading a Committee of Action, Fentener van Vlissingen of the Deutsch-Niederländische Gesellschaft (DNG: German-Dutch Business Association) advised trade and industry to stay working – to 'accommodate'. This stance is explained in *Appeasement en aanpassing. Het Nederlandse bedrijfsleven en de Deutsch-Niederländische Gesellschaft 1936-1942*, (Appeasement and Adaptation. Dutch Companies and the German-Dutch Business Association 1936-1942), by Madelon de Keizer. According to de Keizer, the Dutch business world joined with the politics of appeasement from the crisis of 1939. In the interests of peace it was felt that a moderate political and economic policy should be fostered with Berlin. This would keep Hitler's policy of expansionism in check. However, the ideological aspects of Germany's trade policy eventually emerged. German hegemony was bent on war and the German branch of the DNG used the *Gesellschaft* only for propaganda purposes. For de Keizer, the moderate Dutch had taken their eye off the ball; they were caught in a loop.[27]

While, for some, accommodation seemed the only option available, this attitude was scorned in other quarters as 'collaboration'. According to Langemeijer, a procurator fiscal in The Hague, the only way in which the Dutch population could have limited this so-called 'collaboration' was by committing mass suicide on 15 May 1940, the day of capitulation.[28] The politics of 'accommodation' did not mean that people were pro-German or pro-National Socialist. The Netherlands found itself having to deal with, not only being in the war, but also suffering the indignity of Nazi occupation.[29]

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[27] M. de Keizer, *Appeasement en aanpassing: Het Nederlandse bedrijfsleven en de Deutsch-Niederländische Gesellschaft 1936-1942*, ('s-Gravenhage: Staatsuitgeverij, 1984), pp.231-232.
[28] H.J. Neuman, *Arthur Seyss-Inquart. Het leven van een Duits onderkoning in Nederland*, (Utrecht / Antwerp: Veen, uitgevers, 1967), p.222.
[29] H.J. Neuman, *Arthur Seyss-Inquart*, p.234.

Bob Moore in *Victims and Survivors* points to the stoic pre-war principles of neutrality held on to by Dutch politicians and mirrored by the general public mood. On 10 May 1940 the German armed forces attacked the Netherlands along a broad front. On hearing the news the Dutch were psychologically unprepared for the blow. In theory every man and woman had to make a decision – 'to go or to stay'. To 'stay' meant living under German occupation but to 'go' meant abandoning home, security, assets and family for an uncertain future. Occupation left an orderly Dutch society in chaos and disorder.[30]

In the political sphere, H.J. Neuman illustrates in *Arthur Seyss-Inquart. Het leven van een Duits onderkoning in Nederland* (Arthur Seyss-Inquart. The life of a German Viceroy in the Netherlands) that Hitler considered the Dutch as part of the Greater German race. In place of a military occupation the task of Hitler's direct appointment, the 'diplomatic' Arthur Seyss-Inquart, as *Reichskommissar* was to win over the 'pure bred' Dutch population to National Socialism. Seyss-Inquart took up his position on 29 May 1940 in the *Ridderzaal,* the main hall of the Dutch Houses of Parliament. In his address he promised that the rights of the Dutch would, as much as possible, be left untouched. Germany had come not to destroy the land or deny it its freedom. For himself, he would play a part in Government decisions only where absolutely necessary. There would be no other changes.[31] In effect Seyss-Inquart's civil management drew a line through any plans that had been fostered for a degree of political independence from National Socialist Germany.

According to Moore, the first months after the Dutch armed forces had surrendered to the invading Germans were remarkable, not because the German occupation brought so many

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[30] B. Moore, *Victims and Survivors: The Nazi Persecution of the Jews in the Netherlands 1940-1945,* (London/New York: Arnold, 1997), pp.42-51.
[31] H.J. Neuman, *Arthur Seyss-Inquart,* p.234.

changes to everyday life in the Netherlands but precisely because there were so few changes. Initially, German policy was to minimise the effect of occupation and retain as much normality as was practical. The Dutch were, after all, fellow *Aryans*. When the German army arrived in those areas not already taken by military action, the soldiers obeyed orders and adopted a wholly 'correct' attitude towards the civilian population. During May the Netherlands remained under military control, but this was superseded from the 29th when the German civilian government led by Seyss-Inquart was appointed. However, the installation of Seyss-Inquart's new regime took some time and, according to Moore, this may help to explain why no immediate steps were taken against the Jews in the Netherlands. Also the war in France was still in progress and, for the time being at least, the main German objective was to keep the Netherlands quiet and free from disturbance with the minimum use of resources.[32]

In *Crisis, Bezetting en Herstel. Tien studies over Nederland 1930-1950*, (Crisis, Occupation and Recovery. Ten studies on the Netherlands 1930-1950), Johan Blom states that, to say the Dutch population or the administration and political elite had been prepared for possible occupation is obviously untrue. However, almost everywhere in society the same thing happened more or less automatically, that was to carry on as normal and wait to see what developed. The Dutch army had lost, the Cabinet had left and the German occupation established itself. What position other than trying to carry on was possible? For the Dutch administration that was left there had to be consultation with the occupier and it was self-evident that, in principle, his insructions had to be followed. If not there would have been chaos and that would have been bad for the population as a whole. At the time, the paternalistic Dutch civil servants simply did not think of staging any resistance. Although unconsciously done, May and June of 1940 saw the first steps of Civil Service collaboration. Once they were on that path it was difficult to choose a time when it should no longer be followed. In fact, with the exception of the railway strike in 1944, the Dutch Civil

[32] B. Moore, *Victims and Survivors*, pp.42-51.

Service never came to a collective decision. This gave the occupier the opportunity to replace difficult Civil Servants with more malleable ones, mostly members of the German supporting Nationaal Socialistische Beweging (NSB, National Socialist Movement). In this way the apparatus of Government remained in place but it remained for the occupiers own ends.[33]

On the economic front, Blom states that the occupier was completely successful in the exploitation of the Netherlands. While, the long term the ambition to join the Dutch and the German economies failed, in the short term the Dutch economy was successfully turned to work for the German economy. This happened in two ways. The first was simply the German requisitioning of goods that were available in the Dutch industrial and agrarian sectors. The second was by Germany placing special orders with Dutch industry to service the needs of the Germany's war effort. It was only later in the war that Dutch 'go slow' techniques, sabotage and complete refusal to cooperate played a role. It was also much later in the war that the occupier took a rougher form of economic exploitation, which Blom describes as 'actual robbery'.[34]

Gerhard Hirschfeld, the German historian, gives a detailed description of the full economic cost to the Netherlands for its occupation in *Bezetting en collaboratie. Nederland tijdens de oorlogjaren 1940-1945* and the English translation *Nazi Rule and Dutch Collaboration. The Netherlands under German Occupation 1940-1945.*[35] According to Hirschfeld the economic effect of Nazi politics on the Netherlands can be explained by three factors: firstly, with the occupation the Netherlands lost her markets and raw materials and became dependent on the German economy; secondly, the aim of the German occupier was to squeeze as much as possible

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[33] J.C.H. Blom, *Crisis, Bezetting en Herstel. Tien studies over Nederland 1930-1950*, (Rotterdam: BV Universitaire Pers Rotterdam, 1989), pp.67-72.
[34] J.C.H. Blom, *Crisis, Bezetting en Herstel*, p.80-85.
[35] G. Hirschfeld, *Bezetting en collaboratie: Nederland tijdens de oorlogjaren 1940-1945*, trans. P. Jarsma, (Haarlem: Becht, 1991); *Nazi Rule and Dutch Collaboration: The Netherlands under German Occupation 1940-1945*, trans. L. Willmot, (Oxford / New York / Hamburg: Berg Publishers Ltd., 1988).

out of the Dutch economy; and, thirdly, the Dutch employers and those responsible in the Civil Service had to pay all the costs incurred for their own productivity and earning capacity in order to keep Dutch trade and industry up and running. No exception was made to the demands of the New Order.[36]

The Dutch economic historian Hein A.M. Klemann, editor of selected essays addressing the economic impact of the Second World War on Dutch industry entitled *Mooie jaarcijfers... Enige onderzoekenresultaten betreffende de Nederlandse economische ontwikkeling tijdens de Tweede Wereldoorlog* (Good Annual Results... An investigation into Dutch Economic Development during the Second World War), confirms Germany as one of the two most important pre-war trading partners of the Netherlands. Britain was the other. However, anticipating war and wartime shortages, the Dutch government looked to their experiences of the First World War and had taken steps to try to protect the population. Following the 1936 Rhineland crisis *Rijksbureaus* (State Departments) were established under which food and raw materials were stockpiled. The first *Rijksbureau*, for food, came into being in April 1937.[37] While, for the German occupier the existence of such well-organised distribution framework initially offered the prospect of an easy grip over supplies for Germany, for the Dutch it meant that the occupier remained tied into the *Rijksbureau* distribution centres and, therefore, remained under the influence of Dutch organization.[38]

Undoubtedly, as Klemann points out, what the occupation did for the Dutch economy was to re-open the previously isolated German market and as German orders were received the Dutch

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[36] G. Hirschfeld, *Bezetting*, p.256.
[37] H.A.M. Klemann, redactie, *Mooie jaarcijfers: Enige onderzoekenresultaten betreffende de Nederlandse economische ontwikkeling tijdens de Tweede Wereldoorlog*, (Utrecht: Vakgroep Geschiedenis der Universiteit Utrecht, 1997), p.28.
[38] H.A.M. Klemann, *Mooie jaarcijfers*, pp.48-51.

economy benefited. Goering's intention to take from the occupied territories but not to exploit them seemed, in the Netherlands, to be holding true. Initially the 'gains' from the occupied Dutch industrial output could be seen to have filtered through to the workforce. In 1940 unemployment fell by 40,000; in 1941 by 125,000.[39] It would appear, therefore, that the first two years of occupation were an improvement on the pre-war situation. However, by 1942 the prolongation of the war put pressure on German national resources. Acquisition of raw materials for the German war effort became prioritised in occupied territories and this, in turn, meant that the Netherlands encountered severe difficulties. The result was shortages not only for Dutch industry but also for the Dutch population.

In 1942 the task of bolstering Germany's flagging war effort fell to the economic policies of Albert Speer. As with all other occupied territories the Netherlands was intensively exploited. In 1942 Dutch production for Germany reached a new high. Figures from the Dutch Central Bureau of Statistics show percentages at 39% in 1942 but 1943 and 1944 at 54% and 55% respectively. Also, in a series of actions Speer's compulsory work policy took as many men as possible from the occupied territories to Germany to work. In the years 1942 and 1943 between 99,000 and 110,000 men were taken from the Netherlands against their will. In facing resistance Speer took the pragmatic step of agreeing to end forced labour. By leaving workers at home Speer sought to increase productivity for the German war effort. However, by 1944 Germany's fear of leaving available young men for the possible creation of a second front-line prompted *razzia* tactics. These *razzias*, or unexpected raids, had the specific purpose of rounding up males for work in Germany, and, as a result, more fled underground.[40]

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[39] H.A.M. Klemann, *Mooie jaarcijfers*, p.17.
[40] H.A.M.Klemann, *Mooie jaarcijfers,* pp.14-19.

Klemann has expanded on the economic history of the Netherlands with his book *Nederland 1938-1948. Economie en samenleving in jaren van oorlog en bezetting* (The Netherlands 1938-1948. Economy and Society in the Years of War and Occupation).[41] In doing so he brings the wartime experience of Dutch industry directly to the wartime experience of Dutch society, a workforce that needed to earn a living. A point echoing van der Heijden's '*grijs verleden*'.

Consequently, from an initial beginning of seemingly increased prosperity, the economic history of the Netherlands during the Second World War can be seen to end with the Netherlands as an instrument of the German war machine. The initial upsurge in economic life during the first two years of the war led later to national shortages of raw materials, enforced labour and the *hongerwinter* (hunger winter) of 1944-45. Goering's New Order ended with Speer's slave state.

The *hongerwinter* lasted from September 1944 until May 1945. It started when the German occupier denied the transport of food and fuel to the western Netherlands. This was in retaliation to the September 1944 transport strike by the Dutch. The call for the strike had come from the Dutch Government-in-exile, in London. It was an attempt to help the Allies at Arnhem. It was well supported. De Jong puts the number on strike at 'almost 30,000'.[42] However, Arnhem's Operation Market Garden failed and the Dutch strikers were compromised. They could not go back to work. They could not stay at home. They were forced to *onderduik*, to go into hiding. The occupier solved his own transport problems by bringing in railway personnel from Germany but left the Dutch population to flounder. The following winter was one of the most severe the Netherlands had experienced in terms of weather. It was also one of the most severe experienced

[41] H.A.M. Klemann, *Nederland 1938-1948: Economie en samenleving in jaren van oorlog en bezetting*, (Amsterdam: Boom, 2002).
[42] L. de Jong, *Het Koninkrijk*, Vol. 10a, (s'Gravenhage: Martinus Nijhoff, 1980), p.366.

by the people in the western Provinces in terms of food and fuel shortages. Lack of transport meant lack of provision.

Gerard Trienekens in *Tussen ons volk en de honger. De voedselvoorziening 1940-1945* (Between Our Nation and Starvation. Food Provision 1940-1945) addresses the claim that there was a general lack of food for the 8.8 million Dutch population from the beginning of the occupation until the blockade of September 1944.[43] As a forerunner to the expected war he highlights the 1938 *Distributiewet* (Distribution Law), which planned a production and distribution system in order to protect the population at large from wartime shortages. He contends that, during the occupation there was a unity of German and Dutch interests in keeping the Dutch people fed. Food exports to Germany, therefore, remained limited.[44] Nonetheless he does accept that the situation pertaining to the *hongerwinter* needs to be treated separately from the rest of the Dutch wartime experience when, in the face of raging black market prices, women and children walked to the agricultural northern provinces in search of food to take back to their families.[45] Men could not; the occupying forces would have detained them. Ultimately, the extreme hunger of those in the western Provinces was recognised by the Red Cross. Supplies of white bread mix were delivered via Sweden, through the port of Delfzijl in the north. This gesture was the forerunner to the Allied food airdrops of April/May 1945.

De Jong's Volume 10b, *Het laaste jaar II,* (The Last Year II) deals specifically with the events of April/May 1945. From this we learn that Eisenhower spoke, through the BBC and Radio Orange, directly to the Dutch people informing them of the first food drops, which would take place on 28 April. These drops would be made at the airfields of Ypenburg, Delft; Duindigt, The Hague;

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[43] G.M.T. Trienekens, *Tussen ons volk en de honger. De voedselvoorziening, 1940-1945*, (Utrecht: Stichting Matrijs, 1985), Abstract.
[44] G.M.T. Trienekens, *Tussen*, Abstract.
[45] G.M.T. Trienekens, *Tussen*, Chapter 12.

Valkenburg. Leiden; and, Waalhaven, Rotterdam. During these drops the German occupiers had agreed to stand aside. Ground distribution of the food would be organised by the Dutch themselves. De Jong further details the involvement of the 21st Army Group 2nd Tactical Air Force and lists the British contents of the food contained in 'Operation Manna' and their American counterpart, 'Operation Chowhound'.[46] In his book, *Operation Manna / Chowhound. The Allied Food Droppings April / May 1945*, H. Onderwater, offers a wider view of the exactness of these drops and their contents.[47]

At the end of the war de Jong explains the situation at the time of liberation in two ways, firstly from the perspective of the liberated 'land' and secondly from the perspective of the liberated 'people'.[48] He begins by listing the physical damage left by the occupier. He states that, during the liberation process the retreating German military deliberately flooded 8% of the country. Cities and towns along the coast had been destroyed. Half a million land mines had been laid from the coast inward, which coupled with abandoned tanks hampered transport. More than 900 bridges had been blown up. Of the 50 bridges essential to traffic transport only 9 remained and only two railway bridges were still usable. These were the ones that the *Wehrmacht* had needed for their own use up to the point of their capitulation. In Amsterdam and Rotterdam the harbour areas had been destroyed. Moreover, from the 48,000 transport lorries that had existed before the war only about 20,000 remained and all were badly in need of repair. Of the 21,000 canal barges only about 10,000 were left and of the 28,000 railway wagons no more than 4,000 were available. All of which meant that the physical recovery of the country would be very slow, a situation with clear economic repercussions.[49]

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[46] L. de Jong, *Het Koninkrijk*, Deel 10b, (s'Gravenhage: Martinus Nijhoff, 1981), pp.1344-1351.
[47] H. Onderwater, *Operation Manna / Chowhound. The Allied Food Droppings April / May 1945*, (Weesp: Romen Luchtvaart Unieboek, 1985).
[48] L. de Jong, *Het Koninkrijk*, Deel 10b, pp.1440-1449.
[49] L. de Jong, *Het Koninkrijk*, Deel 10b, pp.1440-1443.

For the people of the Netherlands, de Jong says, most were much poorer.[50] Homes had been destroyed or damaged. There were shortages of food and clothes. There was a joy of liberation but it brought with it a dark shadow. A sadness for those families who had been split up not knowing what had happened to each other, and for those who had not survived. There was a 'will' to progress but beside hope for the future there remained an anxiety. Behind faith in the future an uncertainty permeated the population.[51]

In 'The Second World War and Dutch Society', Blom puts forward the premise that usage of the expressions 'before the war' and 'after the war' show the Second World War as a turning point in recent Dutch history.[52] 'Before the war' called to mind solidity, quality and decency but also unemployment, social misery and archaic relations. On the other hand, 'after the war' switched between instability, uncertainty and unrest to material prosperity and greater compassion. However, for Blom, it is not the degree of pre- and post-war change that stands out in post-war Dutch society, it is the degree of continuity. He maintains that life quickly resumed its pre-war *verzuild* pattern, that of denominational segregation. Society, with its four main pillars: Catholic, Christian-Protestant, Liberal and Socialist, reasserted itself. [53]

Carla Tromp depicts the post-war reconstruction of the Netherlands in *Na de oorlog* (After the War). She offers an insight into the time when Dutch society experienced not only the euphoria of liberation but also the economic benefit of high employment, as the people returned to work for the physical rebuilding of their country. Tromp submits that it was a time when freedom, mixed

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[50] L. de Jong, *Het Koninkrijk*, Deel 10b, p.1446.
[51] L. de Jong, *Het Koninkrijk*, Deel 10b, p.1448.
[52] J.C.H. Blom, 'The Second World War and Dutch Society. Continuity and change', Chapter 11 in Duke, A.C. and Tamse, C.A., eds., *War and Society*, Vol. VI, *Britain and the Netherlands*, (The Hague: Martinus Nijhoff, 1977), pp.228-248.
[53] J.C.H. Blom, 'The Second World War and Dutch Society', p.247.

with the excitement of American rock'n'roll music, gave an air of 'moving on', of improvement. However, 1949 saw no end to rationing. It was 1952 before the last rationed item, coffee, became freely available. It was 1953 before the first shopping centre, the *Lijnbaan* in Rotterdam, opened. For many reconstruction took too long, one in five wanted to emigrate.[54]

The Development of Dutch Penicillin 1940-1950. The Role of the Nederlandsche Gist- en Spiritusfabriek, Delft.

In addressing the wartime experience of the Nederlandsche Gist- en Spiritusfabriek in Delft, one source of information is *Bezettingstijd 1940-45* (The Occupation 1940-1945) written by Horst G.O. Boelema.[55] According to Boelema, it was while listening clandestinely to a 1943 BBC transmission that news of the use of penicillin caught the attention of researchers at the Gistfabriek, as NG&SF was locally known. This, coupled with information on the new wonder drug contained in the propaganda newspaper *De Vliegende Hollander*, stimulated action. Until then, Boelema claims, the researchers in Delft had known nothing of the progress made on Fleming's original work by Florey and Chain or of the great strides being made in its production in the United States. Spurred on by the fact that they had the necessary fermentation techniques, NG&SF management decided to begin secret experimentation under the codename Bacinol. At the end of the war, the airlift of food brought with it medicines including American-made penicillin. Comparison with the Delft product showed that they were the same. Both were 50% pure. The name 'Bacinol' was changed to 'penicillin'.[56] Although here it has to be noted that neither de Jong nor Oudewater, as will later be shown, mention the inclusion of medicines or penicillin in their lists of 'food drop' contents.

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[54] C. Tromp, *Na de oorlog*, (Den Haag: Sdu Uitgevers, 1995), p.15-17.
[55] H.G.O. Boelema, *Bezettingstijd 1940-45*, (Delft: Stedelijk Museum Het Prinshof, Mei 1990).
[56] H.G.O. Boelema, *Bezettingstijd*, pp.43-5.

The former Gist-Brocades Director of Research, B. Elema offers an introduction to the history of penicillin at NG&SF in his company-sponsored book *Opkomst, evolutie en betekenis van research gedurende honderd jaren Gistfabriek* and the English translation *The rise, evolution and importance of research during one hundred years 'Gistfabriek'*.[57] Like Boelema, Elema states that the penicillin used as a comparison with Bacinol came with the food drop at Ypenburg (Delft).[58] However, he says little of research with Bacinol or those who did it. In fact Elema allocates only two pages to what happened at NG&SF during the years 1940-45.

The Gist-Brocades company brochure, 'Van Fleming tot Flemoxin Solutab, markante momenten in 60 jaar penicilline' (From Fleming to Flemoxin. Defining Moments in 60 years of Penicillin) published in 1989, begins by describing how news of the new microbiological wonder drug penicillin came to Delft via a 'front page' article contained in the *Vliegende Hollander*.[59] It gives no date as to when this took place. From here, the brochure continues with a description of the work of Louis Pasteur, the founder of modern bacteriology; the 'official' discovery of penicillin in Fleming's 1929 publication; and, the subsequent development of the isolation process by Florey and Chain with their team of workers in Oxford. In relating the wartime experience of the NG&SF with Bacinol, the brochure confirms the influence both of *De Vliegende Hollander* and radio transmissions. It also refers to the influence of Kluyver and Querido. However, although the brochure highlights the research and production of penicillin from secret, wartime laboratory scale to post-war mass market, it gives no indication of those involved in the production of Bacinol or of the post-war effort to bring it to large-scale production.

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[57] B. Elema, Opkomst, evolutie en betekenis van research gedurende honderd jaren Gistfabriek, (Delft: Koninklijke Nederlandsche Gist- en Spiritusfabriek, 1970); B. Elema, The rise, evolution and importance of research during one hundred years "Gistfabriek", (Delft: Koninklijke Nederlandsche Gist- en Spiritusfabriek, 1970).
[58] B. Elema, *Opkomst*, pp.41-44.
[59] Gist-Brocades, 'Van Fleming tot Flemoxin', pages not numbered.

As stated earlier, many of the questions about those involved in the research with penicillin at NG&SF during the war have largely been answered by two publications.[60] However, before their removal to the Delft *Gemeentearchief* (Delft Local Authority Archive), research in the Gist-Brocades Central Archive (GB:CA) brought to the fore additional material covering the experience of the Nederlandsche Gist- en Spiritusfabriek not only during the war period but also in the years shortly afterwards. Added to that, fresh sources in the Research and Development Library of DSM in Delft, where the Research and Development Archives of Gist-Brocades (GB:R&D) are housed, extended the story of NG&SF and its involvement with the production of Dutch penicillin up to 1950. A period about which little has been written.

Another informative source on daily life at the Gist- en Spiritusfabriek, is the company newspaper, *De Fabrieksbode*. A weekly newspaper for the personnel, publication began in 1882. During the occupation publication continued, although both the quality of paper and its length diminished. Eventually, towards the end of the war publication was limited to one small (A4) page and the title reduced to *Mededeling* (Announcement). Shortly after liberation the *Fabrieksbode* returned with an extended issue. On 30 June 1945 the front page celebrated freedom with a portrait of the Queen and a photograph of Princess Juliana with her husband, Prince Bernhard, and their three daughters. The coloured red, white and blue of the Dutch flag was placed under the banner *Vrij*, free.[61]

However, it was not until November 1945 that penicillin was mentioned in the *Fabrieksbode*, and then only as a proclamation of its benefits to modern medicine. The source of information for this article was given as '*Kijk*' ('Look'), a publication from the American Information Department.[62]

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[60] M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin'; M. Burns, J. Bennett and P.W.M. van Dijck, 'Code Name Bacinol'.
[61] *De Fabrieksbode*, No. 1, 30 June 1945, p.1.
[62] *De Fabrieksbode*, 3 November 1945, p.2.

Nonetheless, company publications, such as '1928-1978 Penicillin Changes the World', cite the *Fabrieksbode* as a source of reference on the development of NG&SF penicillin. Consequently, a fuller investigation of the contents of the *Fabrieksbode* is envisaged in order to expand on the members of the Delft team, their research and their production techniques.

Additionally, an examination of the Company's *Jaarverslagen* (Annual Reports) will be undertaken. Available from the year 1912, these Annual Reports containing the Report of the Directors offer a basis for the examination of NG&SF's wartime activities. They also offer an insight into the post- war production of NG&SF and its place in the business world. Bearing in mind that it is claimed that by 1946 the NG&SF was supplying all the penicillin needed by Dutch hospitals; that by 1948 the Gistfabriek supplied all penicillin requirements for the whole of the Netherlands; and, that by 1949 NG&SF began exporting penicillin, eventually to become one of the world's largest producers of penicillin,[63] it seems strange that so little has been recorded of this accomplishment. What, if anything, overshadowed the Delft team's secret wartime achievement with Bacinol as NG&SF sought to market their product?

It was, after all, only shortly after liberation, November 1945, that the recovery of Maria Geene indicated the success of NG&SF's Bacinol. Of importance to the development of penicillin in the Netherlands is a television documentary entitled *De revolutie van het geneesmiddel. 50 jaar Penicilline* (The Revolution in Medicine. 50 years of Penicillin).[64] In this programme, Evert Verschuyl, a surgeon at Delft's Bethel Hospital and NG&SF Company doctor, recounted being part of the medical team to use NG&SF penicillin on the first two patients. His memories add to information on the first clinical application with NG&SF penicillin.

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[63] Gist-Brocades, 'Van Fleming tot Flemoxin Solutab', pages not numbered
[64] Video Recording: *De revolutie van het geneesmiddel. 50 jaar Penicilline,* W. Lindwer, Producer, AVA Productions, Amstelveen, The Netherlands, 1991.

Adding to the above, the remit of this thesis is to re-asses the secret development of NG&SF penicillin under the codename Bacinol during the war years. It is also to introduce the commercial development of NG&SF penicillin at the end of the war. In January 1946 NG&SF inaugurated a new department, Afdeling Antibiotica (Antibiotics Department). What role did this department play in introducing NG&SF penicillin, not only to the contemporary Dutch medical scene, but also to the wider medical world?

In order to do so an examination of available literature regarding the Dutch medical and pharmaceutical industry during the war years will be made. Information on Dutch medicines and their wartime supply is contained in J. Masereeuw in 'De rol van het Nederlandsch Tijdschrift voor Geneeskunde als Verschaffer van Medische Informatie tijdens de Bezetting' (The Role of the Dutch Medical Journal as a Provider of Medical Information during the Occupation).[65] According to Masereeuw, the maintenance of an optimal public health system for citizens under occupation in fact demanded more effort for those involved. In contrast to peacetime, Dutch General Practitioners (GP) were frequently confronted with little known, very varied and sometimes practically insoluble medical problems. It was, therefore, crucially important that the GP or specialist had access to good medical information. In the occupied and isolated Netherlands, whether such information could have been kept to a reasonably acceptable level during the years 1940-45 is questionable.[66]

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[65] J. Masereeuw, 'De Rol van het Nederlandsch Tijdschrift voor Geneeskunde als Verschaffer van Medische Informatie tijdens de Bezetting' in Lieburg, M.J. van en Mijnhardt, W.W., redactie, 'Geneeskunde en Gezondheidszorg in Nederland 1940-45', Themanummer, *Tijdschrift voor de Geschiedenis der Geneeskunde, Wiskunde, Natuurwetenschappen en Techniek, (GEWINA)*, 14, 4, (1991).
[66] J. Masereeuw, 'De Rol', pp.254-255.

The position of the Dutch pharmacists is described by J. Bosman-Jelgersma in 'De Nederlandse Farmacie tijdens de Tweede Wereldoorlog' (Dutch Pharmacy during the Second World War). In particular she illustrates how it became more and more difficult for Dutch pharmacists to perform their duties as the grip of the occupier relentlessly changed daily life.[67] Also, an investigation into the pre- and post-war experiences of the Dutch pharmaceutical industry is explained in the first 1999 issue of *Gewina, Tijdschrift voor de Geschiedenis der Geneeskunde, Natuurwetenschappen, Wiskunde en Techniek,* (*Gewina,* Journal of the Dutch Society for the History of Medicine, Science, Mathematics and Technology). This issue is completely given over to 'Farmacie: Wetenschap, Industrie en Markt' (Pharmacy: Research, Industry and Market) and it is from this issue that a clear explanation of the post-war ideals of the Dutch medical world will be shown.[68]

Further consideration will also be given to the impact of war and occupation on academic life and research. For example, at a recent conference of the Koninklijke Nederlandse Akademie van Wetenschappen (KNAW: Royal Netherlands Academy of Arts and Sciences), Peter Jan Knegtmans considered the academic in war time and asked the question: Who led the academics? Nazification of academics was, as Knegtmans illustrated, an aim of the occupier but contact was seldom directly with the academics. Nazification came through administrative channels. According to Knegtmans, one of the greatest fears of academics under occupation was the loss of intellectual freedom.[69]

The loss of intellectual freedom is highlighted by the removal of Jewish academic staff in September1940. In November 1940, university staffs and students of Delft and Leiden protested

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[67] J. Bosman-Jelgersma, 'De Nederlandse Farmacie tijdens de Tweede Wereldoorlog', in Lieburg, M.J. van en Mijnhardt, W.W., redactie, 'Geneeskunde', pp.210-221.
[68] *Gewina* , 22, 1, (1999).
[69] KNAW, Studiedag 'De KNAW en de Nederlandse wetenschap tussen 1930 en 1960', 2 December 2003.

about this removal and went on strike. Retaliation by the Occupier resulted in the closure of both. Leiden University did not open again until after the war but Delft was given permission to re-open in March 1941.[70] Later *razzia* tactics were employed to swoop on students who were then transported to Germany for forced labour. Ultimately, academic life ground to a standstill and, at the end of the war, the culture of academic research had to be completely rebuilt.

The Kluyver Archive (KA) offers an illustration of the loss of intellectual freedom in Dutch academic institutions during the war years. In 1922, the Director of the Centraalbureau voor Schimmelcultures, Johanna Westerdijk, had agreed to let Kluyver take over its yeast collection. Taken from the CBS in Baarn, it was housed in Kluyver's department at Delft and during its time there the yeast collection, like the Baarn collection, became an international centre for taxonomy. Under Kluyver's leadership, comparisons between various yeast cultures led to one of the subjects for which he is most famous, namely comparative biochemistry. However, the occupation began a period during which the population of his laboratory was steadily reduced. Students and staff were sequestered for work in Germany. Materials needed to keep the laboratory up and running, not only became scarce, but, as the war progressed, completely ran out. Pillaging by the occupier for German needs also took its toll. Contact with other European territories, reduced drastically and, following the entry of the United States in the war in December 1940, contact with countries outside Europe stopped. The exchange of information between academic institutions through journals and library loans, therefore, stagnated.

At the end of the war, G. Alberts points to a change in Dutch society and a change in Dutch academic groups. There was an acknowledged need for the Netherlands to 'catch-up', to make up for the time lost whilst under occupation, but to do so there was also a will to cooperate. This 'will' materialised in the context of a 'Compact' between academic research and the State. While

[70] *Delta*, 14, 28-04-2005, 'Vijf verwarrende jaren. Studeren in Delft tijdens de bezetting', p.17.

there was no longer a 'blind trust' in academic opinion, there was academic inclusion in government reports and advisory groups. The post-war era brought 'Teamwork' and 'Big Science', which, in reality, meant a pact between academics and the civil service. This, in turn, brought public control of scientific knowledge and State involvement. What role this 'Compact' would play in the *wederopbouw* of the Netherlands and the development of penicillin between the years 1945-1950 will be explored through governmental organisations.[71]

For example, archival material from the Rijksinstituut voor Volksgezondheid en Milieu (RIVM: National Institute for Public Health and the Environment) reveals the level of Dutch State involvement in the development of penicillin in the Netherlands at the end of the Second World War. On the other hand, the Kluyver Archive will be used to show the consequences of war for Dutch academic research and the will to move forward, to 'catch up'. Yet, in this reconstruction, the Gist-Brocades Central Archive affords an insight into the difficulties of such cooperation.

At the same time, the extent of Kluyver's influence on those at NG&SF, not only in their wartime development of NG&SF penicillin, but also in their post war academic and industrial reintegration, will be addressed. At the end of the war those at Delft were not young men. In 1945 the advisor Querido was a relatively young 33 years old. Kluyver was 57 and the team leader, F.G. Waller, was 50. Waller's decision to accept the challenges involved in the scaling up and marketing of NG&SF penicillin could not have been taken lightly. At a time of economic crisis, a new department was created and new personnel employed specifically for the development of the new drug, penicillin. What, therefore, motivated NG&SF to enter the new world of large-scale penicillin production? In this decision making process the Kluyver Archive reflects the influence of long-lasting friendships, not only within the Netherlands, but also with those abroad and

[71] KNAW, Studiedag 'De KNAW', 2 December 2003.

especially those in Britain and the United States. What influence these contacts had on the development of NG&SF penicillin, both during and after the war, will be explored.

In conclusion, whereas, there would appear to be more than sufficient sources addressing the history of the Netherlands under Nazi occupation during the Second World War, as de Jong has shown omissions have been made and opinions have changed. In part this is due to the historical perspective taken. While it is acknowledged in Gist-Brocades publications that research and development of penicillin at the Nederlandsche Gist- en Spiritusfabriek did happen under the extreme difficulty of occupation by Nazi Germany, its place in the development of penicillin during the Second World War and afterwards is not generally known. The aim of this thesis, therefore, is not just to 'tell the story' but to give the experience of those involved in the development of penicillin in the Netherlands a wider perspective. Ultimately, what started in Delft during the Second World War took its place on the world stage in 1950 when NG&SF penicillin deservedly and successfully joined the international penicillin market.

Chapter 2

A General History of Penicillin

In his book *Penicillin in Perspective*, David Wilson states the standard version of the penicillin story thus:

> ...penicillin, the first of the antibiotic drugs. First observed by Sir Alexander Fleming in 1928 when he noticed that a stray mould had killed germs on one of his culture plates. Developed by Lord Florey and Professor Sir Ernst Chain at Oxford in 1940. Mass produced by the US pharmaceutical industry, it saved the lives of thousands of Allied servicemen and came into world use after the end of the Second World War.[1]

While no single item of this story is untrue, Wilson submits that the whole adds up to a myth. Beginning with Fleming, Wilson claims that he misinterpreted and misunderstood what he saw on his laboratory plate. He never found what was causing the effect he saw and never showed that 'penicillin' had any therapeutic or curative effect. Initially, according to Wilson, Fleming did not see the antibiotic potential of penicillin. Florey and Chain did successfully develop penicillin into a drug in their Oxford laboratory but this was not what they had set out to do in their original research programme. It had been a purely scientific investigation into the phenomenon of bacterial antagonism. Fleming's observation, reported in scientific literature ten years previously, had been virtually forgotten by 1938. For Florey and Chain, the idea that penicillin might have curative effects in man emerged later in their research and only gradually did the qualities of penicillin begin to dominate their work. Moreover, although mass production did take place in the United States, large-scale production also took place in Britain and Canada. However, for Wilson, the greatest distortion of the truth in the development of penicillin comes simply in the presentation of the penicillin story in a chronological order. While scientists, and most of the rest of us, have been brought up to

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[1] D. Wilson, *Penicillin in Perspective*, (London: Faber & Faber, 1976), p.3.

believe that there is a steady build-up of knowledge and experimentation from the first observation of biological activity until the final product is marketed, this was certainly not the process in the case of penicillin. As Wilson points out, throughout its history penicillin has been marked by the effects of luck, both good and bad, and sheer chance.[2]

In researching the development of penicillin in general, therefore, this Chapter will assess the successful development of penicillin in Britain and the United States both in pre-war peacetime and after the outbreak of the Second World War. Further, it will explain the importance of the large-scale production of penicillin that took place in Canada during the war years. Following this, case studies of unsuccessful penicillin producers, Germany, France and Japan will be examined. Finally, the extent of knowledge about penicillin and its proliferation in Axis, occupied and neutral countries will be revealed through the archive of the Centraalbureau voor Schimmelcultures at Baarn, the Netherlands. In so doing, this Chapter highlights the prime position of those at the CBS, one of the world's best fungal culture collections, and the critical role this would play in the development of penicillin in the Netherlands.

The Development of Penicillin in Britain and the United States: General.

To some extent Wilson's argument is correct. While the term 'penicillin' is now usually used to refer to a particular group of bacterial beta-lactam metabolites, e.g. penicillin G, it was originally introduced to describe the antibacterial principle of a 'mould juice'[3]. In 1928 the 'chance' observation of Alexander Fleming discovered the antibacterial properties of the filtrate from a *Penicillium notatum* culture. For this active principle he coined the name

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[2] D. Wilson, *Penicillin*, pp.4-5.
[3] In modern terms 'fermentation broth'.

Penicillin. However, although Fleming's 1929 publication 'On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to Their Use in the Isolation of *B. influenzae*' came to be regarded as a model for further research,[4] his poor communication skills led his colleagues in the Inoculation Department at St. Mary's Hospital Medical School in Paddington, London, to regard it as a substance of no major importance. Nonetheless, Fleming's awareness of its biological importance is illustrated by the fact that he preserved it and sub-cultured the contaminant for future use. The original Fleming strain of *Penicillium notatum* was designated No. 4222 in the British National Collection of Type Cultures and is preserved in the Lister Institute in London. According to Chester S. Keefer, it is plain to anyone who reads the original paper that Fleming did everything except get a sufficient quantity of penicillin to use it intravenously.[5] Also, as Hobby points out, Fleming did not just observe penicillin in 1928, he discovered it. He named it, described its properties and suggested cautiously that the use of the substance as a laboratory tool might be secondary in importance to its possible use in the treatment of bacterial infections.[6]

Critically, however, for the future development of penicillin, in his publication Fleming also described a further eight unspecified species of *Penicillium*, one of which had cultural characteristics identical to his own isolate and which also produced an inhibitory substance. This indicated that penicillin production by *Penicillium* might not be confined to a single strain and the prospect of isolating similar penicillin producing strains from a random collection of species did exist. Moreover, those strains and species closely related to Fleming's isolate might offer a higher probability of success.[7]

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[4] A. Fleming, 'On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to Their Use in the Isolation of *B. influenzae*', *British Journal of Experimental Pathology*, 10, (1929), pp.226-236.
[5] G. L. Hobby, *Penicillin*, p.12.
[6] G. L. Hobby, *Penicillin*, p.3.
[7] A. Fleming, 'On the Antibacterial Action..., p.227; G. Shama and J. Reinarz, 'Allied Intelligence Reports on Wartime German Penicillin Research and Production' in *Historical Studies in the Physical and Biological Sciences*, 32, 2, (2002), p.355.

In 1932 Harold Raistrick, a leading biochemist at the London School of Hygiene and Tropical Medicine tried but failed to purify the penicillin metabolite. Working with R. Lovell, a bacteriologist, and P.W. Clutterbuck, a young biochemist, Raistrick cultivated the organism in a semi-synthetic medium containing salts and glucose called Czapek-Dox medium. This medium was later used by many others to produce penicillin. However, their publication, 'The Formation from Glucose by Members of the *Penicillium chrysogenum* Series of a Pigment, an Alkali-Soluble Protein and Penicillin – the Antibacterial Substance of Fleming', in the *Biochemical Journal* remained inconclusive.[8] They did succeed in isolating the pigment, *chrysogenum*, which was produced with the antibacterial substance during growth of the fungi and which gave the filtrate its yellow/green colour. They were also able to extract the active substance into ether. However, they were unable to recover it from the ether. During their attempts at extraction most of the activity was lost when they evaporated off the solvent into which the penicillin had been dissolved. As a result of penicillin's apparent instability Raistrick discontinued his study.

In 1935, Roger Reid of Pennsylvania State College in the United States published the results of an extensive survey of fungi he had examined to determine whether any produced Fleming's antibacterial substance. Using Fleming's strain of *Penicillium notatum*, as classified by the mycologist Thom, Reid showed that it could be grown in both veal infusion and synthetic media. He also demonstrated its ability to produce an antibacterial substance

[8] P.W. Clutterbuck, R. Lovell and H. Raistrick, 'The Formation from Glucose by Members of the *Penicillium chrysogenum* Series of a Pigment, an Alkali-Soluble Protein and Penicillin – the Antibacterial Substance of Fleming', *Biochemical Journal*, 26, (1932), p.1907-1918.

and confirmed Fleming's observations on its spectrum of activity. However, Reid too found this antibacterial substance extremely unstable and difficult to separate from the culture fluid.[9]

Although no other publications using Fleming's penicillin appeared, interest in bacterial antagonists continued. As Selman A. Waksman illustrates in his book *My Life with the Microbes,* towards the beginning of 1939 various approaches to the subject of the inter-relationships among micro-organisms in the soil seemed to point to the advisability of undertaking a detailed study of the effects of various micro-organisms upon disease-producing bacteria.[10]

In the United States, Hobby submits that by 1939 extensive studies by Rene Dubos, at the Rockefeller Institute for Medical Research, and Selman A. Waksman, at Rutgers University, had made it clear that many inhibitory substances are produced by micro-organisms in nature that inhibit the growth of other organisms living in association. Of prime importance was the study by Dubos. He is credited with introducing the first antibiotic, called Gramicidin, to be used in the treatment of infections in human beings. At this point Hobby defines an 'antibiotic' as 'a substance produced by a micro-organism and capable of inhibiting growth of certain other micro-organisms'.[11] According to Hobby, the ability of micro-organisms to produce chemicals that could inhibit the growth of other organisms *in vitro* or *in vivo* had been accepted.[12] By 1939 therefore, although penicillin had not been produced in significant quantity or in any degree of purity, many of its biological properties were known and conditions were ripe for further development.[13]

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[9] R.D. Reid, 'Some Properties of a Bacterial-Inhibitory Substance Produced by a Mold', *Journal of Bacteriology*, 29, (1935), pp.215-221; G.L. Hobby, *Penicillin,* p.46.
[10] S.A. Waksman, *My Life with the Microbes*, (London: Robert Hale Ltd., 1958), pp.193-5.
[11] G.L. Hobby, *Penicillin*, p.35.
[12] *In vitro* means in a test tube, *in vivo* means in an animal or a human.
[13] G.L. Hobby, *Penicillin*, p.35.

In the pre-war years, Howard Florey's main interest in Fleming's research was the continuation of research with lysozyme in order to clarify the function of the lymphatic system. In 1935 Florey moved from Sheffield University where he had been Professor of Pathology to become the Sir William Dunn Professor of Pathology at Oxford. In 1938 he and Ernst Chain, his biochemist, secured a grant to study a small group of possible antibacterial compounds. They started with Fleming's penicillin. Their first article, entitled 'Penicillin as a Chemotherapeutic Agent', was published on 24 August 1940 in *Lancet*.[14] Although short, this article reflected a team effort. It reported on the methods that had been devised to extract significant amounts of penicillin from the culture broth and to assay its inhibitory power. It was this extraction method that was the first breakthrough in the further development of penicillin.

This first publication also reported on toxicity testing of penicillin in mice, rats and cats. In addition preliminary studies were conducted into the chemotherapeutic activity in mice experimentally infected with strains of haemolytic streptococci, *Staphylococcus aureus* and *Clostridium septique*.[15] The conclusion drawn was that penicillin, which 'does not appear to be related to any chemotherapeutic substance at present in use', could combat potentially fatal bacterial infections *in vivo*.[16]

On 27 January 1941 the first dose of penicillin was administered parenterally[17] to a human at the Radcliff Infirmary in Oxford. The patient was not suffering from any infection and the

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[14] E. Chain, H.W. Florey, A.D. Gardner, N.G. Heatley, M.A. Jennings, J. Orr-Ewing and G.A. Sanders, 'Penicillin as a Chemotherapeutic Agent.' *Lancet*, 2, (24 August 1940), pp.226-228.
[15] G.L. Hobby, *Penicillin*, p.66.
[16] E. Chain, *et al*, 'Penicillin as a', pp.226-228.
[17] Parenterally means 'not orally'; in humans usually it means injected.

injection was administered only to evaluate the possible toxicity of the preparation. There were no untoward effects.[18]

On 16 August 1941 Florey and his team published a second article on penicillin entitled 'Further Observations on Penicillin' in *Lancet*.[19] This paper contained a detailed description of the conditions required for the production of large amounts of penicillin by their strain of *Penicillium notatum* as well as extracting, purifying and assaying procedures.[20] Further articles followed but it was these two publications that rekindled worldwide interest in the therapeutic potential of Fleming's penicillin nearly eleven years after his initial publication.

The Development of Penicillin in Britain and the United States: The War Years.

At the time of the Oxford publication of August 1940 the United States was not yet at war. This would not happen until December 1941 following the Japanese attack on Pearl Harbor. Before that, however, American interest in penicillin took hold.

According to Hobby, it was within two weeks of the first Oxford team publication on penicillin reaching the United States that she, with Martin Dawson and Karl Meyer, at Columbia University 'naively undertook to make some penicillin'.[21] In order to do so they obtained a subculture of *Penicillium notatum* from Roger Reid who, as stated earlier, had worked on penicillin in the United States in the early 1930s.[22] Hobby, Dawson and Meyer started their research on 23 September 1940 and by October 1940 had confirmed the Oxford results. Hobby claims the first parenteral administration of penicillin took place in the United

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[18] G.L. Hobby, *Penicillin*, p.69.
[19] E.P. Abraham, E. Chain, C.M. Fletcher, A.D. Gardner, N.G. Heatley, A. Jennings, and H.W. Florey, 'Further Observations on Penicillin', *Lancet*, 2, (16 August 1941), pp.177-189.
[20] E.P. Abraham, *et al*, 'Further Observations', pp.177-189.
[21] G.L. Hobby, *Penicillin*, p.72.
[22] G.L. Hobby, *Penicillin*, p.69.

States on 15 October 1940 at Columbia Presbyterian Hospital, New York. The material used was a crude, slightly purified preparation in butyl alcohol. Low toxicity was noted. From January 1941 it was clear that if properly purified and available in sufficient quantity, penicillin could be used parenterally and effectively in the treatment of infections due to susceptible microorganisms. On 5 May 1941 Dawson presented their findings to the American Society for Clinical Investigation and from then on the interest was enormous.[23]

Press reports heralding the 'germ killer ...mold' appeared in both the *Philadelphia Bulletin* and *The New York Times* of 5 and 6 May 1941 respectively. Soon afterwards, commercial companies initiated penicillin research. The work of Hobby, Dawson and Meyer found commercial interest through Chas. Pfizer & Co., as Waksman had with Merck & Co. Inc., and Geoffrey Rake with E.R. Squibb & Sons. Slowly, studies in the United States were set up with a view to the mass production of penicillin. However, according to Hobby, the magnitude of this task only became apparent as time passed.[24]

In the United Kingdom, lack of personnel and the wartime demand for other products severely hampered the British pharmaceutical industry. Florey decided to seek help with the further development of penicillin in the relative safety of America. He took his penicillin-producing fungus to the United States in July 1941. His travelling companion, Norman Heatley, had been responsible for the methodology that allowed the production of penicillin in large enough quantities for Florey to initiate the Oxford clinical trials. Florey's stated reason for this trip was 'to explain to American scientists the experience of the Oxford Laboratory in the production of penicillin'.[25] They first went to the Rockefeller Institute. This Institute had part-funded Florey's research in Oxford and it also provided financial support for the trip. Due

[23] G.L. Hobby, *Penicillin*, pp.72-73.
[24] G.L. Hobby, *Penicillin*, p.79.
[25] G.L. Hobby, *Penicillin*, p.80.

mainly to Florey's friendship with John F. Fulton of Yale University Medical School, who had attended Magdalen in Oxford at the same time as Florey, within four days Florey and Heatley's course of action had been mapped out and introductions made.[26] Their purpose in coming to the United States was not only to 'explain' to the American medical and academic fraternity, it was also to interest the US pharmaceutical industry in the large-scale production of penicillin.

This they did through Ross G. Harrison, Chairman of the National Research Council, and Charles Thom, who had long been involved in studying *Penicillium.*[27] Thom took Florey and Heatley to meet Percy A. Wells, Assistant Chief of the Bureau of Agricultural and Industrial Chemistry. Wells was temporarily in charge of four regional research laboratories, one of which, the Northern Regional Research Laboratory at Peoria, Illinois, had a special pilot scale, shallow-pan, aluminium fermenter. A meeting was arranged between Florey, Heatley and Robert Coghill of the NRRL Fermentation Division. From this meeting Coghill's staff started work on penicillin. It was to continue for the next four years. Hobby maintains that it during this time that most, if not all, of the major biological contributions to the large-scale production of penicillin were made.[28]

From mid-1941 reports on penicillin began to appear in both the British and American press. For example, in the United States, *Time* magazine published an article entitled 'Mold for Infections' on 15 September 1941.[29] In Britain, *The Times* published three articles focusing on penicillin in 1942.[30] The first, on 27 August was a report of 'recent' discussion in the *Lancet*

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[26] G.L. Hobby, *Penicillin*, pp.80-83.
[27] C. Thom, 'Mycology Presents Penicillin', *Mycologia* 37, 4, (August 1945), pp.460-475.
[28] G.L. Hobby, *Penicillin*, p.90.
[29] *Time*, 15 September 1941, pp.55-56. Source: Website www Health, Medicine and American Culture, 1930-1960. Primary Source Bibliography, 04/09/03.
[30] *The Times*, 'Penicillium', 27 August 1942; 'Penicillin', Letter to the Editor, 31 August 1942; 'Penicillin' Letter to the Editor, 2 September 1943. Source: www infotrac.galegrouyp.com 02/05.2004.

on *Penicillium notatum*; the second was a letter from Almoth Wright, the Head of Fleming's department, naming Fleming as the discoverer of 'penicillin'; and, the third, from R. Robinson of Oxford University, pointing to the work of Florey and his team of collaborators. In December of the same year the Coconut Grove fire in Boston resulted in Boston Press reports of patients being treated with Merck penicillin.[31] A further two *Time* articles, entitled 'Penicillin' and 'Rush on Penicillin', were published on 8 February 1943 and 30 August 1943 respectively.[32] On 28 August 1943, *The Times* reported 'No Penicillin for the Public: Fighting Services First',[33] and on 30 August 1943, *Newsweek* declared 'Public vies with army for penicillin, miracle drug that comes from mold'.[34] This latter article reported on the first use of penicillin in the battlefield during the North Africa military campaign of 1943. It illustrated penicillin's ability to cure soldiers not only of wound infections but also syphilis and other grave bacterial infections. In both Britain and the United States propaganda from the battlefield stated 'Thanks to Penicillin ... He Will Come Home'.[35]

Publications on the clinical use of penicillin from the North African battlefield also began to appear in British and American medical journals. For example, in the United States, J.E. Sheehan published 'Burns as War Wounds' in September 1943,[36] while, in Britain, R.J.V. Pulvertaft published 'Local Therapy of War Wounds. I. With Penicillin' in *Lancet*.[37] Florey and Brigadier Hugh Cairns collated the whole North Africa experience in a report entitled 'A Preliminary Report to the War Office and the Medical Research Council on Investigations

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[31] M. Burns, J. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', pp.25-31.
[32] *Time*, 8 February 1943, p.41; *Time*, 30 August 1943, pp.44-46. Source: Website, Health, Medicine and American Culture, 1930-1960. 04/09/03.
[33] *The Times*, 'No Penicillin for the Public: Fighting Services First', 28 August 1943. Source: www infotrac.galegrouyp.com 02/05.2004.
[34] *Newsweek*, 30 August 1943, pp.68-70. Source: Website, Health, Medicine and American Culture, 1930-1960. 04/09/03.
[35] Source: Website, Health, Medicine and American Culture, 1930-1960, 04/09/03.
[36] J.E. Sheehan, 'Burns as War Wounds', *American Journal of Surgery*, 61, (September 1943), pp.331-338.
[37] R.J.V. Pulvertaft, 'Local Therapy of War Wounds. I. With penicillin', *Lancet*, 2, (18 September 1943), pp.341-346, and *Lancet* 2, (25 September 1943), pp.379-384.

Concerning the Use of Penicillin in War Wounds'. The Report went to the British War Office and the Medical Research Council, however, an abstract entitled 'Penicillin in War Wounds' appeared in the *Lancet* in December 1943.[38] Another publication, 'The Treatment of War Wounds with Penicillin', by P. Garrod, appeared in December 1943 in the *British Medical Journal*.[39] The high level of academic interest in the medical properties of penicillin is further illustrated by the fact that between November 1943 and January 1944 Florey's publication, 'Discussion on Penicillin', appeared not only in the *British Medical Journal*, but also in *Lancet*, the *Proceedings of the Royal Society* and the *Journal of the American Medical Association*.[40] All of the above serve to illustrate the important role allocated to penicillin as a vital factor in the war effort. Its use in front-line military hospitals ensured the rapid healing of wounds and the subsequent quick return of military personnel to their fighting units. The benefit to the Allied armies, as Montgomery pointed out, was enormous. Added to that, these articles clearly illustrate the volume of information being published on the clinical properties of penicillin in Britain and America by the end of 1943.[41]

Penicillin Production in Britain and the United States 1940-1945.

According to Ingrid Pieroth, there was an enormous build up of penicillin facilities in the United States between 1941 and the end of the war. In 1941, even though the United States was not yet in the war, the hope was to obtain a medicine that could effectively treat infected war casualties.[42] Accordingly, a consortium of government laboratories and private

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[38] H. Florey and H.C. Cairns, 'Penicillin in War Wounds. An Abstract of a Preliminary Report to the British War Office and the Medical Research Council on Investigations Concerning the Use of Penicillin in War Wounds', *Lancet*, 2, (11 December 1943), pp.742-745.
[39] P. Garrod, 'The Treatment of War Wounds with Penicillin', *British Medical Journal*, 2, (11 December 1943), pp.755-756.
[40] H. Florey, 'Discussion on Penicillin', *British Medical Journal*, 2, (20 November 1943), pp.654-656, (in *Society Proceedings*); *Lancet*, 2, (November 1943); *Proceedings of the Royal Society of Medicine*, (January 1944); *Journal of the American Medical Association*, 124, (8 January 1944).
[41] Source: Merck Co. Inc., *Annotated Bibliography of Penicillin. Merck*, Company Publication 1945, pp.151-158; KA, Penicillin Reprints Box.
[42] I. Pieroth, 'Penicillin', p29.

pharmaceutical companies were charged with developing methods for a massive scale-up of penicillin production. Ultimately, microbiologists at the NRRL found that many strains of *Penicillium chrysogenum* were better penicillin producers than Fleming's *Penicillium notatum*. In particular, one strain of *Penicillium chrysogenum*, NRRL 1951, not only produced high yields, but was able to do so in submerged culture. Large fermenters were built for growing this and by 1944 a deep fermentation technique was operating, which produced enough penicillin to supply all the needs of the Allied armed forces.[43]

Whilst Pieroth's account is not incorrect it does miss some finer points. For example, in her account of the British wartime development of penicillin, Hobby describes Florey's experience.[44] In order to obtain greater quantities of penicillin he had turned the problem of large-scale production over to the United States. However, after the Japanese attack on Pearl Harbor of 7 December 1941 America entered the war. All Florey could then do was wait. At Oxford, he and his team continued their work and the small but significant amounts of penicillin they produced proved enough to keep their research going.

In March 1941, at the behest of the Ministry of Supply, the Therapeutic Research Corporation of Great Britain was formed. Five companies agreed to organise and pool their research with penicillin. To begin with these were Boots, British Drug Houses Ltd., Burroughs Wellcome Ltd and May and Baker Ltd. Imperial Chemical Industries officially joined the group in 1942, although it had in fact been working with Florey and Heatley in their research on the extraction of penicillin since June 1941. In March 1943 the British Medical Research Council took over the clinical studies on penicillin.[45] By early 1943 the British pharmaceutical

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[43] I. Pieroth, 'Penicillin', pp.29-30.
[44] G.L. Hobby, *Penicillin*, p.115.
[45] G.L. Hobby, *Penicillin*, pp.126-129.

industry was producing penicillin in amounts that permitted the undertaking of clinical trials. These were the trials that took place during the 1943 North African military campaign.

However, in 1943 it became evident that penicillin would be needed by the military in quantities far greater than originally expected. Following the success of Florey and Cairns' battlefront trials, the rapid healing of wounds and subsequent quicker return of troops to the front meant that penicillin evolved into a battlefield requirement. For example, when Prime Minister Churchill was asked if the use of penicillin should be restricted to war wounds or also used to cure soldiers with venereal disease his reply was simply that it should be used to the best possible military advantage.[46] Penicillin production had become critical to the Allied cause.

Research into the development of penicillin in the United States was also boosted by government action. Between 1941 and 1945 the production of penicillin and its clinical evaluation fell under the Office of Scientific Research and Development and the War Production Board. According to Hobby, these government institutions had been planned and set up when it became clear that Great Britain and the United States would be drawn into a war. However, like Britain, until July 1943 virtually all the penicillin used for clinical purposes in the United States was made by only five companies: Merck & Co., E.R. Squibb & Sons, Chas. Pfizer & Co., Winthrop Laboratories and Abbott Laboratories.[47]

In 1943, the War Production Board assumed full responsibility for the production of American penicillin. A goal of 200 billion units of penicillin per month was set as the target - two years earlier Florey had asked for 10,000 litres of culture fluid from the US

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[46] Personal Communication K. Brown February 2002.
[47] G.L. Hobby, *Penicillin*, p.171.

pharmaceutical industry, the equivalent of 5 million units or less. The jump was enormous. More than 175 companies were investigated to determine their ability to produce penicillin in the quantities needed. Twenty-two were selected, and, as a result of this concerted wartime effort, the stage was set in the United States for the mass production of penicillin.[48]

The experience of Allied research in the development of penicillin during the war years is aptly described in the Merck booklet of 1943.[49] This publication confirms that it was the 1940 publication of Florey and the Oxford group that stimulated clinical interest in penicillin in the United States. After the Japanese attack on Pearl Harbor, wartime conditions added the element of urgency to the therapeutic possibilities of penicillin and the decision to produce penicillin.

However, the difficulties of producing even limited quantities of the new drug made it imperative that all supplies were controlled rigidly. Publications were devoted only to such investigations that appeared most likely to contribute materially to the knowledge of its use. For this reason, the Committee on Medical Research of the Office of Scientific Research and Development appointed the Chairman of the Committee on Chemotherapeutic and Other Agents to supervise the distribution of all stocks of penicillin available for clinical research. Under this arrangement clinical investigation with penicillin was conducted on a relatively wide scale, and the collective results were collated and summarised. In July 1943 the War Production Board restricted the sale of penicillin.[50]

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[48] G.L. Hobby, *Penicillin*, p.172.
[49] Merck & Co., *Bibliography of Penicillin Merck. Its Action and Uses*, Merck 1943; Source: KA, Penicillin Reprint Box.
[50] *Journal of American Medical Association*, 122, (17 July, 1943), p.816: Source: Merck & Co. Inc., *Annotated Bibliography of Penicillin Merck*, 1943, Item No. 99.

In describing his experience of early American penicillin production Robert D. Coghill of the NRRL Fermentation Division addressed the Annual Meeting of the American Chemical Society at Cleveland, Ohio, on 5 April 1944 thus:

> Seldom within our memory has any topic so taken the interest of the scientific and lay worlds as has penicillin. For the past two years or more it has played Cinderella to the mycologists, chemists, and engineers of the whole English-speaking world. Product of the humble molds, which until comparatively recent years have been something to control rather than cultivate, it has miraculously been clothed with the raiments of $20,000,000 worth of plants, is now attended upon by hundreds of footmen, and the party is proceeding with fanfare galore. Penicillin is very patently taking the limelight from its older sulfa sisters.[51]

In his paper Coghill spoke on behalf of the hundreds of people who had made the development of penicillin possible. In his estimation, it was the NRRL discovery of the action of corn steep liquor that was possibly the greatest single factor in making the commercial production of penicillin feasible. He continued:

> Originally begun in an attempt to increase yields and investigate the feasibility of producing penicillin in submerged culture, it has been expanded to include studies of recovery methods, purification, chemistry, and an intensive search for new organisms... (However)... The numerous reports on this work have been classified as "Restricted" and can be obtained only from Dr Richards, Chairman, (of the) Committee on Medical Research.[52]

Yet, as yields increased and more clinical data began to accumulate Coghill acknowledged that the results reached could not have been obtained had the work been done independently in a number of centres. In his address he concluded:

> The whole penicillin development has been a monumental undertaking. Its success has been due to the persistence and determination of government and industrial research workers, the vision and drive of our pharmaceutical and chemical manufacturers, and the whole-hearted backing of the Army, Navy, and War Production Board. ...We at the Northern Regional Research Laboratory are very conscious of the privilege it has been to play our part in what may well turn out to be one of the outstanding developments of the war.[53]

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[51] R.D. Coghill, 'The Background of Penicillin Production. Penicillin – Science's Cinderella', *Chemical and Engineering News*, 22, (1944), pp.588-593; Source: KA, Penicillin Reprint Box, Reprint pp.1-14.
[52] R.D. Coghill, 'The Background', KA Reprint, p.4.
[53] R.D. Coghill, 'The Background', KA Reprint, p.14.

Almost sixty years later, Kevin Brown continued to highlight the success of this teamwork in the development of penicillin. He also highlighted the importance of the 'transatlantic cooperation' and the sharing of information that had taken place between Britain and the United States.[54]

The Development of Penicillin in Canada.

On 10 September 1939 the Canadian Parliament unanimously decided to join the 'united strength and power of the British Dominions' and entered the Second World War.[55] However, as David Wilson has pointed out, little acknowledgement is given to the role Canada played in the successful wartime production of penicillin.[56] That Canada played a pivotal role in the wartime production of penicillin is illustrated by Ronald Hare, in his book *The Birth of Penicillin and the Disarming of Microbes*.[57] A former colleague of Fleming at St. Mary's in London, Hare had taken a post at the Connaught Laboratories in Toronto in August 1936. The Connaught was nominally part of the University of Toronto but for all practical purposes it was a separate, independent, institution. He had been asked to study the newly discovered influenza virus and as a result saw little of the early anti-bacterial developments. He recalled that in September 1940 he 'was brought up with a jolt' when he came across the Chain led publication.[58] He described it as 'one of the most astonishing papers I have ever read'. It reported that methods for the purification and preservation of penicillin had been found. Also, sufficient penicillin had been produced to demonstrate that it was not only harmless but could protect mice against infection by haemolytic streptococci, staphylococci and one of the species that cause gas gangrene, *Clostridium septique*. The product was then freeze dried.

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[54] K. Brown, Lecture, 2001.
[55] *Legion Magazine* : The Decision to Enter WWII – Part 1. September / October 1995. Source: www legionmagazine.com 17/06/05.
[56] D. Wilson, *Penicillin*, pp.3-5.
[57] R. Hare, *The Birth of Penicillin and the Disarming of Microbes*, (London: George Allen and Unwin Ltd., 1970).
[58] E. Chain, *et al*, 'Penicillin as a', pp.226-228.

'And it was this that had really saved the day. For, once dried and in a vacuum, it was stable.'[59]

By the time this news reached Toronto, the Battle of Britain was reaching its climax. There was a fear that Britain would fall. Hare goes on to recall a meeting with Florey, Heatley and R.D. Defries, the Director of the Connaught Laboratories, in August 1941. According to Hare, during the meeting Florey told how the Oxford team had succeeded in producing 'mould juice'[60] in porcelain containers and how Chain had purified sufficient for the treatment of six patients with staphylococcal infections. Two of the patients had died but only because they had run out of penicillin. The paper describing this work had been published that August in *Lancet* but the journal had not yet reached Toronto. Fortunately, Florey had brought a typed copy. The main purpose of Florey's visit was to persuade the Connaught Laboratories to make penicillin in quantity, as it was impossible to do so in war-torn Britain.

When it was ascertained exactly what Florey meant, the problems for the Connaught became formidable. Rooms large enough to grow the fungus would be required but the method of purification seemed difficult to adapt for large-scale production and the Connaught chemists were against the growth of fungus in some kind of container. They thought that a chemical synthesis could not be far off. Added to that, it seemed an unnecessary duplication of the investigations into large-scale production already taking place in the United States. Accordingly, Florey was told that the Connaught Laboratories could not undertake the assignment.[61]

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[59] R. Hare, *The Birth*, p.169.
[60] 'Mould juice' is Fermentation broth.
[61] R. Hare, *The Birth*, p.173.

Hare, underscores Florey's hope that, for further trials in Oxford some penicillin would come from the United States. However, following the entry of the United States into the Second World War in December 1941, these supplies were denied them. According to Hare, it was Florey's visit to a military field hospital in Africa in 1943, which amply demonstrated that provided enough penicillin could be instilled into a wound it could be closed soon after infliction. Because of this, severe infection could be prevented from developing. Ultimately, it was this 'need' of the allied war-wounded which brought the Connaught Laboratories back into penicillin production.[62]

Hare was put in charge of penicillin production at Connaught and Philip Greey, a bacteriologist, began to produce as much fermentation broth as his facilities permitted. F.S. Macdonald, a chemist, developed a method of extraction based on that of Chain. Early in 1943, Hare visited the NRRL at Peoria where the advantages of using corn steep liquor to enhance the 'mash' were explained.[63]

With Greey and Macdonald, Hare was asked to make 50,000,000 units of penicillin a day and to have stocks ready for D-Day, which they were told would be some time in the summer of 1944. In order to do so they needed greater space. This was solved in September 1943 with the acquisition of an old seminary building known as Old Knox College. Most rooms were converted into incubators in which the fungi were grown. The internal temperature had to be kept at exactly 75.5°F (24°C). In order to ensure this, the windows were blacked out to exclude any effect of the sun. An enormous air-conditioning plant was established in the basement, with yards of air ducts going to each room.

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[62] R. Hare, *The Birth*, p.174.
[63] R. Hare, *The Birth*, pp.174-185.

Procuring apparatus was a complicated operation. Everything was in short supply and many essentials governed by priority. To facilitate production, all Canadian and American factory supplies were given top priority and placed under the order of Washington. Ultimately, Canadian penicillin was grown in bottles about the same size as milk-bottles but with longer sides and more rounded shoulders. There were 250,000 of them stored under the stands of the University football ground. Every 24 hours, 30,000 were put in the incubation racks, lying on their sides. They contained 150cc (5 ounces) of broth on which the penicillin could grow. At the end of incubation they were moved to the emptying tank, emptied, washed, filled with new medium, plugged with wool, sterilised, cooled, inoculated with spores, taken back to the incubator room and piled on the racks to undergo the cycle again. Extraction of the penicillin from the broth was no longer a difficulty but, for stability, the resulting product had to be freeze-dried.

In order to achieve freeze-drying, four enormous stainless steel milk separators, many electric motors and pumps and twenty tons of refrigeration was necessary. At the same time, wartime pressure brought recruitment problems as nearly 100 workers had to be trained to operate the site 24 hours a day 7 days a week. On 26 April 1944, six months from the move into Old Knox College, the first penicillin from the Connaught Laboratories came off the production line – 20,000,000 units in about a litre of fluid. Unfortunately it smelt strongly of goats because of traces of the caprylic alcohol the chemists had used to prevent frothing. It had to be re-processed. Subsequent batches were less 'goaty' and on 20 May 1944 the Government of Canada accepted the first vials of dirty-yellow powder containing penicillin. They had been delivered in time for the allied, June, D-Day landings.[64]

[64] R. Hare, *The Birth*, pp.174-185.

The Development of Penicillin in Germany.

In order to better understand what transpired in Germany between 1928, when penicillin was discovered, and 1946, when it became available for widespread clinical use via the United States and Britain, Hobby submits that an understanding of the scientific climate of that period is necessary. For example, in 1935 Gerhard Domagk, Director of the Institute of Experimental Pathology, part of the large research complex of IG Farben at Elberfeld, Germany, published the results of studies which had been carried out in 1932. These showed the remarkable therapeutic effectiveness of the first synthesised sulphonamide, Prontosil (from *Prontosil rubrum*), against haemolytic streptococcal infections.[65] Pieroth shows that, by 1936 the sulphonamides had become accepted throughout the medical world for the treatment of bacterial infections. However, the sulphonamides were not only successful chemotherapeutic agents, they were also very profitable for the German companies that produced them. According to Pieroth, it was this profitability that brought the lack of early German interest in penicillin. Penicillin was not seen as representative of a new class of chemotherapeutic drugs that could compete with the sulphonamides.[66]

Reporting on his research in the 1942 Annual Report of IG Farben at Elberfeld, Domagk wrote in an amendment, 'We ... took up work on the isolation of inhibitors produced by fungus, to determine if these substances could become of importance against sulphonamides in the treatment of bacterial infection'[67]. His original aim, therefore, was only to compare fungal inhibitors with sulphonamides. Isolation of penicillin type substances in large quantities was, at that time, not Domagk's primary concern. This decision was to prove a costly mistake, not only for IG Farben but also for Germany.

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[65] G.L. Hobby, *Penicillin*, p.xviii.
[66] I. Pieroth, 'Penicillin', p.33.
[67] I. Pieroth,'Penicillin', p.35.

On the other hand, given IG Farben's interest in chemotherapeutic agents, it was to be expected that the wartime production of penicillin in Britain and the United States would arouse interest among research scientists in Germany. Pieroth's explanation for the lack of penicillin research in Germany is that German pharmaceutical companies only had small penicillin research groups. The *Reich* did not become interested in the industrial production of penicillin until the military campaigns of 1943. In October 1944 a conference on penicillin did take place at Potsdam-Babelsberg in Berlin, under Professor Rostock, the Commissioner for Health. In attendance were representatives from industry and those universities that had started work on penicillin. Industrial companies in attendance included IG Farben Elberfeld and Hoechst, Merck in Darmstadt, Knoll in Ludwigshaven and Schering in Berlin. Two other institutions of importance were the bacteriological laboratory of the glass factory, Schott & Genossen in Jena and the Four Year Plan Institute in Prague. However, no German governmental support for the production of penicillin was given.[68] According to Gilbert Shama and Jonathan Reinarz, this was because by 1944 raw materials in Germany were scarce or could not be obtained. There was no yeast, no acids, no supplies or materials – it was all over.[69] German interest in the wartime production of penicillin, limited as it was, quite simply came too late.

To an extent Shama and Reinarz agree with Pieroth that a lack of urgency and central organisation thwarted German progress with penicillin.[70] However, they put forward the premise that there was German interest in penicillin from as early as April 1941. Moreover that, after the first publication of the Oxford team, Florey was concerned about possible German interest in reproducing his work. Only after accepting the opinion of Sir Edward Mellanby, Chairman of the Medical Research Council, that his fears were unfounded did

[68] I. Pieroth,'Penicillin', pp.33-36.
[69] G. Shama and J. Reinarz, 'Allied Intelligence', p.347.
[70] G. Shama and J. Reinarz, 'Allied Intelligence', p.347-348.

Florey proceed with the second Oxford publication.[71] They further contend that although wartime restrictions did prevent Florey's *Lancet* articles reaching Germany through the normal channels, they probably entered Germany through Sweden. Nonetheless, according to Shama and Reinarz, industrial, academic and *Reich* research with penicillin remained hampered through 'duplication of effort, petty squabbles over the ownership of particularly prized pieces of information, and the usual rivalries between various branches of the armed forces'.[72] Unlike Coghill's experience in the United States, therefore, in Germany there was no concerted effort or sharing of information.

As the base for German interest in penicillin, Shama and Reinarz highlight a German academic publication which referred to 'therapeutically active substances from fungi'. Published in *Klinische Wochenschrift* (Clinical Weekly) of 17 April 1943, it originated from the *Arbeitsgemeinschaft* (Work Group) of Kiel University. The authors are Josef Vonkennel, Josef Kimmig and Andreas Lembke and it is entitled 'Die Mycoine, eine Neue Gruppe Therapeutisch Wirksamer Substanzen aus Pilzen', (The Mycoines, a New Group of Therapeutically Active Substances from Fungi).[73] Reminiscent of Fleming's 1929 publication on penicillin, which had suggested that penicillin production might not be confined to a single strain, this article proposed the term 'mycoines' as a group name for the penicillin-like antibacterial agents produced by many kinds of fungi.[74] The sources referred to by Vonkennel *et al* in their publication illustrate the influence of Fleming, 1929; Raistrick, 1932; and, the Oxford publication by Abraham, *et al*, of 16 August 1941. Far from reflecting Pieroth's perceived lack of interest in penicillin in Germany in favour of sulphonamides, from this evidence an ongoing wartime interest in penicillin research in Germany can be detected.

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[71] G. Shama and J.Reinarz, 'Allied Intelligence', p.348.
[72] G. Shama and J.Reinarz, 'Allied Intelligence', p.352
[73] J. Vonkennel, J. Kimmig und A. Lembke, 'Die Mycoine, eine Neue Gruppe Therapeutisch Wirksamer Substanzen aus Pilzen', *Klinische Wochenschrift*, 22, 16-17, (17 April 1943), p.321.
[74] A. Fleming, 'On the Antibacterial Action', p.227; G. Shama and J. Reinarz, 'Allied Intelligence', p.356.

Also, Shama's later claim that the publication by Vonkennel, Kimmig and Lembke 'is possibly the only article on antibiotics published in Germany during the war',[75] ignores the publications of Th. Wagner-Jauregg, 'Die Neueren Biochemischen Erkentnisse und Probleme der Chemotherapie' (The New Biochemical Discoveries and Problems of Chemotherapy) of 16 July 1943,[76] and that of Manfred Kiese of 7 August 1943, 'Chemotherapie mit Antibakteriellen Stoffen aus Niederen Pilzen und Bakterien' (Chemotherapy with Antibacterial Substances from Moulds and Bacteria).[77] As will be shown, these publications played an influential role in the development of penicillin in the Netherlands.

In particular, a point missed by Shama is highlighted by the August 1943 publication of Kiese, Professor of the Pharmacological Laboratory in the University of Berlin. This publication affords an insight into the amount of information on penicillin research available in wartime Germany. For example, Kiese gave detailed descriptions of penicillin production, its chemistry, activity, pharmacology and clinical effects. He listed sixty-one references, which illustrate a wide variety of, not only German, but also French, British and American publications. They include medical, biological and chemical engineering sources and contain Fleming's first publication of 1929 and another of 1942; Raistrick's British publication of 1932 followed by German journal publications in 1938 and 1942; Dubos, 1939; Waksman 1940 and 1941; Vonkennel, Kimmig and Lembke, 1943; and Oxford group publications of 1940, 1941, 1942 and 1943. Under severe wartime restrictions the availability of foreign publications available to Kiese is nothing less than striking.

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[75] G. Shama, '*Pilzkrieg*: the German Wartime Quest for Penicillin', *Microbiology Today*, 30, (Aug 2003), pp.120-123.

[76] Th. Wagner-Jauregg , 'Die Neueren Biochemischen Erkentnisse und Probleme der Chemotherapie', *die Naturwissenschaften*, 31, (16 July 1943), pp.335-344.

[77] M. Kiese, 'Chemotherapie mit Antibakteriellen Stoffen aus Niederen Pilzen und Bakterien', *Klinische Wochenschrift*, 22, 32-33, (7 August 1943), pp.505-511.

Furthermore, Shama claims that the first contact from IG Farben at Hoechst specifically requesting a strain of *Penicillium notatum* from the Dutch Centraalbureau voor Schimmelcultures in Baarn was on 28 September 1942.[78] However, the CBS archive illustrates an earlier IG Farben Hoechst interest in *Penicillium notatum*. Replying to a request from Hoechst, Pharm-Weis Laboratorium, Frankfurt/Main-Hoechst on 10 June 1942 the CBS stated that a culture of *Penicillium notatum* was not to hand but they hoped a new culture would arrive soon. As soon as one was available it would be sent on.[79] The strain was forwarded on 17 September 1942.

At the time the CBS archive shows Hoechst was not alone in its quest for *Penicillium notatum*. On 17 September 1942 a strain of *Penicillium notatum* was forwarded to the pharmaceutical companies Hoffman-La Roche, Basel, Switzerland; Noury & v.d. Lande, Deventer, the Netherlands; Alfred Benzon, Copenhagen, Denmark, and, IG Farben Werk Wuppertal-Elberfeld. The accompanying correspondence to IG Farben Elberfeld stated that they, the CBS, knew nothing about other fungal cultures that could produce penicillin.[80]

The fact that two divisions of IG Farben, Hoechst and Elberfeld, applied separately to CBS for a strain of *Penicillium notatum* and information on other fungal cultures reflects the lack of coordinated effort on early penicillin research in Germany. In the end, large-scale production of penicillin did come to Germany but it came post-war, under licence and with the assistance of the Allied authorities.[81]

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[78] G. Shama, '*Pilzkrieg*', pp.120-123.
[79] CBS Archive, 1942, Correspondence File, No. 126.
[80] CBS Archive, 1942, Correspondence File, Nos. 192; 317; 11; 135.
[81] I. Pieroth, 'Penicillin', p.38-41.

An official military request helps explain the position of penicillin research and development in Germany at the end of the war. From the British Zone of Occupation, Colonel B.K. Blount wrote to the American Society of Bacteriologists in October 1946. He wrote on behalf of German scientists who 'are desperately anxious to find out what has been going on in their own field during the past six years'. In order that they could, Blount appealed for reprints. He stated that while 'at present it is not possible to send reprints, books or journals directly to individuals in the British Zone' they could be forwarded through him if the name of the German scientist or Institution for whom they were intended was written on the packet. He pointed out that de-nazification of universities and institutes in the British Zone had been carried through and it was the non- or anti- Nazi scientists who were suffering from the 'present' conditions. In particular he mentioned as specific cases the Microbiologische Institute at Gottingen and the Bacterialogische Institute at Kiel, who 'would greatly appreciate reprints on microbiological substances notably those dealing with growth factors, bioassay methods, milk bacteriology, penicillin and other antibiotic agents'.[82]

The Development of Penicillin in France.

The position of penicillin development in Occupied France, like Germany, further serves to highlight the acquisition and dissemination of information on the research and production of penicillin during the war years. According to Andre Maurois, during the war news on penicillin reached France by way of Spain and the Netherlands. The Spanish connection, Maurois contends, happened in 1942 when the French academic, H. Penau, went to a conference in Madrid. At this conference a Spanish colleague gave Penau a copy of the *British Medical Journal* that contained an article on the extraordinary cures achieved by penicillin. He also gave Penau a culture of the mould. Maurois states that a second culture of

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[82] KA, Catalogue Number 1990263, Folder not numbered, Report on 1946 Meeting of American Society for Bacteriologists.

a penicillin producing mould came to Penau through the Centraalbureau voor Schimmelcultures in Baarn, the Netherlands, although he gives no date for this.[83] As will later be shown, Penau was sent a sub-culture of *Penicillium notatum* from the CBS in September 1943. He also visited the CBS in December 1943.[84]

An article published during the war by Penau, with others, affords an overview of the journals and articles on penicillin research available to French researchers. For example, in June 1943 Penau published with C. Levaditi, R. Perault and L. Erichsen on 'Sur un Principe Staphylolytique Élaboré par une Variété de Penicillium, (Penicillium *notatum**)' (A Treatise on an Anti-staphyloccocal Substance Produced by a Strain of Penicillium (Penicillium *notatum**)).[85] The first footnote contains three references. Two refer to British publications of Abraham and Chain in *Nature* 1940 and Abraham *et al* in *Lancet* of 16 August 1941. The third is the German publication of Vonkennel, Kimmig and Lembke in *Klinische Wochenschrift*, April 1943. This latter has been shown to play a significant role in the dissemination of information on penicillin in Germany.[86]

In December 1943, Penau published another article with F. Hagemann entitled 'Essais d'Extraction d'une Bactèricide d'Origine Fungique' (Attempts to Extract a Bacterial Substance of Fungal Origin), in which they state that their research with fungal cultures

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[83] A. Maurois, *Het Leven van Alexander Fleming de Ontdekker van de Penicilline*, 6th ed., trans. by Th. Oegema van der Wal, (Brussel / Den Haag: Uitgeversmaatschappij A. Manteau, 1959), p.207.
[84] This thesis, this Chapter, p.70.
[85] C. Levaditi, H. Penau, R. Perault et L. Erichsen, 'Sur un Principe Staphylolytique Élaboré par une Variété de *Penicillium*, (*Penicillium notatum**)', *Comptes rendus des Séances de la Société de Biologique et ses filiales*, 137, 11-12, (June 1943), pp.359-360.
[86] This thesis, this Chapter, p.52.

started as early as September 1942.[87] This ties in with Maurois' Spanish connection, when Penau attended 'a conference in Madrid'.[88]

While information on penicillin was circulating in France during the war years, French researchers were unsuccessful in taking these initial steps further, as the book *La Penicilline et ses Applications Cliniques* (Penicillin and its Clinical Application) illustrates. Published in 1945 this book is jointly authored by the Chief Medical Officer of the hospital of the Pasteur Institute, René Martin, Department Head, Frédéric Nitti, Medical Assistant, Bernard Sureau, and, Jean Berrod, Internist.

Introducing the subject of penicillin research the authors state that penicillin was first used in France at the beginning January of 1944 when an infant of 4½ months afflicted with a pneumococcal meningitis was admitted to the Pasteur Hospital. After several days of treatment with sulphonamide all hope of saving the child was lost. It was then that they were tempted to try treatment with the small amount of 'still imperfect' penicillin that they had managed to produce. A remission was effected. The child was very nearly saved. This treatment, they claim, was the first time penicillin was used in a human in Occupied Europe.[89]

Martin continued that 'at this time we only knew a few facts'. They had heard of the Allied interest in penicillin 'from a broadcast of *radio-Londres*' in either September or October 1943' which gave them 'a glimpse of the almost miraculous recoveries being reported'. However, efforts to learn more about the Anglo-American work being done on penicillin were in vain, and they were forced to wait a further 'two long months' before they received parts of

[87] H. Penau et F. Hagemann, 'Essais d'Extraction d'une Bactericide d'Origine Fungique', *Comptes rendus des Séances de la Société de Biologique et ses filiales*, 137, 23-24, (December 1943), pp.724-725.
[88] A. Maurois, *Het Leven*, p.207.
[89] R. Martin, F. Nitti, B. Sureau, J. Berrod, *La Pénicilline et ses Applications Cliniques*, (Les Éditions Médicales Flammarion: Collection de L'Institut Pasteur, 1945), Introduction, no page numbers.

publications smuggled across the border with Spain.[90] While this information confirms Spain as a source, unlike Penau, Martin had to wait until December 1943 for firm information on the production of Allied penicillin. Penau had published in June 1943.

Therefore, while Martin and his colleagues' claim to be the first to use penicillin *in vivo* in occupied Europe in 1944 lends itself to the general history of penicillin, Penau and his colleagues have shown that there was an earlier interest in the development of penicillin in France. Also, the fact that Penau's sources refer to British and German publications indicates that information on penicillin was getting through to French researchers albeit under the duress of occupation. However, perhaps like Germany, the French communication system failed. Penau was based at the Institut Alfred Fournier et Services Scientifiques des Laboratories Roussel (Alfred Fournier Institute and Roussell Laboratories). Martin was at the Pasteur Institute. Both were in Paris.

Martin and his co-authors, say that their research was enhanced through contact with the Rhone-Poulenc company. In particular they state that M. Grillet, the Director General of Rhone-Poulenc, managed to obtain publications that gave them more complete information on penicillin. Although no further detail is given. From these publications, a joint programme of work began between the Pasteur Institute and the laboratories of Rhone Poulenc. Starting with a strain of *Penicillium notatum* from the Pasteur Hospital's own culture collection, a small penicillin process was set up. Although the techniques and doses employed by the Anglo-American groups were unknown to these French researchers, soon a small amount, which had a titre of 30-60 units per milligram, was available. This was the product used to treat the

[90] R. Martin, *et al*, *La Pénicilline*, Introduction, no page numbers.

infant mentioned above. According to Martin, it was thanks to Phone-Poulenc that research with penicillin continued at the Pasteur Hospital during the war years.[91]

After the liberation of France in 1944, Martin says that the French Military received 'English' *Penicillium* strains, and, under the direction of three officers of the French Medical Service, namely Major Broch, Captain Koch and Captain Netchk, the French Military Research Centre started work. But, the scale-up of penicillin production remained a stumbling block and it was not until the end of the war that quantities of penicillin were eventually obtained. This came through Professor Garrod in London who, with the permission of the British authorities, put an appreciable quantity of this precious medicine at the disposition of the French, as did the British Ministry of Health.[92]

The Development of Penicillin in Japan.

Research on penicillin in Japan was initiated by medical journals brought from Germany by Japanese diplomatic personnel during the war.[93] According to Yukimasa Yagisawa, on 21 December 1943, Katsuhiko Inagaki, a surgeon and promoter of penicillin research visited the Ministry of Education where he met Willi Nagai of the Research Section.[94] At this meeting Inagaki was given a few copies of medical journals brought from Germany by submarine. He was particularly interested in a review article written by Manfred Kiese on therapy with antibacterial substances obtained from lower fungi and bacteria.[95] This was the article, published in *Klinische Wochenschrift*, of 7 August 1943, in which Kiese had abstracted

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[91] R. Martin, *et al*, *La Pénicilline*, Introduction, no page numbers.
[92] R. Martin, *et al*, *La Pénicilline* Introduction, no page numbers.
[93] Y. Yagisawa, 'Early History of Antibiotics in Japan', in Parascandola, J., ed., *The History of Antibiotics: A Symposium*, (Wisconsin: American Institute of the History of Pharmacy, 1980), Pp.70-71.
[94] Y. Yagisawa, 'Early History', p.69.
[95] Y. Yagisawa, 'Early History', p.69.

papers from the Oxford group and others that been reported between 1940 and 1943.[96] After consultation with his colleagues at the Tokyo Imperial University School of Medicine, it was decided to prioritise research into penicillin production and its applications.

By 5 January 1944 Kiese's article had been translated into Japanese and a research group established. On 18 January, permission was sought from S. Koidè of the Medical Affairs Bureau of the Ministry of War to begin research on penicillin and other fungal metabolites. Following this, on 27 January an official notice was sent from the Hygienic Section of the Ministry of War to the Military Medical College requesting that the Military Medical College control and promote research on the purification and synthesis of penicillin and other antibacterial substances; that practical applications for military medicine should be investigated; and, that a budget to finance this work should be allocated. It was also stated that non-military researchers should work in their own laboratories doing fundamental research as non-regular staff members of the military. On 1 February 1944 the Penicillin Committee held its first meeting in the Military Medical College in Tokyo. Research was expected to be completed by August 1944.[97]

January 1944 also brought the first 'popular' news of penicillin to Japan. In the *Asahi*, one of the most popular daily newspapers, a cabled article from a correspondent in Argentina, Y. Imai, appeared. Printed over two days, Imai's article described the methodology used to manufacture penicillin; its use in the treatment of infections; and, reported on the large-scale production being carried out at the NRRL in Peoria.[98] According to Yagisawa, Imai's article included the mistaken claim that penicillin had saved the life of Winston Churchill, the British Prime Minister, from a severe pneumonia infection which he had contracted after the Cairo

[96] This thesis, this Chapter, p.53.
[97] Y. Yagisawa, 'Early History', p.70.
[98] Y. Yagisawa, 'Early History', p.70.

Conference with President Roosevelt and Chiang Kai-shek in December 1943. Nonetheless, Imai's article stimulated keen interest in the research and development of penicillin in Japan.[99]

As stated earlier, the Japanese Penicillin Committee had met for the first time on 1 February 1944. This was also the day US Marines landed in the Marshall Islands in the Pacific Ocean. By the third Penicillin Committee meeting of 16 May, it was reported that from the testing of 750 fungal strains against *Staphylococcus aureus*, 50 strains had been found to produce a broth that was effective at 5-times dilution, 20 at 20-times and 5 at 100-times or more. What also became clear at this meeting was that some strains were indeed producing penicillin. The rumour that penicillin must be a trick of the Allies, therefore, was groundless. [100]

The fourth meeting of the Penicillin Committee, held on 4 July 1944, reported almost no improvement in broth potency and little progress in *in vivo* tests and purification. However, the war situation was serious. In Europe, the Allies had landed in Normandy on 6 June 1944; in the Far East, the Americans were close to taking Saipan; and, on 20 July, Premier Tojo would resign. Nonetheless, in August 1944 more literature on penicillin was received. This included a short article on penicillin written by Florey; a review on non-pathogenic microbes as sources of antibacterial substances by C. Hallauer of Berlin University; a review on experimental and clinical results written by A. Wettstein of the Ciba Institute in Basel; a summary of recent penicillin treatment in Britain and the United States written by C. Rieben; and, a Spanish paper on penicillin production by P. Gonzarez.[101]

By the fifth meeting of the Penicillin Committee, held in September 1944, the decision was taken to proceed with further experiments using 3 *Penicillium* strains. These were Iowata-50,

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[99] Y. Yagisawa, 'Early History', p.70.
[100] Y. Yagisawa, 'Early History', pp.71-72.
[101] Y. Yagisawa, 'Early History', pp.72-73.

P-176 and P-233. Animal experiments and production for large-scale surface culture, in a large iron cylinder equipped with trays, were proposed. A four month prolongation of research was also announced.[102]

On 26 October 1944, a *Penicillium* strain and literature obtained through the Robert Koch Institute of Berlin arrived in Tokyo. However, when tested the *Penicillium* strain received was found to be no better than the Japanese strains already in use. Ultimately, in November 1944 purification methods and clinical trials signalled the success of Japan's own penicillin.[103] It had taken the joint research team only nine months to complete their fundamental studies.

At its sixth meeting, the Penicillin Committee, promoted the industrial production and clinical application of penicillin. Presentation of experimental results was permitted at scientific meetings and reported in the daily newspapers. To further stimulate research, Professors of the Imperial Universities in Sendai, Sapporo, Kyoto and Osaka were added to the Penicillin Committee. However, scouting flights over Tokyo and other cities by US F-13 planes had started and, on 24 November 1944, Tokyo was attacked for the first time by 70 B-29 bombers.[104] These attacks clearly illustrated the deteriorating war conditions for Japan.

Inagaki, the original promoter of penicillin research, sought factories for penicillin production that were not manufacturing munitions. Eventually he acquired a milk and food plant that belonged to the Morinaga Milk Company. Four technical staff of the company were appointed as members for penicillin production and a sterilised room, used for canning products, was converted to a culture room. Autoclaves, centrifuges, culture bottles, whey and other necessary materials were provided from other plants of the company. Penicillin production,

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[102] Y. Yagisawa, 'Early History', p.73.
[103] Y. Yagisawa, 'Early History',p.74.
[104] Y. Yagisawa, 'Early History', pp.74-75.

using strains P-176 and P-233, overseen by H. Umezawa, M. Masuyama and K. Sato, was started immediately. By 23 December a small amount of purified solution had been sent to the seventh Penicillin Committee meeting. A month later, the Banyu Pharmaceutical Company started production of penicillin in its Okazaki plant. It had previously been a silk plant.[105]

The seventh meeting of the Japanese Penicillin Committee followed the trend of using Japanese names to replace foreign names. It renamed penicillin 'Hekiso', which means 'a blue principle'.[106] Standardisation within the regions followed. By the end of February 1945, a definition of potency and methods of potency assay and toxicity tests were discussed at the eighth Penicillin Committee meeting. Meanwhile, the war situation for Japan had become increasingly serious. The Americans had taken Iwo Island and Tokyo started suffering from blanket bombing. By March most of Tokyo had been destroyed. In April the Imperial Palace was damaged in an air attack and the Military Medical College was instructed to move to Yamagata, a small town in northern Japan. On 7 May 1945 the unconditional surrender of Germany was reported and the Battle of Okinawa entered its final stage. For Japan the Second World War ended on 15 August 1945 when, following the bombings of Hiroshima and Nagasaki, the Japanese Emperor broadcasted that Japan had decided to accept the Potsdam Declaration.[107]

There was, however, still a will to produce Japanese penicillin. By December 1945 penicillin production had been restarted by Morinaga and Banyu and, in January 1946, a standard was set by the Ministry of Public Health and Welfare. This Ministry also controlled the manufacturer's price. On 26 August 1946, at the initiative of the US, the Japanese Penicillin

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[105] Y. Yagisawa, 'Early History', p.75.
[106] Y. Yagisawa, 'Early History', p.75; In Japanese the colour blue is considered to bring good fortune. Personal Communication J. Burns, June 2005.
[107] Y. Yagisawa, 'Early History', p.76.

Research Association was established. This Association included a mix of academic and commercial interests. In November 1946, the Public Health and Welfare Section of the GHQ, under Colonel Weeber, Lieutenant-Colonel Riordan and Major Cummings, introduced Jackson W. Foster to I. Keimatsu, vice-minister of the Welfare Ministry and the head of the Pharmaceutical Section. A former pupil of Selman Waksman at Rutgers University, Foster was not only an Expert Consultant to The Surgeon General of the US Army, he was also a member of the Department of Bacteriology of the University of Texas. As such he had been very active in the research and development of American penicillin during the war years. As the 'newly appointed officer in charge of penicillin' his remit was 'to assist the penicillin industry in Japan'.[108]

Foster's first action was to hold a three-day symposium on penicillin production. This was followed by visits to newly designated central laboratories for fermentation and purification, and to the central assay laboratory. *Penicillium* strains for surface culture, NRRL1249-B21, NRRL 1951-B25 and NRRL 1978-B2, from the Northern Region Research Laboratory along with submerged culture, Wisconsin Q-176, were given to the Japanese central laboratories. Samples of corn steep liquor and phenylacetic acid, a side chain precursor, were also supplied. Using submerged culture, the monthly production of penicillin rapidly increased and the official price rapidly decreased. As a result, Japanese public health quickly improved. [109]

In the foreword to the first *Japanese Journal of Penicillin* of March 1947 published by the Japan Penicillin Research Association, Jackson W Foster wrote:

> The development of the penicillin industry is a great challenge to Japan. There is not, nor could there scarcely be, any greater test of Japanese initiative, resourcefulness and ingenuity ... So complex is this task that each phase demands the concerted effort of separate specialists. And yet, the affairs of one are the affairs of all. In this project the industrialist and

[108] Y. Yagisawa, 'Early History', pp.77-79.
[109] Y. Yagisawa, 'Early History', pp.79-81.

> the academician share responsibility equally. The factory man will find himself dealing with curious theoretical problems and the scholar will be confronted with the expediencies of mass production.... But as compensation we have the guidance of six years of the enormous American experience in this field. My government has asked me to bring this to you. I ask you to use it well and quickly'.[110]

At the end of the war, therefore, penicillin came to Japan with American expertise and under American licence. The influence of the American academic world on Japan's penicillin research and development cannot be ignored. On 13 June 1947 Foster wrote to Kluyver, at the TH, Delft:

> As a person closely connected with or interested in matters relating to penicillin you will be interested in the Japanese Journal of Penicillin, the first number of which I herewith enclose. ... It is planned to provide an English summary of each Japanese language article ... (but) expected that many of the original articles will appear entirely in English. ... The first (Journal) may appear mediocre but its publication is a real triumph over the incredible hardships, obstacles, and conditions under which it was produced. I trust you will arrange to have this Journal available to others in your institution; possibly you may wish to deposit it in your departmental or general library. The object is, of course, to make all technical information obtained in Japan available to workers in other countries.[111]

The intention of experts like Foster, therefore, was to share their knowledge and expertise with 'other countries' and certainly through network groups of academics familiar with each other. However, to some extent this intention was only partially successful as is borne out in Kluyver's reply to Foster of 7 July 1947 when he wrote:

> .... we are somewhat jealous when we read that your government has asked you to bring the guidance of six years of the enormous American experience to the Japanese industry. It would have been nice of your government if they had taken the same steps on behalf of the allied countries. I can only hope that we shall see you here in a similar mission soon but let me add you will be welcome without such a mission. [112]

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[110] KA, Penicillin Reprints Box.
[111] KA, Penicillin Reprints Box.
[112] KA, Catalogue Number 1990091, Folder 2, 1947, Letters D-H, Kluyver to JW Foster, 7 July 1947.

Ultimately, the failure of Japan to develop penicillin during the war years is very dissimilar to the experience of Germany and France. In Germany lack of concerted effort hindered individual efforts. The same could be said of Occupied France. However, from the outset Japan reflects a well-organised, institutional approach. At the end of the war Japan seemed to be on the point of success in the large-scale production of penicillin. They were beaten, however, by another well-organised wartime effort, namely the atomic bomb.

European Interest in Penicillin 1940-45 as reflected by the Archive of the Centraalbureau voor Schimmelcultures.

That there was a Europe-wide interest in penicillin following the 1940 Oxford Team publications in *Lancet* can be seen from the archives of the Centraalbureau voor Schimmelcultures. Established in 1904 this institution had been an independent Foundation since 1934. As noted earlier, it was known to house one of the best fungal culture collections in the world. The overall Director of the Institute, from 1907 to 1957, was Professor Johanna Westerdijk.[113]

From the CBS Annual Report of 1940, the international importance of the CBS collection and the threat of the impact of war on it can be gleaned. At the beginning of May 1940 a letter was received from the Rockefeller Foundation, which offered to take the CBS collection to the safety of neutral Lisbon. It was to be housed in the Institute of Dr Souza in Cammara and looked after by the Rockefeller Foundation. Plans to do this were made at a meeting on 4 May 1940 but, as the Annual Report for 1940 shows, 'understandably the carrying out of this plan did not occur'.[114] On 10 May 1940 the Netherlands was invaded and occupied by Germany.

[113] Johanna Westerdijk was the first female Professor appointed in The Netherlands. The appointment was at the University of Utrecht, 14 March 1917. She was also appointed Professor at the University of Amsterdam, 5 May 1930. Source: www inghist.nl. *Biografisch Woordenboek van Nederland*, 01/07/2005.
[114] KA, Catalogue Number 1990349, No Folder, CBS Annual Report, 1940.

Research in the CBS archive shows that up to 1938 there was little interest in *Penicillium* species. The first request for eight *Penicillium* strains arrived in Baarn from the Elberfeld section of the German conglomerate, IG Farben, on 28 November 1938.[115] *Penicillium notatum* is not on this list. This was the only request for *Penicillium* strains that year. On 16 March 1939, IG Farben Elberfeld requested two strains, namely *Pencillium flavo-glaucum* Biourge and *Penicillium fuso-glaucum* Biourge.[116] There are no requests for *Penicillium* strains noted in CBS archives for 1940 and 1941.

However, in May 1942 the request for a sample of *Penicillium notatum* from F. Hoffman- La Roche & Co.,[117] in Basel, Switerland, stimulated CBS action. On 8 June 1942 Westerdijk wrote to two well-known mycologists. The first was Professor R.Westling at his private address in Djurscholm, near Stockholm, Sweden, and the second was Professor T. Biourge, at the Institut Garnoy, Louvain, Belgium. She asked them for a culture of '*Penicillium notatum* Westling' which, Westerdijk wrote, was 'indispensable' to her collection. She further asked that, if they did not have a sample, could they provide her with an address where such a culture might be found. [118]

Although no record of a source for *Penicillium notatum* is noted in the CBS archives, as stated earlier, on 17 September 1942 the CBS sent a letter confirming that *Penicillium notatum* was now available to IG Farben Main-Hoescht, Germany; Hoffman- La Roche & Co. A.G., Basel, Switzerland; and, to Noury & v.d. Lande, Deventer, the Netherlands. Each letter

[115] CBS Archive, 1938, Correspondence File, No. 180.
[116] CBS Archive, 1939, Correspondence File, No. 180.
[117] CBS Archive, 1942, Correspondence File, No. 188.
[118] CBS Archive, 1942, Correspondence File, Nos. 449; 40.

included a sample of the culture. [119] On 9 October 1942, Alfred Benzon, Copenhagen, Denmark ordered one culture of *Penicillium notatum* to be sent as soon as possible.[120]

On 26 November 1942, Westerdijk wrote to L.H.C. Perquin at the Microbiology Department of Delft's Technical Hoogeschool, of the many requests she was receiving for *Penicillium notatum* because of its apparent penicillin forming properties. Unfortunately, she could find no information on *Penicillium notatum* and asked for Perquin's help in finding more information and literature sources. On 27 November 1942 Perquin replied:

> Apart from articles by Fleming in the *British Journal of Experimental Pathology* Vol. 10, 226, 1929 and Vol. 11, 127, 1930 and an abstract of an article in 1932 (which at that moment I cannot find) I can only produce an article by R.D. Reid in the *Journal of Bacteriology* Vol. 29, 215, 1935 in which Reid wrote that Fleming had observed a mould which he identified as *Penicillium rubrum* (Biourge), but which more closely resembles *Penicillium notatum* (Westling) and belongs to the group of which *Penicillium chrysogenum* is the type species.[121]

This group of *Penicillium*, Perquin explained, seemed to be able to produce a substance that inhibited the growth of certain bacteria. As Perquin further explained to Westerdijk, according to the mycologist Reid, from the twenty differing mould cultures identified by Thom, it was possible that the *Penicillium notatum* culture used by Fleming might not be the only penicillin producing culture. Although he was not hopeful, he did not exclude the fact that other variations of *Penicillium chrysogenum* may also be able to produce 'penicillin'. Accordingly he recommended that Westerdijk read an article by H. Raistrick which had been printed in the German journal, '*Ergebnisse der Enzymforschung*, volume 1, 1932', from which he quoted that:

> Fleming describes the production by a species of *Penicillium* originally supposed to be *P.rubrum*, but now known to be a strain of *P.chrysogenum*

[119] CBS Archive, 1942, Correspondence File, Nos. 128; 192; 317.
[120] CBS Archive, 1942, Correspondence File, No.12.
[121] CBS Archive, 1942, Correspondence File, No.340.

> Thom, of a metabolic product, at present not isolated, called by its discoverer penicillin[122]

Perquin continued that he was not sure how Raistrick had come to this conclusion but concluded that it was possible that Raistrick had tried to take Fleming's research further. Perquin ended his letter with the suggestion that for any research into penicillin he 'would certainly use *P. chrysogenum*'.[123]

Written in late 1942 Perquin's command of pre-war knowledge and information on *Penicillium* strains remains striking. Having completed his studies under Kluyver, by 1942 he had reached the position of Senior Scientist in Kluyver's Laboratory. His knowledge of *Penicillium* strains would have been invaluable to any penicillin research taking place in the occupied Netherlands.

From 1943 CBS archival evidence shows a marked increase in the request for samples of various *Penicillium* cultures. Orders were received on an almost daily basis from IG Farben Elberfeld, IG Farben Hoechst and, Hoffman-La Roche, Basel. In March 1943 Alfred Benzon, Copenhagen, Denmark, add to their order a note which told Westerdijk that Fleming's culture of penicillin could be found in the British Collection of Type Cultures in the Lister Institute under catalogue number 57 and 152.[124]

During 1943 orders for *Penicillium* cultures were also placed by Astra, Sweden; Alfred Jorgensen, Copenhagen; University for Pathology, Copenhagen; Nederlandsche Instituut voor Volksvoeding, Amsterdam; Wenner-Grens Institut, Stockholm; Merck Chemical Factory, Frankfurt; Institute Pasteur, Paris; Interpharma, Prague; N.V. Organon, Oss; and, H. Penau,

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[122] CBS Archive, 1942, Correspondence File, No.340.
[123] CBS Archive, 1942, Correspondence File, No. 340.
[124] CBS Archive, 1943, Correspondence File, No. 20.

Roussel Laboratory, Paris. The build up of European interest in *Penicillium* strains from 1943 is nothing short of enormous.

In fact Penau, whose joint publication with by Levaditi, Perault and Erichsen had appeared in June 1943, asked for more than culture samples. On 7 July 1943 he asked Westerdijk if she could tell him if there was a specialist mycologist in Holland who could determine a *Penicillium* strain for him, he thought might be *Penicillium notatum.*[125] If not, he asked if she knew of anyone in Belgium, Germany or Denmark who could do such a determination. In September 1943 Westerdijk provided Penau with a sub-culture of the CBS culture of *Penicillium notatum* from which she hoped he would able determine his series. Shortly afterwards CBS sent Penau four 'tubes' of a strain of *Penicillium notatum* that, in their opinion, was a 'particularly strong culture'.[126] At the point of his publication with Hagemann, Penau also visited the Netherlands. On 22 December 1943 he wrote to Westerdijk to thank her for hospitality; for her support in his 'particularly delicate mission'; and, for the introduction to Professor Jansen with whom he had long conversations about penicillin.[127]

Although no further discussion takes place in the CBS archive on the 'delicate mission' faced by Penau, it would appear that Westerdijk did find a specialist in the Netherlands who was able to discuss *Penicillium* strains. At the time the CBS archive places a Professor B.C.P. Jansen as the Director of the Nederlandsche Instituut voor Volksvoeding (National Institute for Nutrition) in Amsterdam. On 4 June 1943 Jansen had asked Westerdijk for a sample of *Penicillium notatum.* He was the first Dutch government official to do so.[128]

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[125] CBS Archive, 1943, Correspondence File, No. 246.
[126] CBS Archive, 1943, Correspondence File, Nos. 248; 249.
[127] CBS Archive, 1943, Correspondence File, No. 22.
[128] CBS Archive, 1943, Correspondence File, No. 226.

Archives of the CBS for 1944 further reflect requests for an increasing number of *Penicillium* strain cultures. A pattern of bulk ordering follows the *Penicillium* strains as listed in the CBS catalogue of 1943. For example, on 9 February 1944, Astra in Sweden ordered 68 *Penicillium* samples, in alphabetical order. On 15 May 1944, IG Farben Elberfeld requested 1 *Aspergillus* and 46 *Penicillium* strains listed A to G and on 30 May 1944 requested a further 56 *Penicillium* strains listed H to P. On 11 May 1944, the Four Year Plan Institute Prague requested a staggering, 102 *Penicillium* culture samples.[129]

Referring back to the conclusions of Pieroth, that there was no governmental support for penicillin research in Germany, and that of Shama and Reinarz, that it came too limited and too late, the above archival evidence from the CBS in Baarn illustrates that, when it did come, German interest in penicillin was no different to other interested European parties. For all, the rush for penicillin strains came in 1944. Tellingly, the last contact between the CBS in Baarn and IG Farben Elberfeld was on 3 December 1946 with a notification stamp that IG Farben was 'In Dissolution, *In Auflosung'*.[130]

Conclusion.

In looking at research in the United States and Britain it is clear that in spite of the June 1943 embargo on information relating to the research and development of penicillin, publication on Allied penicillin research did not diminish. In fact, from 1943 there was a marked increase in publications regarding penicillin development in both Britain and the United States. Moreover, the importance of penicillin to the war effort is marked, not only by the continued circulation of information in academic journals, but also by the adulation of penicillin in the press and propaganda material. The allure of the 'wonder drug' is aptly summed up by

[129] CBS Archive, 1944, Correspondence File, Nos. 28; 132; 133.
[130] CBS Archive, 1946, Correspondence File, No. 137.

Coghill's description of the 'humble mold ... now attended on by hundreds of footmen' and the party proceeding with 'fanfare galore'.[131]

At the same time, the influence of commercial concerns acting with academic research in the development of penicillin in both the US and the UK has to be borne in mind. At the time, Coghill described it as a 'monumental undertaking' that had reaped success 'due to the persistence and determination of government and industrial research workers'.[132] The experience of Canada also underscores the success of such joint ventures in the large-scale production of penicillin. A production Coghill anticipated would become 'one of the outstanding developments of the war'.

That information on penicillin and its therapeutic possibilities reached, not only the Axis countries, but also the Occupied Zones is illustrated by the publication of well-informed German and French articles. However, while Pieroth and Shama and Reinarz may be correct in their assumption that the failure of the German development of penicillin lay in a lack of communication, the same might be said for the French. For Japan, the critical publication, *Klinische Wochenschrift*, came from Germany. Japan's near success, therefore, further highlights the failure of German researchers given that they had the same, if not more, information.

On the other hand, Penau's publications illustrate that in occupied France groups of researchers publishing their research; they were communicating. Between occupied countries, however, this communication was not always through the medium of print as Penau's visit to

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[131] This thesis, this chapter, p.45.
[132] This thesis, this chapter, p.45.

the CBS in Baarn illustrates. Personal meetings did take place and these allowed opportunities for the dissemination of information about penicillin.

Such evidence of interest in penicillin outside Britain and the United States appears to uphold David Wilson's premise of the penicillin 'myth'. The development of penicillin was certainly not chronological. Each country moved in its own way and in its own timescale. Each country had its own 'luck' or lack of it but it cannot be said that, of the countries dealt with in this Chapter, any were aided by 'chance'. In Britain, America and Canada penicillin was developed by determination, hard work and shared experience. At the end of the war, penicillin came to France with the help of the British, for Germany it came from both Britain and America while, for Japan it came with the expertise of personnel, such as Jackson W. Foster, from the United States.

However, pivotal in the development of penicillin in the Netherlands is the prime position of those at the CBS at Baarn. As one of the world's best fungal culture collections the CBS could supply mould cultures not only on an international scale but also on a local scale. Yet archival evidence points to September 1942 before a strain of *Penicilium notatum* joins the CBS catalogue. Also, that up to 1942 Westerdijk had little knowledge regarding Fleming's research with the strain *Penicillium notatum*. This was rapidly offset through contact with Perquin at Kluyver's laboratory in Delft. Ultimately, it was the coupling of such expertise that was to play a key role in the development of Dutch penicillin.

Chapter 3

Dutch Awareness of Penicillin: Research during the War Years

In the development of penicillin in the Netherlands any interest or awareness of penicillin research during the war years has to be addressed. In order to do so, four main areas will be investigated. To begin with, the consequences of occupation for Dutch health care will be recorded. Thereafter, knowledge within the occupied Netherlands of the existence and successful use of Allied penicillin from 1943 onwards will be featured. Next, reports on wartime Dutch academic and commercial research with another possible therapeutic agent, Expansine, will be explained. For this, academic and press publications, as well as the CBS archive, will be employed. Finally, information over Allied research with penicillin available to those in the Netherlands will be brought to the fore, and the role therein played by Professor Kluyver.

Consequences for Health Care during the Occupation of the Netherlands.

In looking at Dutch medicines and their supply during the war years, J. Masereeuw reports that the maintenance of an optimal public health system for citizens under occupation in fact demanded extra effort from those involved.[1] It was crucially important that the General Practitioner and specialist retained access to good medical information.

At the time, the *Nederlandsch Tijdschrift voor Geneeskunde* (NTvG, Dutch Journal of Medicine) held a prominent position. Published on a weekly basis, it was also the destination for medical questions from doctors. In 1940 there were 6,628 practicing General Practitioners and medical specialists in the Netherlands, 6,000 subscribed to the NTvG. The editors were aware of their unique position but in the first edition of 1940 the Chairman of the editorial board, G. van Rijnbeek, expressed his concern about the future existence of the Journal under

[1] J. Masereeuw, 'De Rol', p.254.

occupation. The unspoken thought behind the Chairman's statement was quite clearly that if the NTvG disappeared then the functioning of the medical profession would be impaired.

However, during the war years, Masereeuw states that high quality articles continued to be published in both general and specialised medical areas. Even at the deepest point of the occupation, 1944 and 1945, the number of articles published in the NTvG totalled 122 and 81 respectively. Moreover, references to other journals, periodicals, dissertations and books, provided an admittedly concise, but nonetheless extremely useful stream of information. In 1943 English language publications had practically dried up but Swiss and Swedish journals provided the NTvG with information about important international medical developments, including antibiotics. Masereeuw specifically says antibiotics and not penicillin. According to Masereeuw, the complete medical isolation of the Netherlands would not have been advantageous to the occupier. It was in the occupier's own interest to ensure that the quality of the German and Austrian medical journals that were provided were no less informative than those from other sources. Also, answers were sought for the many diverse medical questions that arose from the wartime situation. Indeed, Masereeuw contends that the editors and staff of the NTvG succeeded throughout the years of occupation in maintaining medical information at an admirable level, even though they were the victims of increasingly restrictive measures.[2]

According to the NTvG archive there were no publications on penicillin or antibiotics between 1939 and 1943. Three on penicillin were published in 1944. The first was in number 25/26 of the June issue under the title 'Microbiologie en hygiène' (Microbiology and Hygiene),[3] which told of penicillin and penicillin-like substances and reflected the work in France by Nitti and in Germany by Kiese.[4] The second was a news item from abroad that told

[2] J. Masereeuw, 'De Rol', p.254.
[3] A.C. Ruys, 'Microbiologie en hygiène', *Nederlandsch Tijdschrift voor Geneeskunde*, 88, II, 25/26, (17 en 24 June 1944), p588.
[4] This thesis, Chapter 2, p.57; p.53.

of a meeting at the Royal Society of Medicine in London on 9 November 1943 led by Alexander Fleming.[5] The third appeared in the first *Noodnummer* (Emergency number).[6] Dated 7 October 1944, the *Noodnummer* dealt with an article on penicillin as reported in a Swiss Medical Journal of July 1944. More attention will be given to this publication later in this Chapter. In the NTvG *Noodnummers* of 1945, reference is given to penicillin only twice. Both are short 'messages from abroad'. One refers to the Nobel Prize award to Fleming, Florey and Chain; the second noted the award of the Lister Medal to Florey.[7]

The issue of *Noodnummers* offer insight into what happened to the NTvG during the war. As stated above, the first was issued on 7 October 1944. It was the result of a lack of power for the operation of the NTvG printing presses. Staff at the printers had worked together to produce this 'emergency copy' from one hand-driven machine. Although, the editor reported this as a temporary measure,[8] it was to be 29 December 1945 before the last *Noodnummer*, XXXIII, was printed.

J. Bosman-Jelgersma highlights the position of Dutch pharmacists under occupation. She describes how medicines and prescription drugs became scarcer and scarcer and distribution complex. Ultimately, during the war years it became more and more difficult for the Dutch *apotheekers* (pharmacists) to perform their duties.[9] As Bosman-Jelgersma explains, in 1939 membership of the Nederlandsche Maatschappij ter Bevordering der Pharmacie (NMP, Dutch Pharmaceutical Society) totalled around 1,000 members of whom 800 were practicing. The NMP journal *Pharmaceutisch Weekblad* (PW; Pharmaceutical Journal) was also called *Tijdschrift voor Apothekers en Apotheekhoudende Geneeskundigen* (Journal for Pharmacists and Pharmacy Owning Doctors). Published weekly, it was edited by P. van der Wielen.

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[5] *Nederlandsch Tijdschrift voor Geneeskunde*, Berichten, Buitenland, Penicilline, 88, III, 29/30, (15 en 22 July 1944), p.688.
[6] *Nederlandsch Tijdschrift voor Geneeskunde*, Noodnummer I, (7 October 1944).
[7] *Nederlandsch Tijdschrift voor Geneeskunde*, Berichten, Buitenland, 89, 1945.
[8] *Nederlandsch Tijdschrift voor Geneeskunde*, Noodnummer I, (7 October 1944), p.1.
[9] J. Bosman-Jelgersma,, 'De Nederlandse Farmacie', p210-221.

In August 1939, in the face of imminent war, the Rijksbureau voor Genees- en Verbandmiddelen (State Department for Medicines and Medical Supplies) was created. Almost one hundred medicines fell under the remit of this Department, and, during that year the price of most medicines and medical supplies remained fairly stable.

During 1940 distribution rules applied to about 150 medicines. Product supplies from other countries were still available and, at this time, there was no discussion of rationing thanks to the steps that had been taken in 1939 through the *Rijksbureau* (State Department). A form of rationing did take place, but this was only a restriction on the maximum amount that could be ordered. Pharmaceutical wholesalers themselves initiated a distribution system based on their own supplies. This meant that no pharmacists received amounts greater than their need. These measures combined to prevent hoarding and price rises. Even so, 1940 saw shortages and some medicinal preparations were made prescription only. By the end of 1940, the international market began to stagnate and this led to a rise in the use of surrogate and alternative medicines. In the pursuit of replacement medicines, the *Gezondheidsraad* (Health Council) issued a booklet to all doctors and pharmacists in which twenty-five medicinal plants that could be grown in the Netherlands were listed.

During the whole of 1941 the *Pharmaceutisch Weekblad* continued to be published on a weekly basis. It contained academic articles, research results, business reports and literature lists. It covered the introduction of new medicines and reported on the various departments and committees of the Dutch Pharmaceutical Society. However, these weekly publications give an impression of the increasing difficulties of the time. For example, following blackout regulations, pharmacies had to close earlier in the winter months because of the lack of daylight; difficulties in communication hampered pharmacist meetings; supplies of basic and alternative medicines became scarcer; and, packaging materials became difficult to obtain.

In December 1940 the NSB newspaper *Volk en Vaderland* (Nation and Fatherland) reported that a *Medisch Front* (Medical Front) would be created. The intention of the Medical Front was to bring doctors, dentists, veterinarians, pharmacists, their personnel, their unions and their societies under one organisation. In April 1941 the leader of German pharmacists, *Reichsapothekerführer* A. Schmierer, came to the Netherlands to oversee this reorganisation. December 1941 saw the introduction of the Nederlandsche Artsenkamer (Netherlands Medical Association) and, in March 1942, the re-organisation of Dutch pharmacists followed. From that moment all Dutch pharmacists automatically became members of the *Artsenkamer* and they lost the representation they had through the NMP. The Dutch Pharmaceutical Society was disbanded and the last publication of the *Pharmaceutisch Weekblad* appeared on 18 April 1942.

The name *Pharmaceutisch Weekblad* continued until the end of 1942 but with the addition of the subtitle: *Tevens het Nederlandsche Apothekersblad* (Also the Dutch Pharmacists Journal). At the end of 1942 it was renamed *Officiel Orgaan van de Nederlandsche Apothekerskamer* (The Official Voice of the Dutch Pharmaceutical Society) and fell under the editorship of H.P. Stam, a member of the NSB. The contents did not change much, but the influence of the war became more and more apparent as literature references became restricted to German language publications. The *Officiel Orgaan*, in turn, was replaced by a new weekly journal called the *Tijdschrift voor Artsenijkunde* (Journal of Medical Affairs). It was described as a new journal more suited to the times.

The intention was to publish the *Tijdschrift voor Artsenijkunde* weekly, however, during 1944 difficulties with paper supply, publishing and distribution meant that it sometimes did not appear for weeks. From September 1944 onwards this was certainly the case when the south of the country was liberated. From that time on, communication between the liberated south and the non-liberated parts of the country became very difficult. From February 1945

publication of the *Tijdschrift voor Artsenijkunde* virtually ceased. Only occasionally and under specific circumstances would a one-page publication appear for circulation.

At the end of the war, Bosman-Jelgersma continues, deteriorating conditions meant that pharmacists had to improvise even more. Doctors were urgently asked to prescribe less. Certain medicines could only be given to patients when absolutely necessary. Scarcity of gas and electricity meant that the making up of prescriptions had to be kept as simple as possible. Some pharmacies were on call for evening and night duty and, if so, had to work in candlelight or under paraffin or oil lamps. Coal for heating was no longer available. This resulted in medicines being stored in damp conditions, which led to deterioration in potency.

Due to the requisitioning of bicycles by the occupier and the general shortage of bicycle tyres, medical deliveries became severely hampered. Medical wholesalers tried everything in their power to help pharmacists keep up their medical supplies.[10] Often medicines went by boat, for example by canal from Utrecht and Meppel to Amsterdam and from there on to Haarlem. Sometimes the Red Cross managed deliveries by car. In particular, supplies of insulin became scarce because the necessary *bonnen* (official vouchers) became impossible to obtain. Pharmacists often had to go to the Rijksbureau voor Genees- en Verbandmiddelen personally in order to collect and/or hand in the necessary official forms they needed for stock requests.

Until the middle of 1944 the situation was tolerable because medicines were imported from Germany. From September 1944, with the partial liberation of the Netherlands, this supply effectively stopped. The country was left dependent on the stocks it had. No one could foresee how long this situation would go on. During the winter 1944-1945 there was contact with the liberated south for medicines urgently required, such as insulin, sulphonamide and diphtheria

[10] Such as Openbare Pharmaceutische Groothandel (OPG; Public Pharmaceutical Wholesaler) at Utrecht; the Amsterdam Chinine Fabriek (ACF; Amsterdam Quinine Factory) in Amsterdam, and Brocades, Stheeman & Pharmacia, (BS&P) at Amsterdam and Meppel.

serum, but the dispatch of these so-called *cross-line-zendingen* (cross line deliveries) was very limited and very dangerous.[11]

1944. The First Use of Penicillin in The Netherlands: Popular Awareness of the 'Wonder Drug'.

Chronologically, the German invasion of the Netherlands in May 1940 occurred just three months before Florey and his associates published their first report on penicillin in *Lancet.* Because of Allied wartime secrecy, as the CBS archives has shown, it was 1944 before concrete information and a European interest in penicillin production became known in the Netherlands. However, the partial liberation of the Netherlands in September 1944 also brought with it information on the wartime use of penicillin. It was used both by doctors working with the Red Cross and allied military doctors working in the field. Although communication between the south and the rest of the Netherlands was sporadic, the use of penicillin at the battlefront must have influenced Dutch awareness of the 'wonder drug'.

In one of the first noted cases of the use of penicillin in the Netherlands, John Hofmyer recounts his experience as a volunteer with the British Red Cross in his book *The Testament of a Doctor. A life of contrasts.*[12] In September 1944, Hofmyer had just completed in his first year of medical school at St Mary's Hospital, Paddington, when he was asked to help in a British Red Cross hospital team. The team was 'sponsored, equipped and trained by the Guides'.[13] They were to assist in feeding and general relief work, specifically in Belgium and Holland. Hofmyer was also, because of his Afrikaans/Dutch background, to act as interpreter.

The movement and embarkation orders for Hofmyer's team came in March 1945. His first destination was Tilburg. Following the Allied advance, Hofmyer and his team helped set up

[11] J. Bosman-Jelgersma, 'De Nederlandse Farmacie', p.210-221.
[12] J. Hofmyer, *The Testament of a Doctor. A life of contrasts*, (Republic of South Africa: SAMA Health and Medical Publishing Group, 2003; UK: Creda Communications 2003), pp.132-165.
[13] The British Girl Guides Association. Personal Communication John Hofmyer, February 2002.

hospitals and gave medical aid to the Dutch civilian population. Recounting his experiences in the liberated south of the Netherlands Hofmyer tells of the distress and hunger of the Dutch civilian population, the result of severe rationing and the lack of any kind of provisions. Typhus and TB were rampant. In order to prevent the spread of typhus, a lice-borne disease, DDT was used to delouse all refugees and displaced people.[14]

Difficulties in communication with local Dutch doctors surprised Hofmyer. He had been told that all Dutch doctors spoke good English. However, throughout the five years of occupation the English language had not been used, the only language after Dutch had been German. As a result, initial communication with Dutch medical staff was slow and his translation skills soundly tested. The dire lack of transport facilities and petrol also meant that the volunteer medical staff often had to borrow bicycles, not only to visit patients at home, but also to transport patients to and from hospital.[15]

Hofmyer claims that he was one of the first, if not the first, to administer commercially manufactured penicillin to a Dutch civilian. He cites the date as mid-July 1945. A doctor in the Canadian army had donated the penicillin he used. It was administered to Cornelius Fuyschott, then aged seventeen, who had typhoid as well as osteomyelitis of the left shin. He was injected with 10,000 units of penicillin every four-hours. Fuyschott had been in hospital since June 1945 but his condition rapidly improved after treatment with the Canadian penicillin and he quickly recovered. Hofmyer said that everyone was told not to talk about it but it was impossible to keep Fuyschott's recovery confidential. His (Fuyschott's) treatment with penicillin soon became widely known. In a very short time Hofmyer had requests for supplies of penicillin from nurses, doctors and local hospitals. His team, however, had obtained 'enough for one case only' but the requests for penicillin persisted.[16]

[14] J. Hofmyer, *The Testament*, pp.137-140
[15] Personal Communications John Hofmyer November 2001, March 2002.
[16] J. Hofmyer, *The Testament*, pp.159-160.

The use of Allied penicillin in the Netherlands towards the end of the war and knowledge of its healing properties is further confirmed in the *Nederlands Tijdschrift voor Geneeskunde*, in a series of letters published between 1997 and 1998. The series started 20 December 1997 when W.Y. Sijtsema described the experience of his father Jan Sijtsema, a General Practitioner in Hengelo, who, at the end of the war, had a patient suffering from a severe form of *puerperal sepsis*. Sijtsema Snr. administered penicillin obtained through Flight Lt. Kenneth Deeth. Deeth was a Scottish doctor in the service of the Royal Air Force, detached to the First Canadian Armoured Division stationed at *Kasteel Twickel* (Twickel Castle).[17] Originally, Deeth's penicillin had been for the treatment of a young boy in the van Eck family but, on the basis that it was easier to take a full box rather than a few ampoules from the military medical supplies, Deeth had given the van Eck family a small wooden box full to the brim with ampoules of penicillin. According to Sijtsema, tt was known at the time that penicillin had a limited shelf life and had to be kept at '4°C', so, the van Eck family had stored the penicillin in their cellar. A medical colleague of Sijtsema Snr. was a regular visitor to the young van Eck. He knew of the penicillin. He knew that there was more than enough to treat the boy and so, in turn, Deeth's penicillin found its way to Sijtsema Snr.'s patient. It was administered on 12 May 1945 and the patient made a complete recovery.[18]

Responses to Sijtsema's letter brought to the fore instances of the earlier use of Allied penicillin. One claimed that between 17 and 26 September 1944 penicillin obtained from a British field hospital was used on civilian war wounded in the Katholieke Ziekenhuis (Catholic Hospital) at Apeldoorn during the Battle of Arnhem. Another claimed that penicillin had been first been administered in the Netherlands in September 1944 to a patient in the Groot Ziekengasthuis hospital in 's-Hertogenbosch. This penicillin had been obtained through American army doctors. Yet another case was reported to have taken place on 27 October

[17]During the war Twickel Castle had been one of the homes of Arthur Seyss-Inquart, at the end of the war it was temporarily his prison.
[18]*Nederlands Tijdschrift voor Geneeskunde*, 141, 51, (20 December 1997), pp.2517-2518.

1944 in the village of Hilvarenbeek, Brabant, with penicillin donated by the British liberation army.[19]

Whether the use of the 'wonder drug' penicillin became nationally known in the Netherlands towards the end of 1944 remains unclear. South-Limburg was liberated by the Americans in September 1944, and the region Eindhoven-Veghel by the British in the same month. But, following the disappointment of *Dolle Dinsdag* (Mad Tuesday) and the failure of Operation Market Garden at Arnhem, the American and British detachment of the 21st Army Group pushed eastwards towards Germany. The First Canadian Army was left to liberate the north and western provinces of the Netherlands, a task which was to prove demanding in the face of strong German opposition. What is clear, however, is that penicillin first came into use in the Netherlands with the medical sections of the liberating Allied armies in 1944. As such, it stimulated not only medical but also public interest.

The Search for an Antibiotic Substance: Dutch Academic Research 1944-45.

Both academic journals and newspaper articles from the year 1944 point to evidence of Dutch medical research in the search for a penicillin-like therapeutic agent. However, they show that this research took place before the partial liberation of September 1944. There was, therefore, a medical interest and knowledge of penicillin within the Netherlands before the autumn of 1944.

According to Patricia Faase, there had been interest in antibacterial substances in the Netherlands from 1939, based on research with the mould culture *Penicillium expansum* by A. van Luyk at the CBS.[20] Spykens Smit records that during the years of occupation, J.J. Duyvené de Wit, Head of the R&D department of Brocades-Stheeman & Pharmacia, had taken up van Luyk's research. Further, that during the war BS&P was constantly addressing

[19] *Nederlands Tijdschrift voor Geneeskunde*, 142, 7, (14 February 1998), p.142.
[20] Patricia Faase, Personal Communication, July 2005, during discussion of Faase's biography on Johanna Westerdijk.

the question of penicillin research with other agencies such as the CBS in Baarn, the Botanical Laboratory of the University of Amsterdam, the Laboratory for Physiological Chemistry, Amsterdam, and the Bacteriological Laboratory of Amsterdam's local health authority, the Gemeentelijke Geneeskundige- en Gezondhiedsdienst.[21]

The results of this research were published in the combined NTvG of 26 July 1944 and 6 August 1944. The article was entitled 'De Isolering van een Bactericide Stof uit een Penseelschimmel' (The Isolation of an Antibacterial Substance from a *Penicillium* Fungus). It reported that research had resulted in a crystallised product, which had been named Expansine. Spykens Smit's lists the authors as B.C.P. Jansen, J.J. Duyvené de Wit, A. Jarsveld, A. van Luyk, R. Luyken, H.K. Oosterhuis, and J.R. Wybrans.[22]

Indeed, the variety of Institutions engaged in the publication that appeared in NTvG of July/August 1944 is further illustrated by the fact that work on Expansine had been conducted at the Chemical Laboratory of the Vrije Universiteit, (VU, Free University) Amsterdam, by H.K. Oosterhuis and W.Th. Nauta. Toxicity had been undertaken by A.M. Ernst at the Kliniek voor Kleine Huisdieren (Clinic for Small Domestic Animals) in Utrecht; *in vivo* experiments were performed at the Instituut voor Praeventatieve Geneskunde, (Institute for Preventative Medicine), Leiden, by J.D. Verline; and, dermatological testing had been undertaken by J.R. Prakken. The conclusion was, however, not to take Expansine further as it was too toxic for internal use.[23]

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[21] J.H. Sypkens Smit, 'Nederlands Pionierswerk in de Ontdekking en de Fabricage van Penicilline' in Kerkhoff, A.H.M., Luyendijk-Elshout, A.M., and Poulissen, M.J.D., eds, *De nouvis Inventis. Essays in the History of Medicine in honour of Daniel De Moulin on the occasion of his 65th birthday.* (Amsterdam and Maarssen: APA - Holland University Press, 1984), p.455.

[22] J.H. Sypkens Smit, 'Nederlands Pionierswerk', p.460.

[23] B.C.P. Jansen, J.J. Duyvene de Wit, A. Jaarsveld, A. van Luyk, R. Luyken, H.K. Oosterhuis en J.R. Wybrans, 'De Isolering van een Bactericide Stof uit een Penseelschimmel', *Nederlandsch Tijdschrift voor Geneeskunde*, 88, (1944), pp.718-720; J.H. Sypkens Smit, 'Nederlands Pionierswerk', p.456-457.

Adding to medical and pharmaceutical publications, information on research with Expansine was also published in the prominent Dutch national newspaper, the *Nieuwe Rotterdamsche Courant* (NRC). The NRC was one of the two large, liberal, daily papers in the Netherlands.[24] On 12 August 1944, it published an article entitled 'Penicilline: Nederlandsche onderzoekingen met soortgelijke stoffen' (Penicillin: Dutch Research with Similar Substances) reported on research with Expansine and the possibility of it being similar to penicillin. It referred to the fact that sulphonamides had been used to cure infection since 1935 and stated that in 'the last few years' experiments had taken place in Britain and America with '*Penicillium notatum* Westl'. It named Fleming as the discoverer of penicillin and referred to his 1929 publication; it explained that the mycologist Vonkennel had shown that other substances similar to penicillin could be produced by moulds, yeasts and other micro-organisms, substances which Vonkennel had called 'mycoines'; and, continued by reporting that it was 'A. van Luyk' who had started research in the Netherlands using the strain *Penicillium expansum* (Luik). However, like the NTvG, the NRC article concluded with the statement that while penicillin appeared to be completely safe and could be taken internally, Expansine had been found to be '*vrij giftig*' (very toxic) and could not be used internally.[25]

From the above publications, therefore, it can be seen that from 1944 information on the research and development of the anti-bacterial substance Expansine was being openly reported in the Netherlands in both academic journals and the national press. Further, the NTvG and NRC publications point to the fact that there was a collective desire to emulate what had been achieved by the Allies in the production of penicillin. Additionally, although under occupation, there was an organised collaboration in research projects between the Dutch academic world and the Dutch commercial sphere.

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[24] The other was the Amsterdam based *Algemeen Handelsblad.* Source: L. de Jong, *Het Koninkrijk,* Deel 12, *Epiloog*, Eerst Helft, p.406.

[25] *Nieuwe Rotterdamsche Courant*, 12 August 1944. Source: KA, Penicillin Reprints Box.

The archive of the Centraalbureau voor Schimmelcultures confirms a Dutch academic and commercial interest in the search for an anti-bacterial substance. For example on 22 February 1944 a letter from Utrecht University, Hygienisch Laboratorium (Laboratory of Hygiene), to the CBS stated:

> We have received the *Penicillium notatum* that you sent to us. In our test we have a very low yield of an anti-bacterial substance although, naturally, we do not yet know if what we have is penicillin or notatine. The yield was lower than that of the *Penicillium notatum* strain, which we ourselves have and which, if we are correct, is a subculture of your strain. ... We must note, however, that this experiment was more qualitative that quantitative. For quantity we need more experience. When you have more strains to send to us we can do a rough comparison and that way we will have other strains to add to the *Dorylophylum* Dierckx and the few *Aspergillus* strains you have already sent for our research.[26]

On 29 February 1944 the Laboratory of Hygiene again wrote to CBS:

> The 3 *Penicillium* strains and both of the *Aspergillus* that you sent have been received. Please send the bill for seven strains received:
> *P. corylophilium* Thom; *P. corylophilium* Thom, Frankrijk; *P. citrinum* Thom; *P. citreo-roseum* Dierckx; *P. expansum* Thom Stam 106; *Aspergillus flavus* Link strain Nattrass; *Aspergillus clavatus* Desm. strain Abott.[27]

From the Institute for Preventative Medicine, Leiden, J.D. Verlinde wrote on 4 April 1944 that he had received from CBS the culture of '*Penicillium notatum* Westl.' and went on:

> Penicillin is indeed important research and I would like to make use of your advice. I would like to bring *Penicillium coryphilum* Dierckx and *Penicillium corymbiferum* Westl into my research. Please send me some sample cultures. Could you also give me information about the medium used in the culture of penicillin?
> Therapeutic tests with penicillin have only recently taken place during the war in America and England. I do not have much to refer to on how penicillin is made. The literature about it is, as far as I know, not available.[28]

The CBS archive also illustrates the commercial interest of the time when, on 1 July 1944, the offices of Brocades Stheeman & Pharmacia, Amsterdam, wrote to Johanna Westerdijk:

> We are looking for around ten doctors who would be willing to use Expansine in trials against fungal skin conditions. However, the clinical results are only of note when it is known which fungus each patient was infected with. We have therefore asked our doctors to send us samples of their patients' hair, nail and skin from which we can grow and determine the pathogenic fungus.

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[26] CBS Archive 1944, Correspondence File, No. 215.
[27] CBS Archive 1944, Correspondence File, No. 216. The letter *P.* is short for *Penicillium*.
[28] CBS Archive 1944, Correspondence File, No. 255

> It is possible that we will, within a few months, receive 50-100 preparations to identify and our question is: Would it be possible to come to an arrangement with the CBS whereby we could send material to be identified by you? We will, of course, pay the costs for this but would ask if we could obtain a reduced rate as some of the cultures will be identical and the identification time therefore quicker.
> It is our intention to gather the clinical material in statistical form and to publish the results in the *Nederlandsch Tijdschrift voor Geneeskunde.* We would, of course, in this publication give reference to the collaboration with the CBS in determining the results.
> Hoping you can agree. Yours sincerely.[29]

On 5 July 1944 the CBS replied. Johanna Westerdijk agreed to do the work, she would would not, however, agree to a reduced rate.

The researchers of BS&P, both academic and company based, were not alone in their study. That the quest for a culture of Fleming's *Penicillium* strain continued during the war years is illustrated in a letter of 8 September 1944 but so too is the Dutch expectation that the war and occupation would soon be over. On this day the University of Amsterdam, Lab. voor Physiologische Chemie, (Physiological Chemistry Laboratory) wrote to Westerdijk:

> Please send *Penicillium notatum*; *chrysogenum*; *rubrum.*
> Further I would like to inform you that the *Penicillium notatum* of Fleming can be found in the Forschungslaboratorien der Chemische Fabriken J.R. Geigy A.G. in Basle; but perhaps you will shortly be able to get the strain quicker from Fleming himself.[30]

This was not the case for the penicillin-like substance Expansine. As has been shown it was found to be too toxic for internal use and research halted. Yet, BS&P did publish information on their wartime research with *Penicillium expansum.* A copy is contained in Volume I of the *Scientific Communications* of BS&P's Research Department.[31] Under joint authorship of W. Th. Nauta, H.K. Oosterhuis, A.C. van der Linden, P. ven Duyn and J.W. Dienske this publication is written in English and entitled 'The Structure of Expansine, a Metabolic

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[29] CBS Archive 1944, Correspondence File, No. 73.
[30] CBS Archive 1944, Correspondence File, No. 208.
[31] NV Koninklijke Pharmaceutische Fabrieken v/h Brocades-Stheeman & Pharmacia, *Scientific Communications*, Vol. 1, June 1945-July 1951, (Amsterdam: 1951).

Product of *Penicillium expansum* Westling with Antibiotic Properties'[32] It was received by '*Rec. Trav. Chim.*' on 18 August 1945 and published in September/October 1945.[33] At just over a page long, it is acknowledged as a 'Preliminary Note'. It cites the previously mentioned NTvG publications of July and August 1944 and refers to work awaiting publication.[34] Printed barely three months after the liberation of the Netherlands, in effect, this publication stamps BS&P ownership of both academic and commercial wartime research with *Penicillium expansum* in their quest for an antibacterial substance.

Additionally, on 6 October 1945, Brocades, Stheeman and Pharmacia took a full-page advert in the NTvG. The banner heralded '*Research-Werk dat den terreur doorstond!*' (Research work that withstood terror). It detailed the work done with Expansine in chronological form. Starting in 1939 this advert claimed that 'one year before the outbreak of war' BS&P Research Department, 'without contact with the Anglo-American researchers' had started research with fungal cultures. It continued that, in 1940, following the shared research of Prof. V.J. Koningsberger and A. van Luyk at Utrecht, an antibiotic substances was produced from *Penicillium expansum*. In 1943 eight 'work groups' had coordinated their research through an *Amsterdamsch Hoogleerar*, an Amsterdam University Professor. By 1944 Expansine was produced in crystal form and in 1945 was shown to be similar to Raistrick's Patulin 'of 1943'. The advert further claimed that Expansine was more effective than penicillin because it was active against gram-positive and gram-negative bacteria; penicillin's activity being limited to gram-positive. The advert ended with the statement that, clinical trials had shown Expansine to be very effective against fungal skin conditions and large-scale production was underway. In contrast to the earlier stated NRC reports that Expansine was too toxic for internal use, therefore, this advert of Brocades, Stheeman and Pharmacia

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[32] W.T. Nauta, H.K. Oosterhuis, A.C. van der Linden, P. van Duyn and J.W. Dienske, 'The Structure of Expansine, a Metabolic Product of *Penicillium expansum* Westling with Antibiotic Properties, *Rec. Trav. Chim.*, 64, (1945), pp.254-255.

[33] *Rec. Trav. Chim* is short for *Recueil des Travaux Chimimiques des Pays-Bas*. It is the publication of the Dutch Chemical Society based in Amsterdam.

[34] B.C.P. Jansen, *et al*, 'De Isolering', pp.718-720.

concentrated on its commercial success for 'skin conditions' and pointed to the production of a 'salve', or ointment.[35]

In the official BS&P company history, the halt in Expansine production does not refer to toxicity problems. The claim here is that research was not continued because BS&P methods of production not only coincided but also collided with the American and English methods of production, for which patents had been granted during the war years. Added to that, at the end of the war, the lack of availability of raw materials hindered the making of necessary fermentation apparatus. This, in turn, made the possibility of any penicillin-like production impossible. As a result Brocades Stheeman & Pharmacia's Research Department dropped its thoughts on the production of fermentation based pharmaceuticals and sought a new path in synthetic pharmaceuticals.[36]

From the outset, therefore, it is clear from both primary and secondary sources that there was not only an academic interest in the development of a substance similar to penicillin in the Netherlands during the war years, but also an interest in the development of penicillin itself. As BS&P's advert illustrates, in 1943 eight 'work groups' coordinated their research. Added to that, at the end of the war, BS&P were exploring any commercial potential. What is striking is that, under the duress of occupation, the concerted Dutch interest in Expansine was largely left to its own devices. Given the restraints of occupation, research, in both the academic and commercial spheres, continued.

Dutch Wartime Research: The Dissemination of Information on Penicillin.

The post-war publication of BS&P Research Department's Preliminary Note indicates the interest in the research and development of penicillin and penicillin-like substances; it also

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[35] *Nederlandsch Tijdschrift voor Geneeskund*, Noodnummer XXVII, (6 October 1945), p.48. Source: Personal Communication, P. Faase, July 2005.
[36] Brocades. N.V. Koninklijke Pharmaceutische Fabrieken v/h Brocades-Stheeman & Pharmacia 1800-1950. Company publication, 1950, p.46.

illustrates how information on penicillin spread between academic communities during the war. For example, the second footnote of the Preliminary Note refers to a publication by Raistrick in *Lancet* 1943 but which is cited as having appeared in three non-British sources, namely:

> H. Raistrick et al, *Lancet*, 245, 625 (1943) c/f *Chemie*, 57, 79 (1944), *Renseignements Scient. Croix Rouge* Nr. 2, 44 (1944), *Nachr. F. Aussenhandel* Nr. 134 (1944).[37]

Although written in scientific short-form it is easy to follow Raistrick's ongoing influence in the development of penicillin through the Red Cross and German publications. At the time, *Chemie*, or *Die Chemie*, was the journal of the *Deutsche Chemische Gesellschaft* (German Chemical Society); *Nachr. f Aussenhandel* or *Nachrichten für Aussenhandel* (NfA, Foreign Trade News) was a German Trade Journal.

Footnote three of the Preliminary Note refers to another British wartime publication by a member of the Oxford Group, Ernst Chain, in 'E. Chain et al., *Lancet*, 246, 112 (1944)'. This is cited as taken from another journal named as 'C. 1944. II. 25.'[38] Similarly, the fourth footnote cited the American research of 'J.R. Hooper et al.', in '*Science*, 99, 16 (1944)' taken from 'C. 1944. II. 25.'[39] 'C' refers to the German Chemical Society journal, *Die Chemie*.

What these footnotes illustrate is the spread of information on penicillin from British and American sources. They also underscore the fact that information on contemporary research was being published in Germany. Further, although under the limits of occupation, this information was reaching those in the occupied Netherlands.

Adding to BS&P's footnoted sources, the Kluyver Archive affords further insight into the dissemination of information on penicillin within the occupied Netherlands through the NRC

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[37] W.T. Nauta, *et al*, 'The structure', Footnote 2.
[38] W.T. Nauta, *et al*, 'The structure', Footnote 3.
[39] W.T. Nauta, *et* al, 'The structure', Footnote 4.

newspaper. As stated earlier, the NRC had published on Expansine in August 1944. Before that, however, it had reported on penicillin. For example, the first of three articles on penicillin was printed on 23 February 1944. In a column entitled *Wetenschappen* (Sciences) the columnist wrote of an 'important new medicine, penicillin'. After relating the history of sulphonamides, 'a medical colleague' introduced the topic of penicillin and stated that it was 'safe to inject'.[40]

The second article appeared a month later, on 23 March 1944. The source of information for this NRC articles was given as *Nachrichten für Aussenhandel*, in turn, reporting from sources in 'the American press'. It presented 'the following extraordinary facts about the important new medicine Penicillin'. It related penicillin's importance in recovery from open wound infections, lung infection, infected burns, wounds and abscesses. It described penicillin's safety and compared it to the sulphonamides, 'which could cause kidney problems'. Further, this article clearly illustrated the progress of penicillin from Fleming in 1928 to Florey's 1940 publication, and the subsequent influence of the Rockefeller Foundation in the United States in 1941. It reported on the availability of increasing amounts of penicillin. It went on to describe the involvement of the American government and the setting up of twenty-two research groups for the further research and production of penicillin. It described three methods of production as 'surface culture', 'bran culture' and 'submerged culture', and quoted the price of penicillin as '$18,000 per pound, $2 per dose'. It stated that penicillin was a gold brown powder that had to be kept dry and that it had to be injected intravenously or intramuscularly. It ended with a discussion on the possible manufacture of penicillin and of problems still to be solved. It gave as an example, that, in order to produce penicillin the mould cultures had to be grown at the right temperature otherwise the mould would grow but produce no penicillin. It considered the need to understand the molecular structure of penicillin, how it was thought to work and the quest for a synthetic route. The article

[40] NRC, 23 February 1944. Source: KA, Penicillin Reprints Box.

concluded with the hope that 'around summer' there would be enough penicillin to permit civilian use.[41] It is worth noting that this NRC article was published in March 1944.

The third article was published in the NRC on 12 August 1944 which began with a report of the unsuccessful Expansine. It continued, however, with the success of '*Penicillium notatum* Westl.' in Britain and the United States.[42]

Clippings of all three of the above articles have been found in the Kluyver Archive. Research has shown that these are the only articles on penicillin to appear in the NRC during the war years.[43] Although not authored they illustrate a well-informed, up-to-date writer. All have the original source and date noted in Kluyver's handwriting. All have been highlighted by Kluyver at specific points. Initially, these articles underscore a lack of secrecy and open reporting of well-founded information on the development of Allied penicillin. For the development of penicillin in the Netherlands, the fact that Kluyver went to the trouble of cutting out, noting and keeping them illustrates his interest in the subject.

The Kluyver Archive holds further information on wartime penicillin production by the Allies. This was obtained from clippings of articles published in the previously mentioned German trade journal, *Nachrichten für Aussenhandel*. For example on 12 June 1944 the NfA reported from 'Stockholm' on penicillin production in the USA. This report was concise and informative. It told of a presentation given by Robert D. Coghill to the American Chemical Society. As has been shown, Coghill addressed the Americal Chemical Society on 5 April 1944.[44] This article, therefore, contained concrete contemporary information. It gave the United States penicillin production figures for 1943 and 1944. It named Oxford and Imperial Chemical Industries involvement in the development of penicillin in Britain, of the NRRL in

[41] NRC, 23 March 1944. Source: KA, Penicillin Reprints Box.
[42] NRC, 23 August 1944. Source: KA, Penicillin Reprints Box.
[43] Search of all issues of NRC 1944/1945. Source: Koninklijke Bibliotheek (National Library).
[44] This thesis, Chapter 2, p.45.

the United States and the University of Toronto in Canada. It named nineteen American companies involved in penicillin production and two in Canada. It gave clear information on the methodology being used by these companies in the manufacture of penicillin. It referred to other possible penicillin producing moulds and gave Raistrick's work with Patulin, from *Penicillium patulum*, at the London School of Hygiene and Tropical Medicine, as an example.[45]

This article further illustrates the flow of information on penicillin in that it related the above article back to an earlier publication in the NfA of 3 January 1944. Also, reports on penicillin research and development appear in later editions. For example, on 6 July 1944 'Stockholm' told of a joint 'Society of American Bacteriologists, Squibb Institute of Medical Research and Iowa State College' report to the 'National Research Council'. It listed production figures from the War Production Board. It printed, in English, the whole text of a statement by Dr. Keefer in which he concluded that 'penicillin is the best therapeutic agent available' although 'at the moment production is reserved for the military'.[46]

The reference to Keefer clearly illustrates the level of information on penicillin research being reported from in the United States. At the time he was Chairman of the Committee on Chemotherapy of the US National Research Council.[47] His statement reflected the extent of research that had been undertaken with penicillin. Not only did he show the positive effect of penicillin, he also pointed to its limitations with gram-negative infections. He was very specific on the Oxford Unit, which was the amount of penicillin contained in 1 ml of buffer solution that would produce a defined zone of inhibition in an agar plate seeded with staphylococci.[48] He was explicit about how penicillin should be administered. Such reporting

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[45] NfA No. 134, 12 June 1944. Source: KA, Penicillin Reprints Box.
[46] NfA No. 155, 6 July 1944. Source: KA, Penicillin Reprints Box.
[47] G.L. Hobby, *Penicillin*, p.110.
[48] K. Brown, *Penicillin Man. Alexander Fleming and the Antibiotic Revolution*, (United Kingdom: Sutton Publishing, 2004), p.114.

clearly shows the impact penicillin was having in the medical world in 1944 and the NfA highlights this for any reader, friend or foe.

The last NfA article relevant to the development of penicillin in the Netherlands found in the Kluyver Archive was published on 10 July 1944. This edition reported from the American press, again via 'Stockholm', and cited R.D. Coghill, the NRRL and the American Chemical society. It reported on information originating from 'Gotenberg' and referred to the upscaling of penicillin production through fermentation techniques at Parke Davis & Co., Schenley Research Institute and the Chemical Solvents Corporation'.[49] Clearly, therefore, the NfA had the resources and ability to report extensively on the state of penicillin development both in Britain and America. To Kluyver such up-to-date reports would have been invaluable.

However, it has to be noted that, unlike the NRC reports and the NfA publication of 12 June 1944 which are in their original form, the NfA articles of 6 and 10 July 1944 are not. They are typewritten A4 carbon copies. They are titled *Heilmittel* (Cure). Other than the typewritten NfA title with publication number and date, no information is given regarding the source of the document. It could be that these articles were the result of regular reporting to Kluyver through a library information service. It could be that they were passed to him via NG&SF. As a commercial company it is likely that NG&SF, as BS&P has shown, received German trade journals. What they do underscore, is that during the war and under occupation, Kluyver had an active and ongoing interest in the development of penicillin.

Regarding the flow of German based information on penicillin, the Kluyver Archive illustrates yet another source. This is a typewritten summary of articles contained in the German journal *Chemisches Zentralblatt* of 21-28 June 1944. This journal, it is stated, included reports on the publications:

> J.W Foster and H.B.Woodruff, *Chemistry*, vol. 148, p723, 1943; E.C. Roberts et al., *J. Boil. Chemistry*, vol. 147, p47-58, Jan 1943, St. Louis, Univ., School of Med., Dep. of Bacteriol. and Biochem; M.E. Florey and R.E.C. Williams, *Lancet*, vol. 246, p73-81. 15/1 1944, Birmingham, Accident Hosp., Med. Res. Council Unit;

[49] NfA No. 158, 10 July 1944. Source: KA, Penicillin Reprints Box.

> D.A. Joslin. *Science* (New York), vol. 99, p21-22, 7 Jan 1944, Detroit, Mich., Parke, Davis and Comp., Res. Labor; D.L. Augustine, D. Weisman and J. McAllister, *Science* (New York), vol. 99, p19-20, 7 Jan 1944, Harvard Univ., Schools of Med. and Public Health, Dep. of Comparative Pathol. and Trop. Med.[50]

The author of this typewritten page is simply 'Junkmann'. No further information is given. However, this summary is a further illustration that high-quality information on penicillin was reaching the Netherlands and that it came through German sources.

Finally, the Kluyver Archive furnishes another critical piece of information on the research and development of penicillin taking place outside the Netherlands during the war years, but which was openly reported within the Netherlands. It is contained in the Dutch publication *Keesings Medisch Archief* (KMA; Keesings Medical Archive). During the war, like most press-related organisations, Systemen Keesings, as the founding company was known, was given a German overseer. All Jewish workers were sacked and Isaac Keesing, the Jewish founder, fled with his family to the United States. The KMA continued to be published in Amsterdam under the editorship of seventeen Dutch medical Professors and Doctors. Their task was to present articles covering the most important medical publications from inside the Netherlands and abroad.[51]

On 14 July 1944, KMA published an article simply and openly entitled 'Penicilline' (Penicillin). It identified its source as the '*Schweizerische Medizinische Wochenschrift*' (SMW; Swiss Medical Journal) of 10 June 1944. From here the un-named author proceeded to précis the whole issue of this Swiss Journal.[52] The editor of the SMW was named as Prof. C. Hallauer of Bern University. The articles were written by Hallauer; A. Wettstein of Ciba, Basel; and, G. Rieban of Basel University. The whole issue was given over to the reporting of the most up to date information on penicillin as a therapeutic agent that had taken place in

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[50] Source: KA, Penicillin Reprints Box.
[51] Personal Communication, Communication Sonja Weijtboer, Keesing International Publishers BV, Amsterdam, March 2005.
[52] *Keesings Medisch Archief*, (14 July 1944), No. 297, pp.1219-1222.

both Britain and the United States. Included were reviews of publications by Lawrence P. Garrod, Alexander Fleming, Ernst Chain and Howard Florey, all of which were quoted as published in the'British Medical Bulletin, 2, 1, 1944'.[53]

The impact of this edition of SMW in the Netherlands is evidenced by the fact that in October 1944 the Dutch Medical Journal also published an article simply entitled 'Penicilline'.[54] As with Keesings, this article was based on the Swiss Medical Journal of 10 July 1944. Written by Dr. N. Lubsen it was printed on the first page of the first *Noodnummer* of the NTvG under the banner *Oorspronkelijke Stukken* (Original Articles). Lubsen opened with the statement that, up until then only small amounts of information about the new medicine, penicillin, had reached the Netherlands. It was known that penicillin was available to the British and American military. However, the July issue of SMW had highlighted Allied research via the reporting of Hallauer, Wettstein and Ribben. Like Keesings, Lubsen continued with a full description of the preparation of penicillin; the Oxford Unit; physical / chemical properties; bacteriological research; animal tests; and, the clinical application of penicillin in the battlefields of Algeria and Italy. His conclusion highlighted the anticipation of the Dutch medical fraternity, that 'with penicillin, we have at our disposal a highly powerful medicine against many different infections'.[55]

There is no evidence to suggest how Kluyver came to possess the four pages of Keesing Medical Archive or when he actually received them. It is also difficult to understand why others interested in the research and development of penicillin and penicillin-like substances in the Netherlands, for example Nauta *et al*, do not cite this KMA publication as a source of reference. However, the fact that only these pages, only those relevant to the development of

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[53] *Keesings Medisch Archief*, (14 July 1944), No, 297, pp.1221-2.
[54] N. Lubsen, 'Penicilline', *Nederlandsch Tijdschrift voor Geneeskunde*, Noodnummer 1, (7 October 1944), pp.1-4.
[55] N. Lubsen, 'Penicilline', p.4

penicillin, have been found in the Kluyver Archive illustrates his active interest in the development of penicillin.

The Pivotal Role of Albert Jan Kluyver in the Development of Penicillin in the Netherlands.

For Kluyver, the academic and commercial reporting of research with penicillin, such as those contained in the Kluyver Archive, would have been invaluable. Since becoming Professor of Microbiology at the TH in 1921, under his leadership comparisons between various yeast cultures had led to one of the subjects for which he is most famous, namely comparative biochemistry. In addition, whilst at the time the most common way of growing moulds for fermentation was floating colonies on liquid media in stationary vessels, Kluyver, with his post-graduate student, L.H.C. Perquin, had shown that if a fungus was grown submerged and aerated from below it grew as small balls of mycelia, did not form spores and gave easily reproducible results.[56] Kluyver and Perquin had published their findings in 1933. From this work came 'Kluyver's *kolfje*' (Kluyver's flask, Appendix 4a) which is still routinely used for many types of aerobic batch culture.[57]

Kluyver also emphasised the industrial usefulness of his department's research. Not only did he lend books, journals and reprints from his laboratory collection to the bacteriologists employed in industrial laboratories, he was also interested in acquainting his students with the functioning of such industries. He clearly anticipated that these were the settings in which his graduate chemical engineers, trained in microbiology, would be likely to look for employment. As such he actively canvassed industrial employment for his graduates which, in turn, established and maintained a personal contact for Kluyver within industry.[58] His

[56] L. Robertson, 'The Delft School of Microbiology, from the Nineteenth to the Twenty-first Century', *Advances in Applied Microbiology*, 52, (2003), pp.372-379. Personal Communication, ongoing.
[57] L. Robertson, 'The Delft School', pp.372-379.
[58] O. Amsterdamska, 'Beneficient Microbes: The Delft School of Microbiology and its industrial connections' in Bos, P., and Theunissen, B., eds., *Beijerinck and the Delft School of Microbiology*, (Delft: Delft University Press, 1995), p.198.

relationship with NG&SF had been formalised in 1933 and by 1940 his position as advisor within that Company was well established.

In the wider academic world, Kluyver's knowledge and ability in the field of microbiology had earned him an esteemed reputation both in and outside the Netherlands. For example, in 1932 he became a member of the board of trustees for Toegepast Natuurwetenschappelijk Organisatie (TNO, Organisation for Applied Scientific Research) and, from this time, was a member of many of its committees.[59] Internationally, as the proceedings of the meeting of the Second International Congress for Microbiology held in London in July 1936 illustrate, he had contact with and was part of an international elite, which included, among others, Fleming, Raistrick, Clutterbuck and Waksman.[60] Through such contacts it is known that his advice was sought not only in the Dutch academic field but also from abroad.

Cornelius B. van Niel, for example, who had completed his PhD under Kluyver at Delft in 1928, had gone on to Hopkins Marine Station, Pacific Grove, California. In September 1939 he was one of the main speakers at the Third International Congress for Microbiology with other microbiological experts such as Dubos and Waksman. In this high-ranking circle, Van Niel's research was considered, not only scholarly, but also inspiring. Nonetheless throughout his highly successful academic life van Niel constantly paid tribute to Kluyver, his mentor.[61]

It is perhaps ironic that because occupation brought isolation, Kluyver was not aware of his influence on the American production of penicillin. In the Journal of Bacteriology of April 1946, the research of J.W. Foster, H.B. Woodruff and L.W. McDaniel on the production of penicillin in submerged cultures with *Penicillium notatum* was published. The manuscript had been ready for publication in May 1943 but was withheld from publication under the US

[59] A.F. Kamp, J.W.M. La Riviere and W. Verhoeven, *Albert Jan Kluyver. His Life and Work*, (Amsterdam: North Holland Pblishing Company, 1958), p.31.
[60] KA, Catalogue 1990373, 1936.
[61] KA, Catalogue 1990083, Folder 2, Letters S-Z, C.H. Werkman to Kluyver 9 November 1939.

Government secrecy order. In their introduction, Foster *et al* discuss the conditions of agitation and aeration needed to induce the mould to develop homogeneously. The source for their methodology they quote as 'Kluyver and Perquin, 1933'.[62]

Of particular interest in the development of penicillin in the Netherlands is a correspondence between Kluyver and another of his PhD graduates, Johannes C. Hoogerheide. Hoogerheide had completed his studies at Delft in 1935 and by 1940 was employed in the Biochemical Research Station of the Franklin Institute, Newark, Delaware. Barely a month before the occupation of the Netherlands, 25 April 1940, Hoogerheide wrote to Kluyver reporting on data about the 'capsule forming of bacteria'. In this letter Hoogerheide wrote that when he cultivated these bacteria he could produce a substance that inhibited capsule forming and said that his substance was similar to that of Dubos. There was great excitement in the press about it as it was seen as the most potent anti-bacterial substance for gram-positive bacteria known.[63] Almost a year later, 24 March 1941, Hoogerheide wrote to Kluyver regarding his substance, which he had called H1. He said that it had been used in various hospitals for the treatment of very badly infected wounds and the results were 'more than pleasant'. His intention was to go on to find other extracts from soil bacteria with the hope of finding one that was not too toxic and which could be injected. Also, although he could not say much about the detail, some H1 had been sent by plane to treat 'Tommy' and he hoped the result for 'him' would be just as good as for the patients Hoogerheide himself had seen.[64]

Hoogerheide's use of the word 'Tommy' could be a direct link to British military trials with anti-bacterial substances, as well as penicillin, as early as 1941. Further, he mentions a visit to his laboratory by Coghill and of Coghill's own research with penicillin. At this time America was not in the war. Could Hoogerheide's communication be indicative of a British / US

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[62] J.W. Foster, H.B. Woodruff and L.E. McDaniel, 'Microbiological Aspects of Penicillin. IV. Production of Penicillin in Submerged Cultures of Penicillium Notatum', *Journal of Bacteriology*, 51, 4, (April 1946), p.465.
[63] KA, Catalogue 1990132, Folder 3, Letters G to L, J.C. Hoogerheide to Kluyver, 25 April 1940.
[64] KA, Catalogue 1990083, Folder 3, Letters H to Z, J.C. Hoogerheide to Kluyver 24 March 1941

collaboration before American entered the war? The envelope is still attached to the letter. It bears the stamped insignia of a Nazi censor. This confirms that the letter had been opened and passed on without comment. The German supervisor obviously either could not speak Dutch or had no knowledge, or interest, in either microbiology or penicillin.

On 17 July 1941 Kluyver replied to Hoogerheide that he was very interested in his research. He could not access any American journals and, to try to keep up to date, he had to do with reprints. He congratulated Hoogerheide on his visit from Coghill and continued that 'at the moment' there was not much to talk about from Delft. He had not been able to do much research as he had been appointed as Chairman of the Department and an *Assessor* (Examiner). Also, for several weeks he had had to act as the replacement for the Rector Magnificus who had been forced to resign.[65] On 14 October 1941 Hoogerheide wrote to Kluyver of his move to New Brunswick, New Jersey. He had a new job with the Squibb Institute and would be near Waksman's laboratory. His task at Squibb was to produce larger quantities of H1. He also had to do other bacterial extracts of fungi and for this research quoted 'Fleming, 1929'.[66]

At this point the correspondence between Hoogerheide and Kluyver stops. In December 1941, following the Japanese attack on Pearl Harbor, the United States entered the war. Germany, in turn, declared war on the United States. It would be October 1945 before Hoogerheide and Kluyver could correspond again. What these few letters illustrate, however, is that up to October 1941 Kluyver, through a former pupil, had an active and informed interest in the anti-bacterial properties of both soil and fungal cultures.

[65] KA, Catalogue 1990083, Folder 3, Letters H to Z, Kluyver to J.C. Hoogerheide 17 July 1941.
[66] KA, Catalogue 1990083, Folder 3, Letters H to Z, J.C. Hoogerheide to Kluyver 14 October 1941.

The Relationship between Albert Jan Kluyver and the Nederlandsche Gist- en Spiritusfabriek, Delft.

The detailed reporting in the German NfA coupled with reports in a Dutch national newspaper, the NRC, add to Hoogerheide's letters. Together they would have alerted Kluyver of the research and development of penicillin not only in the United States but also in Britain and Canada. Yet, the Kluyver Archive has not produced any evidence of his inclusion in the research with penicillin or penicillin-like substances taking place elsewhere in the Netherlands, such as that at Brocades, Stheeman & Pharmacia. There is, however, evidence of his close association with NG&SF.

This close association is illustrated by the typewritten copy of the article from the NfA of 6 July 1944 contained in the Kluyver Archive and which referred directly to current Allied penicillin production. On the top right-hand corner Kluyver has written the name 'F.G. Waller'.[67] Whether Kluyver intended passing this article to Waller or is noting his source remains unclear. What is clear, however, is that Waller and Kluyver had a similar interest in the development of penicillin.

Kluyver's role at the NG&SF was advisory. Yet, his correspondence with Waller usually begins with '*Amice*', a clear indication of a close personal friendship. During the war years this relationship did not change, he continued to exchange information with them. For example, in a series of correspondence from May to July 1941, NG&SF request certain items: a preparation of beetroot concentrate; information on vitamin B6; and, the exchange of yeast cultures. He passed on to them, cultures of lactic acid bacteria that he had obtained for them through the American Type Culture Collection in Washington.[68] Until America's entry into the war, therefore, Kluyver had access to Washington's Culture Collection, which he shared with NG&SF.

[67] NfA 6 July 1944. Source: KA, Penicillin Reprints Box.
[68] KA, Catalogue 1990084, Folder 1, Letters N – S, Kluyver to NG&SF 1941.

As the war and occupation progressed, however, the change in the availability of academic information can be seen. For example, in September 1942 Kluyver wrote to Waller that he had managed to obtain copies of the two publications Stheeman and Rombouts had asked for through 'the good services of Prof. John Ronstrőm' of the Wenner-Grens Institute in Stockholm, Sweden. Earlier, in August 1942, he had written to Stheeman that he had asked Ronstrőm for the requested articles but that he could 'not do this too often as it puts people to a lot of trouble'.[69] Although the requested articles had nothing to do with penicillin, the fact that Kluyver had taken the trouble to contact a colleague in Sweden illustrates his loyalty and commitment to NG&SF.

A further link of the pivotal role played by Kluyver in the wartime research with penicillin at NG&SF is contained in three photocopies found in the Penicillin Reprints boxes of the Kluyver Archive. All are half A4 paper size with white print on a black background. All are stamped '*Bibliotheek D.B.M.*' (Library D.B.M.). Jan de Flines, a retired Research and Development Director of Gist-Brocades, has explained that, at the time, '*Bibliotheek D.B.M.*' indicated '*Bibliotheek Delft Brugge Monheim*' (Library Delft Bruges Monheim). NG&SF's Head Office was in Delft but had subsidiaries in Bruges, Belgium, and Monheim, Germany. As such this stamp is an indication of the sharing of library and information services between NG&SF headquarters in Delft and its daughter companies in Belgium and Germany.[70]

The first photocopy relates to the French journal *Comptes rendus des Séances de la Société de Biologie et de ses filiales* of June 1943. It is a copy of an article by C. Levaditi, H. Penau, R. Perault and L. Erichsen entitled 'Sur un Principe Staphylolytique Élaboré par une Variété de Penicillium *(*Penicillium *notatum*)*'.[71] This publication contains only six paragraphs, nonetheless, it covers the titre, activity and production conditions for penicillin. The footnotes refer to publications by the Oxford group in *Nature*, 1940, and *Lancet*, 1941 and 'C/f von

[69] KA, Catalogue 1990084, Folder 4, Letters T-A. Kluyver to F.G. Waller 1942.
[70] Personal Communication J. de Flines, February 2003.
[71] C. Levaditi, H. Penau, R. Perault et L. Erichsen, 'Sur un Principe', pp.359-360.

Kennel, Kimmig et Sembke' (sic, Vonkennel, Kimmig et Lembke) in the German publication '*Klin. Woch.*, 1943, 16/17, p.321'. This is a copy of the publication referred to earlier in this thesis concerning the development of penicillin research in France during the war years.[72]

Significantly, however, typed at the bottom of the photocopy's covering folder are the words '*Photocopie nr.6 in triplo*' (Photocopy number six in triplicate). The oval stamp '*Bibliotheek D.B.M.*' appears on the inside cover. On the back of the cover is stamped '*photocopie N.G.&S.F. Delft*' and, hand written in pencil at the top, is the name Prof. Kluyver. Kluyver, therefore, received a photocopy of a publication relating to penicillin research that had been presented in June 1943 in another occupied country, France, through the offices of NG&SF.

The same information holds for a second photocopy of *Comptes rendus des Séances de la Société de Biologie et de ses filiales* of October 1943 which contained an article by H. Penau, C. Levaditi, R. Perault and L. Erichsen entitled 'Propriétés du Principe Staphylolytique Élaboré par le Penicillium *notatum*' (Properties of a Staphylococcal Lytic Substance Obtained from Penicillium *notatum*). This article had been presented to the *Société* on 26 June 1943. Again it is a short article but it includes eleven points on the production of penicillin.[73] A paper folder also backs this photocopy. Typed on the front is the title of the journal and article copied. Bottom left indicates '*Photocopie nr. 7 in triplo*' (Photocopy number 7 in triplicate). The '*Bibliotheek D.B.M.*' stamp is found top left of the inside cover.

The third photocopy is an article by H. Penau and G. Hageman, 'Essais d'Extration d'une Substance Bactériche d'Origine Fungique' which had appeared in *Comptes rendus des Séances de la Société de Biologie et de ses filiales* in December 1943.[74] It had been photocopied '*in triplo*' eight times. This publication has been quoted earlier in this thesis

[72] This thesis, Chapter 2, p.56.
[73] H. Penau, C. Levaditi, R. Perault et L. Erichsen, 'Propriétés du Principe Staphylolytique Élaboré par le Penicillium *notatum*', *Comptes rendus des Séances de la Société de Biologie et de ses filiales*, 137, 19-20,(October 1943), pp.592-594.
[74] H. Penau et G. Hageman, 'Essais d'Extration', pp.724-725.

when covering information circulating France.[75] From all three of the above reprints it is clear that NG&SF had knowledge of and access to information on penicillin published in wartime France.

However, the most stunning piece of information on the development and dissemination of information on penicillin research circulating in mainland Europe during the war years is evidenced by a fourth photocopy found in the Kluyver Archive. It is the whole issue of the journal *Schweizerische Medizinische Wochenschrift* of 10 June 1944.[76] This is the journal mentioned earlier, summaried by Keesings Medical Archive and the NTvG.[77]

On this photocopy, the stamp '*Bibliotheek D.B.M*' appears on top of first page but it is obviously a copy of a copy. Handwritten on the copy cover in pencil is '*ex Prof. Kluyver*' (copy for Prof. Kluyver). A typed label at the bottom left of the cover states '*Photocopie nr.13 in 4 voud*' (Photocopy number 13 four fold). The footnoted citations for each article contained in this Journal run to pages and cover all aspects of contemporary British and American publications. For example, Hallauer, the editor, references 154 footnotes, while Wettstein cites 159 sources. Add to that the fact that Kluyver has used his traditional red pen to highlight specific information on pages 618, 619, 620, 621, and 636 is an indication of the impact of this publication for penicillin research in the Netherlands during the war.

All of the above indicate that Kluyver received photocopies of articles pertinent to the development of penicillin via the library of NG&SF. Yet, it cannot be said exactly when he received them. The date of photocopying is not noted. However, from the CBS archives we know that Penau, the joint author of two of the articles, visited the CBS at Baarn in December 1943, and that he spoke with Prof. Jansen about penicillin.[78] It is feasible that this visit

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[75] This thesis, Chapter 2, p.57.
[76] *Schweizerische Medinizinische Wochenschrift*, 74, 23, (10 June 1944).
[77] This thesis, this Chapter, pp.95-96.
[78] This thesis, Chapter 2, p.70.

stimulated contemporary Dutch interest in Penau's research. Following this, NG&SF may also have been alerted to Penau's research.

Burns and van Dijck have illustrated that the article by A. Wettstein, entitled 'Penicillin', contained in the *Schweizerische Medizinische Wochenschrift* of June 1944 was pivotal for penicillin research and development at NG&SF.[79] Andreas Querido, NG&SF advisor, had clandestinely acquired a copy of the whole of the Swiss Medical Journal when it was only weeks old.[80] While this chance window of opportunity will be discussed later, it has been shown that Querido took this journal to Delft. It is reasonable to assume that the copy of the Journal contained in the Kluyver Archive is a copy of 'Querido's' SMW made at NG&SF. Not only that, but it was copied at least '13' times. Others, therefore, also received copies of a Journal that contained information on penicillin, based on quality publications from both Britain and the United States.

Conclusion.

In conclusion, during the early years of occupation the Dutch medical and pharmaceutical worlds remained relatively unscathed, although occupation brought an attempt to Nazify both professions. As the war progressed, however, the demands of the Occupier intensified. Both doctors and pharmacists felt the strain and, towards the end of the war, the supply of medicines became extremely difficult. To begin with, this was due to a general deterioration in supplies rather than the specific actions of the occupier. However, after the failure of the Allies at Arnhem, the further restriction of medical supplies imperilled the un-liberated population.

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[79] M. Burns, 'Codename Bacinol', p.57, M. Burns and P.W.M. van Dijck, 'The Development of the Penicilin Production Process', p.191; M. Burns, J. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.28.

[80] M. Burns interview with Professor Querido December 1999; A. Queirdo, *Andries Querido*, p.92-93

In the development of penicillin in the Netherlands the first introduction of the 'wonder drug' to the Dutch population came as they were liberated. However, in the academic world, the concept of research with a penicillin-like substance is evident from 1939 in the work by van Luyk. Taken further by the Research Department of Brocades Stheeman & Pharmacia the short history of Expansine illustrates that research continued and gathered momentum from 1943.

The CBS Archive further highlights the dissemination of information on a possible antibacterial agent within the Netherlands during the war years. From 1943 onwards, the existence of an organised collaboration between academics, governmental institutions and commerce in an effort to reproduce a penicillin-like substance is clear. From the outset, therefore, it cannot be said that there was a complete lack of knowledge or a lack of interest in the research and development of an anti-bacterial substance in the Netherlands during the Second World War. On the contrary, it would appear that the concept of anti-bacterial substances was well established in the Netherlands. Certainly before the autumn of 1944, when Allied medical staff brought penicillin into the liberated south, albeit for 'military use only'.

The role played by Albert Jan Kluyver in the dissemination of information on penicillin at NG&SF remains critical. His correspondence with Hoogerheide, a former pupil, illustrates that, up to 1941 Kluyver was aware of pre-war research with anti-bacterial substances taking place in the United States. The fact that he cut out and kept Dutch and German newspaper clippings is indicative of his active and ongoing interest in the development of penicillin. It was an interest he would no doubt discuss with his former pupils at NG&SF.

However, as has been shown, as the war progressed access to academic publications became difficult. Nonetheless, German and French publications on penicillin could be and were accessed. Some were copied in Delft; Kluyver was among the recipients. Also, the neutral

Swiss produced one of the decisive building blocks on penicillin research with the publication of the SMW in June 1944. At NG&SF this was copied several times; Kluyver received the copy'13'.

While it must be noted that the circle of academics both producing and with access to such publications was small, these publications not only offered a platform for research, they were also a way of keeping in touch. As the war progressed, information can be seen to filter through, not only in scientific journals, but also commercial and trade newspapers. These publications offered surprisingly up-to-date information on the Allied development of penicillin at a time of embargo. In the occupied Netherlands, for Kluyver and the staff of NG&SF such information would have been invaluable. That is not to say that their task was made any easier, on the contrary it acts to emphasise NG&SF's success where others failed.

Chapter 4

Bacinol at NV Nederlandsche Gist- en Spiritusfabriek, 1940-1945.

In an interview printed in the Company newspaper *De Fabrieksbode* of 15 October 1960 F.G. Waller, President-Director of the Koninklijke Gist- en Spiritusfabriek, marked his 65th birthday and looked back at the experience of NG&SF during the war years. Then he was Deputy Director but as he explained:

> There was little to do during the war. Exports were cut off and it was difficult to obtain raw materials. Demand for yeast was limited and we did our best to keep the workers inside and the occupier outside our factory walls. We were kept busy by making vitamin C for the Ministry of Health, an endeavour that brought us new technical skills in making synthetic preparations. ... This was something which lay outside our known microbiological area of yeast fermentation but a chemical exercise that, with hindsight, stood us in good stead with penicillin.[1]

Penicillin was, therefore, successfully researched at NG&SF, Delft, during the war years. However, at a time of apparent embargo on information surrounding the development of penicillin in the US and UK, the question has to be asked: How was research in Delft with *Penicillium* strains possible? How did news of penicillin reach Delft? How was this research kept secret from the Nazi occupiers, who could themselves have made good use of the 'wonder drug'? Moreover, how could NG&SF develop penicillin where so many others, as this thesis has shown, failed?

Although occupied by Nazi Germany from May 1940, it has been shown that researchers in the Netherlands did have access to informed French and German publications. Also, publications from neutral countries, such as Switzerland, which were based on Allied publications, managed to filter through. Nonetheless, it needed experts in the microbiological field to understand these

[1] *De Fabrieksbode*, 15 October 1960, p.269.

reports on the methodology used in the development of penicillin, and on the possible existence of other antibacterial substances.

At the same time, the sheer scale of the production organisation available in both Britain and the US stands in stark contrast to the facilities available in occupied Netherlands. As has been seen, in the UK the Medical Research Council had brought together the combined talents of academic research and industrial experience. In the USA the War Production Board did the same. Added to that, the United States and the UK shared information on current research and development of penicillin. How, therefore, did a yeast factory in Delft manage to mirror the achievement of such a joint venture?

The Nederlandsche Gist- en Spiritusfabriek: The Pre-War Years.

For NG&SF, as with most of Dutch trade and industry, the beginning of the occupation period allowed a degree of independence. The plant was allocated an Overseer by the German authorities,[2] and the role of NG&SF as a vital element in the Dutch baking industry allowed the continuation of production. Since its foundation by Jaques van Marken in 1869 NG&SF had been an important producer of yeast, an ingredient required for the production of a daily staple, bread.[3] Willem de Witte, a former Public Relations executive at Gist-Brocades, roots the importance of NG&SF as a producer of yeast as the reason for the lack impact of the pre-war depression on the company. According to de Witte, 'When things are going badly people eat more bread, and, making bread needs yeast'.[4] Burns and van Dijck show that, as yeast was supplied to bakers two

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[2] Personal Communication H.M. de Horn, November / December 1999.
[3] *Brood op de plank. 130 jaar 'De Gistfabriek' in Delft*, Gist-Brocades, 1999, pages not numbered. Literally translated *Brood op the plank* means 'Bread on the Plate', more colloquially 'Earning a Crust'. Van Dale, *Handwoordenboek, Nederlands – Engels*, (Utrecht / Antwerp: Van Dale Lexiografie, 1988) cites *'brood op de plank'* as 'to make ends meet'.
[4] W. de Witte, 'De geschiedenis van ons concern', (The History of Our Company), Personal circulation, unpublished, 1991, p.4; Personal communication W. de Witte 1999.

of the by-products also became profitable. The fermentation liquor was distilled to obtain alcohol and the remaining product supplied to the animal feed industry as fodder.[5] Indeed, the Gist-Brocades company publication *Brood op de plank*, further illustrates the period from 1920 to 1940 as a time of international expansion.[6] Unlike others suffering from the worldwide economic depression, NG&SF took over twenty-seven factories both within the Netherlands and abroad. For example, to the existing subsidiary in Bruges, Belgium, were added a malting factory in Schiedam; alcohol producing plants in Liege and Sappemeer; fermentation plants in London and Manchester in the United Kingdom, Monheim in Gemany; and, Lisbon in Portugal. In Delft two new plants, Factories C and E, were built. The Company developed butanol and acetone for the paint industry and chemically produced ether from alcohol. They also produced the market leader of the yeast industry, *Koningsgist* and followed this with the introduction of a dried yeast product, *Engedura*.[7] The economic crisis that shook the world during the 1930s, therefore, appeared to have had little impact on NG&SF.

Elema points out that NG&SF had built up a prestigious reputation for technical knowledge through their experience and research in fermentation techniques.[8] In May 1923 F.G. Waller Jnr had joined the company and it was in the late 1920s that production processes were developed for butanol and acetone using microbial strains. There is no doubt that these diversifications were brought about by Waller's passion for research and development. Waller was a charismatic figure with exceptional leadership qualities. But, Elema also has no doubt that being a member of the family that owned and directed NG&SF ensured that Waller's innovative ideas reached fruition quicker than might otherwise have been the case. Burns and van Dijck note that between 1928 and 1933 NG&SF research was strengthened by the recruitment of three young

[5] M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.186.
[6] *Brood op de plank*, Section 1920-1930; 1930-1940, pages not numbered.
[7] *Brood op de plank*, Section 1920-1930; 1930-1940, pages not numbered.
[8] B. Elema, *Opkomst*, pp.25-27.

microbiologists/biochemists, A.P. Struyk, A.A. Stheeman and Elema, all of whom were post-graduates from Kluyver's Delft School, and a physical chemist, L.M. Rientsma.[9] From 1935 onwards Waller was Director of Research and Production. By the late 1930s the company headquarters in Delft had laboratories for research and development, a library, instrument makers, glassblowers, and an extensive and well-trained staff of biochemists and microbiologists.[10] They were accepted authorities in their field.

The 1949 NG&SF Annual Report, in celebration of eighty years of commercial activity, contains a short history of the company and illustrates the economic success of NG&SF during the 1930s. At this time the company was under the Chairmanship of F.G. Waller's uncle, President-Director Wilhelmus Hendrik van Leeuwen. His brother, Herman Waller, was, like F.G., a Deputy Director. F.G. Waller was in charge of the Delft factory. In 1930 NG&SF posted an annual dividend of 24% although this fell back in 1931 to 18%. By 1940 the annual dividend was 15% which, considering the time of economic and political unrest, was high.[11]

The Nederlandsche Gist- en Spiritusfabriek: 1940-1945

Technologically the Gist, or Gistfabriek, as NG&SF was locally known, focused on yeast fermentation and on the fermentation industry. Their yeast was needed for bread production, and it was for this reason that during the war years NG&SF was considered a *Rustungsbetrieb* (Public Service Company). On their compulsory identity cards, NG&SF personnel received a stamp noting their status as 'required workers'. This situation continued during the occupation thanks to the fact that the Rijksbureau Voedselvoorziening in Oorlogstijd (State Department for the Supply

[9] M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.127.
[10] M. Burns, 'Codename Bacinol', p.39; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.26.
[11] NG&SF Annual Report 1949, pages not numbered.

of Food in Wartime) had built up enough raw materials to supply NG&SF.[12] As 'required workers' most NG&SF personnel were protected from being taken for forced labour in Germany.

As the war progressed, however, the demand for yeast became restricted to the local market and production had to be cut. In addition, in 1942, Albert Speer deemed distilled alcohol a luxury good and production was curtailed.[13] Such alcohol and *Jenever* (Dutch gin) as there was went largely to the *Wehrmacht*. At the same time, raw materials became scarcer as the rapacity of German demands increased. NG&SF had to embark on other activities to fill its fermenters.[14]

At the behest of the Dutch administration, NG&SF ventured into the production of a new product, Vitamin C. In this NG&SF collaborated with two other Dutch companies, Shell and Chemische Fabriek Naarden under the Dutch Organisation for Nutrition and Food Division, a section of TNO. The Dutch authorities wanted the production of Vitamin C to help counteract the reduction in the quality and quantity of the food available to the Dutch population during the war.[15] The NG&SF pilot plant also worked on processes for the production of yeast extract in the form of a paste that could be used in the manufacture of soup cubes. This resulted in two new brand names, *Gistex* and *Aromex*, which added another valuable food source for the Dutch civilian population.[16] During the war years, therefore, the Gistfabriek by no means lost its inclination for research and development.

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[12] *De Fabrieksbode*, 2 May 1995, pages not numbered; NG&SF Annual Report 1949.
[13] Albert Speer came from the Todt Organisation. He took over from Goering in 1942.
[14] M. Burns, 'Codename Bacinol', p.41; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.188.
[15] B. Elema, *Opkomst*, p.34-35; M. Burns, 'Codename Bacinol', p.42.
[16] B. Elema, *Opkomst*, p.34; M. Burns, 'Codename Bacinol', p43; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.188.

As a result of the above research, new methodologies had to be addressed. Ernest Homburg submits that such wartime innovation and collaboration between companies such as Shell, Naarden and NG&SF was also a way of protecting company workforces, especially those linked into 'essential worker' status.[17] At NG&SF this collaboration brought with it the formation of the *Chemisch Technische Dienst* (CTD; Chemical Technical Service). A new group which soon became indispensable in the realisation of new projects.[18]

Yet, although collaborating with Shell and Naarden, at NG&SF secrecy remained paramount. For example, in a letter of 5 June 1942, Dr Westenbrink, of Amsterdam, wrote to Kluyver that he wanted to organize a Symposium for the Dutch General Society of Microbiology. In it he wanted to discuss yeasts. However, F.G. Waller of NG&SF had refused to allow any of his people to talk at the proposed Symposium because there was no patent protection in this area. According to Westenbrink, Waller had said that if he allowed his people to talk about yeasts he would be bringing everything that his research department had done for the last twelve years into the public domain, and he would not do that. He would be prepared to let one of his employees, Stheeman, talk about the determination of vitamin B12 and B6 but that was all. Westenbrink concluded that because of this the meeting would probably not be held because 'no stars could be brought in from the outside world'.[19] This letter, therefore, not only illustrates the secrecy Waller insisted upon to protect his market position, it also shows the high reputation enjoyed by those employed at the Nederlandsche Gist- en Spiritusfabriek in Delft.

At the same time, the fact that those at NG&SF were allowed to remain at their work place because they had received 'essential' status through their 'special skills' also afforded NG&SF

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[17] Personal Communication Prof. E. Homburg, University of Maastricht, 1999.
[18] B. Elema, *Opkomst*, p.36; M. Burns, 'Codename Bacinol', p.42.
[19] KA, Catalogue 1990084, Folder 4, Letters T-Z, Westenbrinck to Kluyver 5 June 1942.

workers a certain amount of freedom. Fermentation is a round the clock process with yeasts growing and maturing at their own pace. The time to harvest depends on yeast growth. For this reason NG&SF workers had to be able to come and go, even during curfew.

The coming and going of Gist personnel that accompanied the fermentation process was enhanced by the fact that the majority of NG&SF workers lived in the area immediately behind the fermentation plant. Known as the Agnetapark, this area had been specifically built by NG&SF founder Jacques van Marken to house Gistfabriek employees.[20] In the 1940s this situation remained. According to de Witte, during the war years a deep sense of solidarity grew within the NG&SF workforce and brought with it even closer social ties. C.H. Elzenga (Rien), a retired NG&SF employee, provides the atmosphere of a tight knit community in the Agnetapark with the information that F.G. Waller lived in Wallerstraat 1, Rientsma lived in number 3 and van der Lek in number 5. Elzenga lives at number 9.[21]

The *Fabrieksbode* illustrates that during the war years there was also a willingness within NG&SF management to take on new responsibilities for their workforce. While this could be viewed as a paternalistic stance there is no doubt that van Leeuwen and the Wallers did what they could to aid their employees. For example, on 18 January 1941 the *Fabrieksbode* gave notice that a number of *oorlogstuintjes* (war allotments) would be available for employees. Each was 100 square meters, the rent was Fl.2.50 per allotment. The intention was that they be used for growing vegetables. During 1941 the *Fabrieksbode* regularly printed advice on vegetable gardening.[22] On 30 August 1941 notice was given that warm meals for all personnel would be available as from Monday, 15 September 1941. The meal was meant as an addition to the daily diet and was the

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[20] The Agnetapark was named after NG&SF founder J.C. Van Marken's wife, Agneta.
[21] C.H. Elzenga, Personal Communication with M. Burns, 29 April 2005.
[22] *De Fabrieksbode*, 18 January 1941.

equivalent of '¾ of a litre of food'. It was made in a centralised kitchen in 'Factory C'. The food made was, for example, soup, stampot without meat, [23] and *'zuurkool en graanpap'* (pickled cabbage and porridge). It was subsidised and cost '5 cents a plate'.[24] While *zuurkool* is not immediately appetizing, pickled cabbage is known to be an excellent source of Vitamin B. By November 1941 NG&SF provided the children, aged between three and fourteen, of all of their employees with the vitamin A and D supplement, Bluevita, free.[25] The Company shop, maintained its subsidised prices throughout the war years, although under the restriction of rationing. It is also said that management turned a blind eye to *onderduikers* hiding within the factory walls.[26]

As stated earlier, the fermentation process resulted in, not just yeast but also alcohol. During the war the *Wehrmacht* indulged in NG&SF *Jenever.* According to H.M. de Horn, many a German officer could be seen leaving the factory *proef locale* (tasting station) in an unsteady manner.[27] At the time the average annual worker's salary amounted to around 1,400 guilders, but the price paid on the black market for a litre of *Jenever* was 300 guilders.[28] An amount brought into proportion by the bowl of food at 5 cents, albeit subsidised. NG&SF management were, however, aware of the temptations their workers were exposed to, and guard duties for the stocks of 'beet', 'grain' and 'potato' were added to the one for 'alcohol'.[29]

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[23] A popular Dutch dish consisting of a potato and carrot mash topped with sausage and gravy.
[24] *De Fabrieksbode*, 30 August 1941.
[25] *De Fabrieksbode*, 15 November 1941.
[26] Personal communication Jos van Leeuwen, Archivist, NG&SF Central Archive, 2002.
[27] Personal communication H.M. de Horn, 1999.
[28] *De Fabrieksbode*, 2 May 1995.
[29] *De Fabrieksbode*, 2 May 1995.

Penicillin Research at the Nederlandsche Gist- en Spiritusfabriek.

Referring back to F.G. Waller's interview with the *Fabrieksbode*, he specifically recalled the beginning of his interest in penicillin as 1943.

> When we first started looking, in 1943, only one publication was available, that of Fleming 1929. It was on that basis we started our research. By around *Dolle Dinsdag* we had a small amount of a substance, which we hoped, and which later to our joy proved to be, penicillin.[30]

While Waller does not give the source of his reason for 'looking, in 1943' by referring to 'around *Dolle Dinsdag*' he pinpoints Tuesday, 5 September 1944. *Dolle Dinsdag* (Mad Tuesday) was the day after the BBC erroneously reported that Breda had been liberated. The Dutch people assumed that the liberation of the entire country was only days away. Celebrations began and the population, eager to welcome their liberators, lined the streets. The euphoria was short lived. The battle at Arnhem failed. The Allies did not arrive and the German occupation remained. Waller's recollection, therefore, places September 1944 as the time that an antibacterial substance, which he hoped was penicillin, was in his possession

Contrastingly, while Waller marks the beginning of interest in penicillin at NG&SF as 1943, according to Elema it was the beginning of 1944 when the first reports on penicillin, '*dit wonderbaarlijke geneesmiddel van microbiologische oorsprong*' (this wonder medicine from a microbiological source) came to Delft. He cites the source of information as 'listening to the illegal radio' and the propaganda newspaper, the *Vliegende Hollander*.[31]

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[30] *De Fabrieksbode*, 15 October 1960.
[31] B. Elema, *Opkomst*, p.36.

In fact most publications regarding the beginning of penicillin research at NG&SF follow Elema's line. Accordingly, this has become 'the standard story'.[32] All refer to information received through listening to clandestine radio programmes. Some name the radio broadcast source as *Radio Oranje* while others say the broadcasts were from the BBC. Like Elema, most publications refer to information originating from the *Vliegende Hollander*. Moreover, like Elema,[33] all sources claim that penicillin was contained in the food dropped at Ypenburg in May 1945. From these drops NG&SF received a sample of American penicillin. It was against this sample that NG&SF compared their own substance, Bacinol. From this comparison NG&SF researchers found that Bacinol was in fact the same as US penicillin. Ultimately, at the end of the war, it was with this information that the Delft team decided to continue with penicillin production.

Further research indicates, however, that it is not entirely clear how news of penicillin came to Delft. In researching the possibility of hearing about penicillin through clandestine radio programmes, the archival record of written scripts for programmes transmitted through *Radio Oranje* in London have been accessed. No mention of penicillin has been found.[34] Also, as the BBC retains the written scripts of news bulletins for only a limited time, enquiries have been unable to uncover a possible BBC news bulletin as Waller's source on the 'wonder drug'

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[32] G. Verveen, 'De Historie en Bereiding van Penicilline', *T.V.Z.* (*Tijdschrift voor Ziekenverpleging* now *Tijdschrift voor Verpleegkundigen*), 1 March 1960; 'Gist en Geest', *Nederland Nu*, March 1962, pp.41-55; Gist-Brocades Company Publications: '30 jaar Nederlandse pencilline', 1973, '35 jaar penicilline', 1978; 'The Gist-Brocades file on Penicillin', *The Gist*, No. 2, August 1978; Van Fleming tot Flemoxin Solutab. Markente momenten in 60 jaar penicilline, 1988; C.P. van der Beek and J.A. Roels, 'Penicillin production: biotechnology at its best', *Antonie van Leeuwenhoek*, 50, 1984, pp.625-639; M. Burns, 'Codename Bacinol', p.54; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.189; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', pp.25-31.

[33] B. Elema, *Opkomst*, p.38.

[34] NIOD, Radio Orange written transcripts 30 May 1943 – May 1945.

penicillin. However, the BBC Written Archive does list thirteen broadcasts on or including the topic of penicillin between 1942 and 1944.[35]

The first of these broadcasts is dated 4 September 1942. Although not directly pertinent to Waller's date of '1943', this programme does give some insight into the breaches in the secrecy surrounding penicillin reporting, and highlights the inclusion of the mass media in the dissemination of information about the 'wonder drug'. Entitled 'Ariel in Wartime' it was transmitted between 6.45-7.05p.m on the Home Service from London. Presented by Joseph Macleod, the programme included a report on 'a remarkable advance in medicine', and the speaker referred to recent press references to 'a substance called penicillin'. The report continued 'if present hopes of it are realised, penicillin will be one of the most effective, if not the most effective means we possess of saving life in cases of certain diseases due to bacteria'. The broadcast then continued with a history of Fleming's discovery and went on to give a clear outline of the work being achieved with penicillin at Oxford. It reported on the 'purest penicillin yet produced'; that it was soluble in water; and, that laboratory tests had shown that it completely prevented the growth of staphylococci, 'the germs which may cause abscesses, carbuncles, sores and other diseases', in a dilution of between 1 in 24 million and 1 in 30 million'. In very plain English the report described the laboratory treatment of the 'culture medium' in order to 'grow' penicillin. It referred to the aim as being able to produce penicillin from its chemical constituents, which would allow for the build up of a quantity of penicillin 'from simpler, easily obtainable substances without having to use the mould *Penicillium* for its manufacture'. The broadcast concluded that it was 'good to know that even in wartime such vitalizing research is going on,

[35] BBC Written Archive, Ariel in Wartime, 4.9.42; Calling all Students, 2.9.43; Producing the Drug Penicillin (The little yellow weapon against death), 22/23.10.43; Topical Talk 20.12.43; Story of the Moulds, 29.12.43; War Office calling the Army, 24.1.44; Science Notebook, by Prof. A. Fleming, 10.4.44; Wm Holt Reports, Penicillin in Action, 4/5.8.44, 25/26.8.44, 14.9.44; What is it? 5.10.44; Health Magazine, Penicillin, 20.10.44; Science Notebook, Speeches from the opening of the Society for Visiting Scientists, 22.10.44; Penicillin, 14.11.44.

and that this British discovery of penicillin was likely to be followed up by British and American workers in collaboration'.[36] From this transmission any listener, friend or foe, would be aware of the current state of the research and development of penicillin by the Allies.

More in keeping with Waller's statement, was a transmission on 2 September 1943 from the Eastern Service, Purple Network. Entitled 'Penicillin' it was presented by Dr C.M. Fletcher between 10.15 -10.30 GMT. It was part of the Second Scientific Series 'Calling all Students'. This broadcast contained enough information to enable the listener to make crude penicillin and referred to the fact that 'if one mould can produce penicillin, perhaps other moulds will produce other substances with equally valid medicinal properties' and stated that 'this possibility is now being explored and is showing promise'.[37] On 20 December 1943 the 'Topical Talk', entitled 'Penicillin', was given by 'Professor H.W. Florey, F.R.S'. In this broadcast Florey gave a concise overview of the current development of penicillin starting with Fleming in 1929 and continued with a report on his research and that of his co-workers at Oxford. He further referred to raising the 'scale of penicillin production' in the laboratory at Oxford, and of it being given to '15 patients', the results of which had 'now been amply confirmed in this country and in America'.[38] This broadcast was made at the point of Florey's publication with Cairns in December 1943.

Although much about the development of penicillin in the UK in 1943 can be gleaned from these BBC broadcasts it cannot be said that any of these programmes had been listened to clandestinely at NG&SF in Delft. However, archival evidence does point to the existence and regular use of an illegal radio at NG&SF. According to H.C. Grundel, an NG&SF employee, when the occupier had forbidden listening to radio programmes, H.F. Waller had requested that a radio headset be

[36] BBC Written Archive, Ariel in Wartime, 4 September 1942.
[37] BBC Written Archive, Calling all Students, 2 September 1943.
[38] BBC Written Archive, Topical Talk: Penicillin, 20 December 1943.

placed in the *Zolder* (a room in the attic) of the main NG&SF office building.[39] It was put behind the Archive Room on the front-side of the building and could only be accessed by a narrow corridor that ran along the wall under the roof. For many months transmissions were listened to on a daily basis at *'half twaalf'*, (half past twelve: Dutch terminology for11.30am).[40] As the Netherlands is one hour ahead of British time, this suggests listening to a broadcast at 10.30am. The *Radio Oranje* archive shows that news bulletins were broadcast from London twice a day. The first was a brief news bulletin at midday, 12 noon. This would have been 1pm in Delft. The second, longer, transmission was in the early evening, 7.15pm in Britain, 8.15pm in the Netherlands. Grundel's timing, therefore, would suggest those at Delft listened to a BBC transmission.

Regarding the opinion that information on penicillin gleaned from the *Vliegende Hollander* was one of the original sources for those at NG&SF, it is so that in 1948 the *Fabrieksbode* reported on a speech celebrating F.G. Waller's 25 years with the company in which Kluyver reminded Waller of the time information about the 'wonder' medicine published in the *Vliegende Hollander* came to them through 'friendly hands'.[41] However, a search of the *Vliegende Hollander* archive has found no mention of penicillin.[42] Also, the publication *De Vliegende Hollander (22 mei 1943 – 10 mei 1945), fotografische herdruk van alle verschenen numbers*, a reprint of all published *Vliegende Hollanders*, gives no indication of articles on penicillin.[43] On the other hand, its forerunner and contemporary, *De Wervelwind* (The Whirlwind) does.

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[39] The Dutch population were required to hand in their radios in May 1943. Source: *De Vliegende Hollander (22 mei 1943 – 10 Mei 1945), fotografische herdruk*, Foreward: Dr. L. de Jong., pages not numbered.
[40] Delft Gemeente Museum, NG&SF Archive, Number 2210.
[41] *De Fabrieksbode*, 2 June 1948, p.7.
[42] Source: *Vliegende Hollander* Archief, NIOD; *Vliegende Hollander* Archief, NIMH.
[43] *De Vliegende Hollander (22 mei 1943 – 10 Mei 1945), fotografische herdruk van alle verschenen numbers*, (Amsterdam – Alphen aan den Rijn: Buijten & Schipperheijn / Repro Holland, 1976).

Published from April 1942 *De Wervelwind* was a monthly publication. Physically it was small with pages approximately 10 cm broad and 13 cm long. Each issue was about fifty pages in length. Like the *Vliegende Hollander*, it was spread over the Netherlands by Allied aircraft. While the *Vliegend Hollander* was a propaganda newspaper, *De Wervelwind* gave information on the war, but also featured a variety of news articles purporting to describe different aspects of life in the Allied countries. Its sources were based on articles from various magazines and newspapers, for example, Harpers, the Daily Sketch, the Daily Telegraph, the New Statesman, *La France Libre*, *Vrij Nederland* and Radio Orange. Like the *Vliegende Hollander*, it contained official reports of the decisions of the Dutch government-in-exile. In fact, many of the captions used in the *Vliegende Hollander* were repeated in *De Wervelwind* and vice versa.

In December 1943 *De Wervelwind* published 'De nieuwste resultaten der Britsche wetenschap' (The Latest Results of British Scientific Discovery). No author or source was given. In this article penicillin is named as one of five antibacterial substances used in trials during the North Africa campaign. A photograph of both Alexander Fleming and fermentation bottles containing antibacterial substances were shown.[44] Yet, whether the December 1943 issue of *De Wervelwind* was circulated is called into question. According to Leonard de Vries and Jan de Groot, *De Wervelwind*, number 17 is listed as 'NV'. In the code of the time this means *Niet Verspreid*, not distributed, and no date for circulation given.[45]

However, a second publication on penicillin appeared in *De Wervelwind* in February 1944. The author was 'Dr. A.M. Meerloo' and the publication was entitled 'Penicilline het nieuwe wondermiddel' (Penicillin the New Wonder Drug). It reported on the original discovery by

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[44] *De Wervelwind*, No. 17, December 1943, 'De nieuwste resultaten der Britsche wetenschap', pp.37-38.
[45] L. de Vries en J. de Groot, *De Wervelwind, De Vliegende Hollander en andere uit de lucht verspreide vlugschriften: Een fascinerende selectie uit de oorlogsjaren 1940-1945*, (Laren: Skarabee, 1974), p.158.

Fleming and the scale-up in penicillin production by Florey. It noted that the structure was not yet known and that it was a yellow powder. It told that the majority of production was destined for the fighting forces.[46] It is listed by de Vries and de Groot as distributed over the areas 'Appingedam, Delfzijl, Hilversum, Lage Vuursche, Keulen and Rucphen' during the night of 24/25 April 1944.[47] Although this information on the production of penicillin is not explicit, it would have been enough to stimulate interest, perhaps already whetted by radio broadcasts, at NG&SF. Yet this is no earlier that the previously mentioned reports in the Dutch daily newspaper, the NRC. As previously shown, the NRC first published on penicillin on 23 February 1944 and again, more extensively, on 23 March 1944.[48]

Running slightly contrary to the above, Klaas Scheurkogel covered the topic 'Technische bereiding van penicilline' (Technical Production of Penicillin) in the *Chemisch Weekblad* of January 1949.[49] Scheurkogel was the first Head of NG&SF's Antibiotic Department, which had been formed in January 1946. In his description of research with penicillin, Scheurkogel pointed out that between 1941-42 there was some knowledge in the Netherlands of antibacterial substances. This came from Hoogerheide's research with *Bacillus brevis*. He further pointed to some press reports in the German supervised Dutch newspapers about the 'wonder drug' penicillin, and said that, although forbidden, British radio transmissions on penicillin were both enthusiastic and technically informative.

However, Scheurkogel submitted that researchers at NG&SF had first become interested in penicillin through an article in the German journal, *die Naturwissenschaften* (Natural Sciences) of

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[46] *De Wervelwind*, No. 19, February 1944, 'Penicilline het nieuwe wondermiddel', pp.33-34.
[47] L. de Vries en J. de Groot, *De Wervelwind*, p.158.
[48] This thesis, Chapter 3, p.91.
[49] K. Scheurkogel, 'Technische bereiding van penicilline', *Chemisch Weekblad*, 45, (29 January 1949), pp.69-72.

16 July 1943. Although he did not give the author he gave the article as 'Die neueren biochemischen Erkentnisse und Probleme der Chemotherapie' (New Biochemical Experiences and Problems Associated with Chemotherapy).[50] In particular, he said, one sentenced stimulated NG&SF action: '*Es sollen beim menschen schon heilerfolge mit Penizillin erzielt worden sein*' (It is said that therapeutic success has been shown in humans). Following on from this, NG&SF obtained the original publication of Fleming and a few orienting tests were performed. From these tests those in Delft quickly came to the conclusion that for this type of research a team of experts was needed. Quietly and in secret NG&SF began to build a team from within its employees.[51]

The Kluyver Archive has shown correspondence between Kluyver and Hoogerheide over *Bacillus brevis*, which Hoogerheide named H1. Also, that French publications, of June and December 1943, had made their way to the occupied Netherlands. They had been photocopied and circulated through NG&SF library facilities.[52] It has also shown German commercial reporting as well as Dutch press reports.[53] Although forbidden, Grundel has verified that radio transmissions were listened to in NG&SF's *zolder* on a daily basis and *De Wervelwind* has indicated Allied propaganda reports on penicillin. Therefore, while Waller, Elema, and Scheurkogel give slightly differing versions of how news of penicillin stimulated research at NG&SF, it is clear is that, as Waller pointed out, when research started in 1943 there was only one publication to hand, the one from Fleming of 1929. 'It was on that basis a small group started work'.[54]

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[50] The author is Th. Wagner-Jauregg. Source: Chemical Abstracts.
[51] K. Scheurkogel, 'Technische bereiding', pp.69-72.
[52] This thesis, Chapter 3, pp.102-104.
[53] This thesis, Chapter 3, pp.90-94.
[54] *De Fabrieksbode*, 15 October 1960, p.269.

Elema, Scheurkogel and the Gist-Brocades company publication 'Van Fleming tot Flemoxin Solutab', say that it was NG&SF microbiologist Struyk who first assessed Fleming's 1929 publication.[55] Elema also claims that Struyk accessed a copy of the inconclusive results of the biochemical investigation conducted by Clutterbuck, Lovell and Raistrick which had been published in 1932[56] All cite the pivotal source for Delft research as an article written by the German scientist M. Kiese of the University of Berlin, entitled 'Chemotherapie mit Antibakteriellen Stoffen aus Niederen Pilzen und Bakterien' (Chemotherapy with antibacterial substances from moulds and bacteria). This publication appeared in volume 22 of the German journal *Klinische Wochenschrift* of 7 August 1943.[57]

Although Kiese's publication did not give detailed information on how penicillin could be mass produced he gave an overview of known antibacterial substances and the purification method for penicillin. He described what was known of penicillin's chemical structure; its antibacterial activity *in vitro*; its toxicity; pyrogenicity and its therapeutic effect in humans. His footnotes cited a total of 61 sources of research with penicillin published between 1923 and 1943. As well as referring to abstracts of the penicillin-related papers published by the Oxford group between 1940-1943, the whole publication reads like a who's who of those engaged in antibacterial research at that time.[58] What this article would have done for those at NG&SF was make it clear that, from the basic work of Fleming, others had gone on to prove the feasibility of isolating Fleming's penicillin and the viability of manufacturing it.

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[55] B. Elema, *Opkomst*, p.35; K. Scheurkogel, 'Technische bereiding', pp.69-72; Gist-Brocades Company Publication, Van Fleming tot Flemoxin Solutab. Pages not numbered.
[56] B. Elema, *Opkomst*, p.37. Footnote 1.
[57] B. Elema, *Opkomst*, p.37, Footnote 2; *De Fabrieksbode*, 1 September 1978, p.77; M. Burns, 'Codename Bacinol', p.55; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.189; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.28.
[58] Kiese, M., 'Chemotherapie mit', pp.505-511.

The impact of Kiese's article in the Axis countries has already been noted.[59] But this impact was in the academic sphere of research and development with penicillin. At this point the question must be raised: What made a company specialising in yeast fermentation access a German medical journal?

What is not in doubt is the influence of serendipity on research into penicillin at NG&SF, through the experience of Andries Querido. In 1939, Querido had been a post-graduate in medicine at the Pasteur Institute in Paris but returned home to Amsterdam when the Polish crisis brought with it the threat of war. On the advice of Kluyver, F.G. Waller offered Querido a position as advisor at NG&SF. Not wishing to compromise his medical work at Leiden University Hospital, Querido had accepted the post on a part-time basis. His remit, with Stheeman, was to take part in the production of a preparation for the Dutch market, which would provide enough vitamins for the required daily dietary intake.[60]

In 1940 everything changed. As a hospital employee, under the rules of occupation Querido had to sign the *ariërverklaring*. This required the submission of any Jewish family background. Both he and his wife had Jewish ancestors but he refused to fill in the form.[61] Instead, he resigned from his hospital post. His income from NG&SF was sufficient to allow him to do this. Querido and his wife moved from Leiden to Amsterdam, where they lodged with his sister and brother-in-law. In Amsterdam he found work in the Nederlands Israëlitisch Ziekenhuis as deputy head of the tuberculosis department. However, in January 1943 he, his wife and baby son were interned in Barneveld Camp.[62]

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[59] This thesis, Chapter 2, p.53; p.59.
[60] NG&SF Central Archive, Waller Archive, letter Waller to Querido, 11 April 1940.
[61] Querido's wife, Heleen Pimentel, is a prominent Dutch actress.
[62] A. Querido, *Andries Querido*, pp.90-94.

The Jews sent to Barneveld became known as the 'Barneveld Jews'. By August 1943 they totalled six hundred and forty. Made up of prominent Jewish citizens and housed in castle '*De Schaffelaar*' they were seen as a cultural elite who had been awarded a privileged status.[63] According to Adama Zylstra, in reality the 'castle' had been built to house around fifty people. This 'cultural elite' of politicians, writers, and lawyers, found themselves squeezed into wooden huts and bunk-bed dormitories. The noise was incredible as the inmates tried to 'act normally'; holding conversations, taking part in discussion groups and giving children lessons. There was no privacy. But worst of all were the washrooms, where a wooden gutter held the water for a constant queue of people, each waiting to use the water left by the person in front. In Zylstra's opinion, Barneveld, far from privilege, meant deprivation, dirt and misery.[64]

On 29 September 1943 the 'Barneveld Jews' were transported *en bloc* to Westerbork Camp. On 4 September 1944, as the south of the Netherlands was being liberated, they were taken, again as a unit, to Theresienstadt in Czechoslovakia.[65] Nonetheless, until the last day of his internment in the Netherlands, NG&SF stayed in contact with Querido. They cited the reason to the authorities that he was indispensable to the Company.[66] NG&SF employee, Johannes Rombouts, was his contact. Their meetings took place in the *Kommandatur* and, while speaking about scientific material, Rombouts passed Querido news of what was happening outside the camp.[67] It was a similar passing on of clandestine information from one academic to another that was to prove critical for the researchers of the NG&SF.

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[63] L. de Jong, *Het Koninkrijk*, VIII, Tweede Helft, pp.709-712.
[64] A. A. Zylstra, *Vaar Wel Scheveningen!*, (Leiden: A.W. Sythoff, 1974), pp186-187.
[65] L. de Jong, *Het Koninkrijk*, VI, pp.288-290; B. Moore, *Victims*, pp.132-134.
[66] A. Querido, *Andries Querido*, pp.90-94.
[67] A. Querido, *Andries Querido*, pp.90-94; A Querido, Personal Communication, December 1999.

As Querido explained, before being transferred to Theresienstadt from Westerbork he was allowed one last visit to NG&SF in Delft. He was allocated two days leave. This was a double-edged sword, he had two days of freedom during which he had no restrictions but his family remained in the camp, in effect held hostage until his return.[68] However, it was during these two days that chance played a role. When changing trains in Amsterdam Central Station, Querido met a former colleague, S. van Creveld, then Professor of Paediatrics in Amsterdam. Also of Jewish origin, van Creveld was under German supervision but as yet still free to move around. Querido was both surprised and delighted at their chance meeting. Bursting with news van Creveld explained to Querido that he was not only allowed freedom of movement, he was also allowed to receive foreign visitors. He had just had a visit from a colleague from neutral Portugal. This colleague had brought with him the whole issue of the recently published *Schweizerische Medizinische Wochenschrift*, which he had given van Creveld to keep.[69] This publication was completely given over to the subject of penicillin.[70] Querido knew the importance that this information would have for those at the Gist- en Spiritusfabriek and asked van Creveld if he could borrow it. At NG&SF the journal was copied. Later, it was returned to van Creveld via an undercover route. Critically, for those at Delft, this issue of the Swiss Medical Journal contained an article by A. Wettstein. Simply entitled 'Penicillin', it clearly showed the results the Allies had achieved.[71]

For example, as well as naming *Penicillium notatum*, Wettstein gave details of penicillin growth on a maize extract; of scale-up in bottles or porcelain containers; the measurement of strength by

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[68] A. Querido, Personal Communication, December 1999.
[69] *Schweizerische Medizinische Wochenschrift*, 74, 23, (10 June 1944).
[70] A. Querido, *Andries Querido*, p.93: M. Burns, 'Codename Bacinol, p57; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.191; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.30.
[71] B. Elema, *Opkomst*, p.36, Footnote 1; A. Querido, *Andries Querido*, p.93, A. Querido, Personal Communication, December 1999. M. Burns, 'Codename Bacinol', M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.191.

the Oxford unit; a dilution method; physical and chemical properties; animal studies; human studies; and, named bacteria that were either sensitive or insensitive to penicillin. Only a year after Kiese's publication based on 61 sources, Wettstein was able to cite 159 references. According to Elema, when they saw Wettstein article, the only question for the Delft team was: Could their laboratory research possibly achieve something similar?[72]

As the Kluyver Archive has shown, such was the importance of this journal that it was photocopied in its entirety and circulated. No record of photocopying or who received a copy has been found, but the label on Kluyver's copy reads '*Photocopie nr. 13 in 4 voud*'.[73] This journal, therefore, was copied at least thirteen times. There may have been more.

However, it was not just a 'chance' meeting in Amsterdam Central Station that allowed this information to be passed on, 'chance' also played its part in the timing of the meeting. As we have seen, the SMW publication containing Wettstein's article was dated 10 June 1944. Van Creveld had a 'recently published' copy but it had come via Portugal. There would, therefore, have been some delay in time before it reached Amsterdam. Querido, as part of the 'Barneveld Jews', was moved from Westerbork to Theresienstadt on 4 September 1944. Given that Querido's visits to Delft did not occur on a regular basis and that this was his last visit, the window of opportunity that allowed the Wettstein publication to reach Delft must have fallen between the end of June and the end of August 1944. This window of 'chance', therefore, was no more than two months.

Following his release from Theresienstadt, Querido returned to NG&SF in June 1945. It was then that he realised the value Wettstein's article had been to NG&SF researchers. After signing a

[72] B. Elema, *Opkomst*, p37; *De Fabrieksbode*, 1 September 1978, p77.
[73] This thesis Chapter 3, p.104.

secrecy agreement, Querido was shown a bottle of a yellow coloured, rough granular substance. Waller asked if he could guess what it was - it was NG&SF penicillin.[74] A point to be noted here is the strict secrecy policy embedded in NG&SF's working culture. At the end of the war, Waller required one of his senior advisors to agree to a 'secrecy agreement' before showing him the 'yellow coloured, rough granular substance'.

NG&SF Laboratory Research 1944-45

The first communication in NG&SF's Research and Development Archive that indicates research with penicillin is a fiche copy of three R&D Reports numbered 412, 413 and 414.[75] They are concerned with laboratory work undertaken between March and June 1944. The first, Report 412 is entitled 'Bereiding van bacinol – onderzoek van eenige schimmels op haar vermogen tot vorming van een bacteriostatische stof' (Production of Bacinol – research with some moulds for their ability to produce a bacteriostatic substance). To begin, Struyk clearly set out his method of investigation and described his task as an investigation into the possibility of growing a mould culture on Liquitex in order to produce an antibacterial substance. Liquitex was an established NG&SF fermentation mash consisting of a mixture of bran and malt. As his scientific sources Struyk listed Fleming of 1929, Clutterbuck, Lovell and Raistrick of 1932 and Kiese in *Klinische Wochenschrift*, 22, 32-33, August1943. He also cited another article from volume 22 of *Klinische Wochenschrift* by J. Vonkennel, J. Kemmig (sic)[76] and A. Lembke entitled 'Die Mycoine, eine Neue Gruppe Therapeutisch Wirksamer Substanzen aus Pilzen' (The mycoins, a new group of therapeutically active substances from fungi), contained in number 16-17 of April 1943. From volume 25 of the 1943 *Bulletin de la Societe de Chimie Biologique* came the publication by H.

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[74] A. Querido, *Andries Querido*, p.97.
[75] GB:R&D Archive, NG&SF R&D Report 412, 413,414, A.P. Struyk, 'Bereiding van bacinol', March-June 1944, 29 July 1944; M. Burns, 'Codename Bacinol', p.58; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Process', p.200; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.29
[76] J. Kimmig is misspelled.

Penau, C. Levaditit and G. Hagemenn's, 'Essais d'Extraction d'une Substance Bactéricide d'Origine Fungique' (Attempts to extract a bacterial substance of fungal origin). To these Struyk added an American publication, 'Antagonistic Interrelationships among Micro-organisms' from *Chronica Botanica*, Volume 6, 1940, by S.A. Waksman.

In Struyk's original report only the journals and page numbers are referred to. For the purpose of this thesis research in *Chemical Abstracts* produced specific titles. With the exception of the publication by Waksman all of the above articles have been referred to earlier in the development of penicillin in both Germany and France. Struyk's sources, therefore, further confirms that literature recording recent scientific research outside the occupied Netherlands was available to those within.

Struyk's report also illustrates a confident ability in the application of such contemporary information. Beginning with Fleming's article, Struyk articulately explained the background of Fleming's observation of *Penicillium notatum* Westling at St. Mary's Hospital, London, whilst experimenting with *Staphylococcus* infected Petri dishes exposed to the air. From Vonkennel's article, Struyk highlighted the existence of other fungal cultures with similar penicillin-like effects grown from moulds, yeasts and other microbial products that Vonkennel had gathered together under the group name *'mycoinen'*, mycoines. From here Struyk moved onto the Kiese article from which he learned about the 1940 publications of Florey, Chain and others. Finally, Struyk ended his literature review with Clutterbuck, *et al*, where the name of the medium used for growing their penicillin culture was given as 'Czapek Dox', as was the fact that oxidation of the subsequent 'mash', when coupled with a temperature of between 40-45°C, prompted faster growth. Almost as a postscript Struyk informed his readers that the growth of penicillin forming mould cultures on a 'bran mash' had, according to reports in the American press, also been

successful. How Struyk could make this claim is not clear, but it does provides further evidence he had sources other than academic ones.[77]

The fact that this Report is dated March-June 1944 gives a clear indication of Struyk's ability in the microbiological field. As stated earlier, the 'breakthrough' articles in the *Schweizerische Medizinische Wochenschrift* only became available to researchers in the Netherlands around July/Augusty 1944 via Querido. The précis of in Keesing's Medical Archive did not appear until 14 July 1944. Ultimately, NG&SF Report 412 illustrates the depth of Struyk's awareness and understanding of contemporary penicillin research during a time of embargo.

Continuing from his literature overview, Struyk explained his methodology. He began by stating that, in his search for a mould that would produce an antibacterial substance, samples from the *Penicillium* strain had been obtained from the Centraalbureau voor Schimmelcultures in Baarn. In total Struyk used twenty-one mould cultures. Eighteen were *Penicillium* strains and three from another mould source, *Aspergillus*. To these Struyk added two more fungal moulds that had been isolated from old cacao powder found in NG&SF's research laboratories.

Burns and van Dijck suggest that there was a direct ordering of *Penicillium* strains from the CBS because of the marking beside certain *Penicillium* strains in the CBS catalogue of 1943. However, the number of *Penicillium* strains marked on the pages of this catalogue total only nine whereas Struyk used twenty-one. In reality there is no indication when this CBS catalogue was marked or by whom.

[77] As had Kluyver, this thesis Chapter 3, pp.89-95.

The CBS archive has also shown that there was no block ordering between NG&SF and CBS, as had happened between CBS and other commercial companies such as Astra and IG Farben.[78] On the contrary, while there was a close contact between the head of the CBS, Johanna Westerdijk, and Rombouts of NG&SF, the ordering of *Penicillium* strains from Baarn was done more on a strain-by-strain basis. Correspondence between Westerdijk and Rombouts started on 19 January 1944. This was when the first *Penicillium* and *Aspergillus* cultures were sent from CBS to NG&SF. Westerdijk does not list what was sent but Rombouts replied on 25 January 1944 that he had received the 'twelve moulds'.[79] On 25 February 1944 she sent a new *Penicillium* strain, *Penicillium corylophilus*, which she had received 'from France'. On 15 March 1944, Rombouts wrote to Westerdijk:

> The Directors of NG&SF have decided they would prefer to pay for the cultures they have received from you. They appreciate your gesture to give them to NG&SF free but prefer to give the CBS their financial support.... From what I have seen, your P. notatum Westling is not the best producer of mycoines... we have received better producers from you... It really is a great pleasure for me, after almost four years of exclusively conducting animal studies, to work again with moulds and bacteria... Should you hear of another mould producing a good bacteriostatic substance, I should appreciate it if you would forward it to me.' [80]

More strains follow on 16 and 21 March, 1 April, and 15 and 24 May 1944.[81]

Appendix 1 lists the strains used by Struyk. The cultures were arranged in numerical order with the letter P donating *Penicillium* and the letter A, *Aspergillus*. Behind the strain name, the origin of the strain was noted.

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[78] This thesis, Chapter 2, p.71.
[79] CBS Archive, 1944, Correspondence File No. 175.
[80] CBS Archive, 1944, Correspondence File, No. 176.
[81] CBS Archive, 1944, Correspondence File, Nos. 516, 511, 513, 514, 515.

According to *De Fabrieksbode*,[82] Struyk and his technician Lagendijk knew that they had a difficult and time-consuming task ahead. Their assignment meant that they had to cultivate the spores for each of the moulds they had received. From Report 412 we are able to follow Struyk's methodology. He first developed his test method, which would demonstrate any penicillin-like activity from his moulds.[83] He used *Micrococcus aureus (Rosenbach) Migula*, an old name for *Staphylococcus aureus*, which he had obtained from Kluyver's collection, as the test organism to screen for an anti-bacterial substance. He wrote of his first research with a few moulds using dishes coated with the medium, *peptonagar*, (peptone agar) and a thick suspension of *Micrococcus aureus* to which spores of the moulds were added. These were incubated at 26°C for several days. However, even when the 'food' layer, the *peptonagar*, was enhanced, firstly with the addition of glucose, *peptonagar - 1 glucose*, and then with *krijt* (chalk), *peptonagar - 1 glucose - 1 krijt*, in an attempt to stimulate spore growth, Struyk reported this method as unsatisfactory, time consuming and non-discriminating. Both the spores and the bacteria had continued to grow. Struyk then changed his methodology to an 'agar block' test. The results, he concluded, were not only quicker but also more positive. Here, the spores were first germinated on the agar medium and, after different time periods, a small section of the agar layer, with the mould on top, was inverted onto another plate into which the staphylococcal culture had been inoculated. After incubation in a warm area, Struyk looked to see if 'clear' areas, or zones of inhibition, had formed round the mould. If clear areas had formed round the mould that meant that a substance produced by the mould had diffused out of the 'agar block' and had had an inhibiting effect on the growth of the *Micrococcus aureus*. By measuring the diameter of the zone of inhibition a rough guide to the ability of the strain to produce antibacterial substance could be

[82] *De Fabrieksbode*, 1 September 1978, p.77; M. Burns, 'Codename Bacinol', p.60; M. Burns and P.W.M. van Dijck, 'The Developmnt of the Penicillin Production Process', pp.195-196; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.28.
[83] GB:R&D Archive, NG&SF Report 412, 29 July 1944.

estimated. Fleming had called his inhibiting substance 'penicillin'.[84] However, before the Delft researchers could be sure of success or failure in the isolation of a penicillin-like substance this procedure had to be followed for all of the moulds.

From his results Struyk highlighted P6, P7, P9, P11, P13, A14, and, his own, Cacao 1 as active in the production of an antibacterial substance. However, Struyk showed his understanding of contemporary research in his conclusion that P7, '*Penicillium corylophilum* (source France)', had more resemblance to Penau's antibacterial agent, *notatine*, than Fleming's penicillin. It was unstable when heated and its properties more like an enzyme. Ultimately the mould culture with the highest yielding anti-bacterial substance and the one chosen for further study was sixth on the Struyk's list, P6: *Penicillium baculatum* Westling.[85]

In fact, according to Struyk's following Reports, 413 and 414, if *Penicillium baculatum* was allowed to grow in NG&SF's own *Liquitex* base for approximately five days at a constant temperature of 26°C and shaken once a day, the results appeared to be identical to those reported by Fleming using a bouillon mash and *Penicillium notatum.* Added to that, the substance produced by P6 was soluble in acetone and alcohol, which facilitated extraction from the growth mash, and, when mixed with water, its properties were also resistant to boiling. [86]

Furthermore, while the original culture had been grown on open surface Petri dishes, Rombouts showed that *Penicillium baculatum* could be grown on the surface of a liquid medium in Roux

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[84] M. Burns, 'Codename Bacinol', pp.58-65; M. Burns and P.W.M. van Dijck, 'The Developmnt of the Penicillin Production Process', pp.192-197; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', pp.28-29.

[85] GB:R&D Archive, NG&SF Report 412, 29 July 1944, ; M. Burns, 'Codename Bacinol', pp.58-65; M. Burns and P.W.M. van Dijck, 'The Developmnt of the Penicillin Production Process', pp.192-197; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', pp.28-29.

[86] GB:R&D Archive, NG&SF Report 413. A.P. Struyk, 'Bereiding van bacinol – oriënteerende proeven over de vorming March-June 1944, 29 July 1944; NG&SF R&D Report 414, A.P. Struyk, 'Bereiding van bacinol – proeven met zemelen en kiemen', March-June 1944, 29 July 1944.

flasks. A.A. Stheeman, with two NG&SF colleagues J. Knoterus and G.T. Mathu, investigated methods of extraction of the harvested culture fluid. In order to do so they turned to Kiese's publication where Abraham's Oxford Team methodology using buffered ether was described.[87] The result was a watery but acceptable mixture. By June 1944, therefore, NG&SF had produced its first small amount of a gold-brown substance. It was 50% pure.

In all Struyk's reports totalled twenty-eight pages. He covered the growth, extraction and sterile conditions necessary for the production of the antibacterial substance from *Penicillium baculatum*. He named it 'Bacinol'.[88] [89]

The Delft team's research had shown that their results corresponded with the spectrum Fleming had described for penicillin. They could not be sure, however, that the material produced by Struyk's research was the same as that of contemporary American or British penicillin. Elema says, it was because they were not sure of the current antibacterial spectrum of Allied penicillin and because they did not want their German occupier to become aware of their research with the 'wonder drug', that Struyk chose to keep the pseudonym Bacinol for further research.[90]

Struyk's results were reported only to F.G. Waller, A.A. Stheeman and J.R. Rombouts. All three parts, 412-413-414, are clipped together with continuous page numbering, and dated as presented on 29 July 1944. They are not marked secret. The office stamp indicates that they were circulated

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[87]GB:R&D Archive, NG&SF Reports 413 and 414, 29 July 1944, p.28; M. Burns, 'Codename Bacinol', pp.63-66; M. Burns and P.W.M. van Dijck, 'The Developmnt of the Penicillin Production Process', p.193; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.28.
[88] GB:R&D Archive, NG&SF Reports 412, 413 and 414, 29 July 1944.
[89] The American mycologist Charles Thom regarded *P.baculatum* as a member of the group *P.chrysogenum* Thom but he never examined the NG&SF production strain. Source: M. Burns, J.W. Bennett, P.W.M. van Dijck, 'Code Name Bacinol', p.30.
[90]*De Fabrieksbode*, 1 September 1978, p.77, B. Elema, *Opkomst*, p.37; M. Burns, 'Codename Bacinol', p.63; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', pp.193-194; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.29.

by normal office routes. Eventually, the reports covering research with Bacinol in the months March to June 1944 were signed as 'Seen' by Rombouts on 15 September 1944, Waller on 23 October 1944 and Stheeman, almost four months from the date of presentation, on 7 November 1944.[91] Struyk's initial Reports, therefore, do not appear to have been cloaked in secrecy or to have caused an immediate flurry of action.

From July 1944 to March 1945 research with Bacinol took place on a regular basis. Rombouts with his assistant, Ans Addeson,[92] tested for toxicity in *S. aureus* infected rabbits and mice. Although experienced in animal testing, Rombouts would undoubtedly have referred to the publication by Wettstein which reviewed the experiments on infected mice by Chain *et al* in *Lancet*, 1940, and those of Robson and Scott on rabbits published in *Nature*, 1942, and *Lancet*, 1943.[93] Rombouts would have known, therefore, what the outcome should have been. In fact, the animals did recover and the effectiveness of Bacinol was confirmed.[94]

To enhance the growth of Bacinol, Struyk tried various types of flat glass and enamel containers. In the end he chose milk bottles as his fermenter. (Appendix 2) Bearing in mind wartime shortages and the lack of laboratory equipment, milk bottles were still accessible and relatively easy to clean and sterilise. As P.A. Hahn explains, a fermenter is simply a physical container for the fermentation of the broth and microbes. Milk bottles, as Struyk would have known, are referred to as the 'natural' fermenter.[95]

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[91] GB:R&D Archive: NG&SF Reports 412, 413 and 414, 29 July 1944.
[92] Ans Addeson married C.H. Elzenga. Personal Communication April 2005.
[93] M. Burns, 'Codename Bacinol', p.64; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.194; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.29.
[94] *De Fabrieksbode*, 15 September 1978, pp.82-83.
[95] P.A. Hahn, *Chemicals from Fermentation*, p.17; M. Burns, 'Codename Bacinol', p.64-65.

Having found the optimum conditions for the growth of Bacinol, Struyk decided that he could control his experiment more closely by placing his milk bottle containers in one room, which would facilitate supervision. Accordingly, the Head of the Fermentation Plant, J.M. Klokgieters, received the order to empty a room in plant F3 for 'hundreds' of milk bottles. Lying on their side, the milk bottles were part filled with different liquid nutrients. Assistants from Rombouts laboratory regularly came to inoculate the spores taken from *Penicillium baculatum* into the milk bottles. The bottles were then closed with sterilised cotton wool and the production of Bacinol awaited. In order to follow the daily formation of Bacinol, a quantitative biological test was developed from which the concentration of the solution was expressed in '*Delftsche Eenheden*' (Delft Units).[96]

Struyk defined Delft Units as the amount of bacteriostatic substance that just completely suppressed the growth of the test organism *Micrococcus aureus* strain 6, in 1 ml of peptone water at 37°C. While previous publications have referred to a lack of knowledge in Delft over the Oxford Unit,[97] hindsight reflects the similarity of Struyk's method of measurement to the Oxford Cup Method as reported by Kiese.[98] At this point, however, it is clear that Struyk preferred that the research of the Delft team remain purely their own

According to Scheurkogel, the milk bottles were kept for 10-12 days at a temperature of 25°C. After processing, the fluid produced was fairly crude penicillin. Sometimes the surface culture gave problems. Sometimes the filtrate produced was contaminated by penicillinase, an enzyme

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[96] *De Fabrieksbode*, 15 September 1978, pp.82-83; M. Burns, 'Codename Bacinol', p.64-65; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.194-195; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.29.

[97] *De Fabrieksbode*, 15 September 1978, pp.82-83, B.Elema, *Opkomst*, p.37. M. Burns, 'Codename Bacinol', p.64; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.196.

[98] This thesis, this Chapter, p.124; p.129.

that breaks down penicillin. The contents of these bottles were unusable. They had to be disposed of and the team would have to start again. From time to time such 'calamities' seemed insurmountable but they kept going. It was August 1944 before they produced a product that gave them all the desired properties. But, at this point, the Delft team became concerned that the German occupier could profit from their research. They did not want the *Wehrmacht* to be able to use their antibacterial substance. At the time, it was also generally felt that the war would soon end. These two factors led to the decision to put a temporary stop to research.[99]

The D-Day landings had started in June 1944. By August 1944 most of France and Belgium had been liberated. As the allied armies moved through Belgium, it was confidently expected that the Netherlands would be liberated within a matter of weeks. In the aftermath of Operation Market Garden, the hope that the war would soon end was dashed. Arnhem failed and the north and western Netherlands remained occupied. According to Scheurkogel, it was during the dark days of the winter of 1944-45 that the decision was taken to re-commence penicillin research. This led to the further purification of the end product and, by the end of April 1945, NG&SF had managed to create a few ampoules of Bacinol.[100]

NG&SF R&D Archives illustrates the research that took place between July 1944 and March 1945. For example, in R&D Report 847-904, Stheeman and Knotnerus, with G. Mathu, reported on the buffer for the ether extraction of penicillin from the broth culture and on the trials to improve the growth cultures for *Penicillium baculatum* in 'Jena' and 'Roux' bottles.[101] In R&D Report 243, which covered work done in the months of April and May 1945, Stheeman signalled

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[99] K. Scheurkogel, 'Technische bereiding', p.71.
[100] K. Scheurkogel, 'Technische bereiding', p.71
[101] GB:R&D Archive, NG&SF Report 847/904 , July 1944 -March 1945; M. Burns, 'Codename Bacinol', p65-66; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.196; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.30.

the differing levels of success in the search for an improved 'mash' with which to 'feed' Bacinol by growing *Penicillium baculatum* on sugars, beet pulps and grain mixes.. Ultimately, he concluded that the most successful was, quite simply, grain.[102]

It was to be 5 May 1945 before Liberation came for the people of the western Netherlands. The deprivation and starvation experienced during the *hongerwinter* of 1944-45 provide some of the most enduring memories of the occupation period. These memories are invariably associated with the euphoria experienced when allied aircraft began dropping food to beleaguered towns and cities in the last days before the German surrender.[103] An agreement had been reached between the German occupier and the Allies that allowed British and American bombers to drop food parcels in the west of the Netherlands. These drops started on 28 April at the airfields of Ypenburg (Delft), Duindigt (The Hague), Valkenburg (Leiden) and Waalhaven (Rotterdam). The German administration had, under duress, agreed to stand aside. Distribution of the packages was to be undertaken by the Dutch themselves.[104]

According to Boelema, from the drop at Ypenburg, Evert Verschuyl managed to obtain some American penicillin. Verschuyl was a surgeon at Delft's Bethel hospital and NG&SF company doctor. He brought the sample of penicillin to NG&SF.[105] Like Boelema, most Dutch sources relating the history of NG&SF penicillin state that American penicillin was included in the food

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[102] GB:R&D Archive, NG&SF Report 243, April-May 1945; M. Burns, 'Codename Bacinol', p.66; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.196; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.30.
[103] B. Moore, 'The Western Allies and Food Relief to the Occupied Netherlands, 1944-45', *War & Society*, 10, 2, (October 1992), p.91.
[104] H.G.O. Boelema, p.45, M. Burns, 'Codename Bacinol', p.67, M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.197, M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name', p.30; B. Elema, *Opkomst*, p.38, *De Fabrieksbode*, 15 September 1978, pp82-83; Gist-Brocades, 'Van Fleming tot Flemoxin', L. de Jong, *HetKoninkrijk*, Deel 10b, pp1344-1351, H. Onderwater, *Operatie Manna*; *Operation Manna / Chowhound.*
[105] H.G.O. Boelema, p.45.

relief dropped at Ypenburg. Some refer to the part played by Verschuyl, others simply report that American penicillin was part of the food drop.[106]

However, in his account of the food drops, de Jong describes the contents of the packets for the British operation, which was called 'Operation Manna'. The initial intention had been to deliver 'approximately twelve million British Red Cross packets', which were housed in British airfields ready to be dropped to prisoner of war camps in Germany upon Germany's capitulation. But, considering the number of people in need in the western provinces had been approximated at three and a half million, the low content level of the Red Cross packets led the Supreme Headquarters Allied Expeditionary Force (SHAEF) authorities to opt for larger quantities of food packed in jute sacks. Each sack weighed ten kilos.[107] Quoting figures obtained from the Dutch Central Bureau of Statistics, de Jong lists the British contents. There is no mention of medical supplies.[108]

In his two books on the food relief, H. Onderwater offers the exact timings of the British, 'Operation Manna', and the American, 'Operation Chowhound', drops.[109] He also includes photographic evidence of the way in which some of the food containers landed. Many of the sacks smashed into the ground. As a result, the contents, for example flour, sugar, tea, scattered over the ground and were rendered virtually useless. Added to that not all contained only one item, some parcels came as complete, individual, packages. For example, the American aid also contained thousands of packets of an individual soldier's ration. This included biscuits, chewing

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[106]B. Elema, *Opkomst*, p.38; K. Scheurkogel, 'Technische bereiding', p.71; *De Fabrieksbode*, September, 1978; Gist-Brocades Company Publications, '30 jaar penicilline', 1973, '35 jaar penicilline', 1983, 'van Fleming tot Flemoxin Solutab', 1988/89, *Brood op de plank*, 1999, M. Burns, 'Codename Bacinol'p.67, M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.197, M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.30,

[107] De Jong, *Het Koninkrijk*, 10b, p.1344.

[108] De Jong, *Het Koninkrijk*, 10b, p.1349.

[109] H. Onderwater, *Operation Manna / Chowhound*; *Operatie "Manna"*.

gum, cigarettes, matches, water sterilizing tablets, toilet paper, a bottle-opener and a book of Christian prayer. [110]

It is difficult to see why the Allies would or could have dropped penicillin. At the time, the use of penicillin was restricted. Its use was for military purposes only. As this thesis has shown, the input of Canadian penicillin from Connaught was the push to have enough penicillin for the D-Day landings.[111] There was no surplus. On the contrary, as this thesis has shown, penicillin supplies were strictly controlled. It is also difficult to see why the Allies would have dropped penicillin only at one specific place, namely Ypenburg. If it was dropped at Ypenburg, why did no other Delft doctor report the availability of penicillin? Further, why would the Allies drop penicillin to General Practitioners who did not know its properties or have received instruction on how to use it?

At the time, penicillin could only be administered by intramuscular or intravenous injection. It was freeze dried into a powder that had to be mixed with sterile water before an injection could take place Added to that, it needed to be kept under controlled conditions. Given the massive airlift needed for both Operation Manna and Operation Chowhound, how could it have been possible for the new 'wonder drug' to be part of any relief airdrops, let alone only one - Ypenburg?

[110] De Jong, *Het Koninkrijk*, 10b, p.1349.
[111] This thesis, Chapter 2, p.48.

There is another suggestion that the delivery of relief supplies could have brought contact with the liberating forces and their medical supplies. As well as airdrops, food was brought into the western provinces by land and water convoys in a 'hastily improvised' operation called 'Faust'.[112]

For Operation Faust, a 'rendezvous was arranged at Rhenen' where supplies were to be handed over to Dutch officials. The task of transporting these supplies through enemy lines fell to the First Canadian Corps. Two hundred allied trucks from the 21st Army Group were allocated to bring the food from Wageningen, in the liberated Netherlands, to Rhenen, a town on the German side of the frontline. Within the first forty-two hours 1,000 tons were delivered and, prior to capitulation, the total amount of supplies brought in by truck amounted to 5,500 tons. These supplies came from a stockpile of over 50,000 tons held in 'dumps' in the liberated south, near Den Bosch and Oss. The intention had been to use these stockpiles to bring food relief the moment the complete liberation of the Netherlands had been achieved. In addition to supplies of food was: 'fuel, medical supplies, ordnance stores (including soap, clothing, blankets and footwear)'.[113] The 'medical supplies', however, are not listed.

Nonetheless, the fact that the First Canadian Corps was the major liberating force in the Netherlands adds to the possible explanation that penicillin came to Delft with the liberating forces. As has been shown earlier, Allied military doctors brought with them penicillin which, on occasion, they were willing to share.[114] It was the Canadian 48th Gordon Highlanders who officially liberated Delft on 8 May 1945.[115] As will later be shown, the Delft team were to profit from written information on penicillin provided by the Canadian military experience.

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[112] Canadian Military Headquarters, Historical Section, Report No. 172, Canadian Participation in Civil Affairs/Military Government. Part IV: Belgium and the Netherlands, General Historical Survey, pp.42-44. Source: website: users.interstroom.nl, fooddrops, foodtrucks, 20/07/2004.
[113] Canadian Military Headquarters, Historical Section, Report No. 172, pp.42-44.
[114] This thesis, Chapter 3, pp.80-83.
[115] Personal Communication, Delft Gemeente Archief, 23/08/05.

What did happen in May 1945 is shown in NG&SF R&D Report 750 in which Stheeman, with the assistance of C.W.F. Spiers, dealt with the analysis of 'a penicillin preparation of unknown origin'. They note the claim of 'the manufacturer' that, this preparation was the crystalline sodium salt of penicillin and its strength was 1600 Oxford Units. Stheeman's conclusion, however, was that it was neither crystalline nor had the stated potency. He could not say whether this had to do with the fact that the preparation had been kept 'too long'; or had been kept at 'too high' a temperature; or that the *Staphylococcus aureus* strain in his test was less sensitive than the strain used by the manufacturer. What he could and did say was that the preparation he had analysed was not pure.[116] There was, therefore, no point in using it to determine the properties of penicillin.

In July 1945, Struyk's reported to F.G. Waller in R&D 244-246 that, from a sample of American penicillin he had equated the ratio of Units used for the Delft measurements with those of Oxford as 10:1 respectively. More importantly, that this American penicillin, made by Chas Pfizer & Co. and supplied by Upjohn of Kalamazoo, Michigan, had been found to possess the same properties as NG&SF Bacinol.[117] It was July 1945, therefore, before the NG&SF Delft researchers knew they were in possession of an antibacterial substance that not only matched Fleming's penicillin but also mirrored the penicillin that had been mass-produced in the United States.

However, Report 244-246 also illustrates that, at the end of the war, research with penicillin from the mould culture *Penicillium baculatum* at the NG&SF had not stopped. In this report Struyk

[116] GB:R&D Archive, NG&SF Report 750, A.A. Stheeman, 'Onderzoek van een Penicillinepreparaat', 15 May 1945.
[117] GB:R&D Archive, NG&SF Report 244-246, A.A. Stheeman, 'Penicilline – Cultures van Penicillium baculatum op verdund graanbeslag', 5 July 1945; B. Elema, *Opkomst*, p.37; M. Burns, 'Codename Bacinol', p.67-68; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.197; M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.30.

indicated the results of experimentation with different mash nutrients as he sought to find a higher yielding mould strain, one that would surpass the level of penicillin production then achieved by *Penicillium baculatum*. Noticeably, in this dossier, the name Bacinol falls away. It is replaced with the word 'penicillin'.[118]

Critically, in the development of Dutch penicillin, by the end of the war, NG&SF had successfully researched their own penicillin using their own mould culture, *Penicillium baculatum*. In comparison with American penicillin it possessed the same antibacterial properties. The decision now was, whether or not to continue research? In order to do so, they would have to establish their own production techniques. Before that though, they had to be sure that their antibacterial product was safe.

NG&SF Penicillin: First Clinical Application.

According to Scheurkogel, the first clinical application took place shortly after the end of the war, when the doctor of a very ill patient in Delft Bethel hospital approached NG&SF. In the doctor's opinion their penicillin was her only chance of survival. Those at the Gist were unsure about using their product. The doctor persuaded them by citing the extremely good results that had been achieved in the many animal trials NG&SF had run. It was this pressure that finally allowed the first use of NG&SF penicillin in a human.[119] Scheurkogel does not name the doctor.

The *Fabrieksbode* says that permission to use NG&SF penicillin was first sought from the Koninklijke Maatschappij tot Bevordering der Geneeskunde, (KMBG, Royal Society for the Promotion of Medicine). The claim here is that this was as much to bring Delft's penicillin to the

[118] GB:R&D Archive, NG&SF Report 244-246, July 1945; M. Burns, 'Codename Bacinol', p.68.
[119] K. Scheurkogel, 'Technische bereiding', p.45.

attention of Dutch doctors as to prove its efficacy[120] Neither Scheurkogel or the *Fabrieksbode* provide a date for this first application of NG&SF penicillin.

Evert Verschuyl's version of how he came to be involved with NG&SF penicillin runs contrary to the above. In a 1991 television interview Verschuyl stated that it was November 1945, as a result of a phone call from 'one of the directors', he went to the NG&SF headquarters. It was then that he was shown a phial of NG&SF penicillin. Following this, he considered using NG&SF penicillin in a patient.[121] The implication here is that it was NG&SF who offered their penicillin to Verschuyl for use in his hospital, not the other way round.

Whichever path was taken, what is known is that, in November 1945 the recovery of Maria Geene, underscored the successful production of penicillin at the NV Nederlandsche Gist- en Spiritusfabriek, Delft. In her 1991 television interview with Willy Lindwer, she described her feeling of joy when she realised her life had been saved. The medical staff, too, were overjoyed, showing their happiness and relief as they hugged her.[122]

However, in November 1945 she was not the only patient to receive Dutch penicillin. As the attached temperature charts illustrate. (Appendix 3),[123] at the time two patients received NG&SF penicillin.[124] The first, a twenty-year-old woman, had been admitted to the Bethel Hospital on 26 October 1945. She was critically ill with a staphylococcus infection. She had been treated with sulphonamide to no effect. Her condition remained poor and her temperature high, 39-40°C. On

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[120] M. Burns, 'Codename Bacinol', p.87-88. *De Fabrieksbode*, 2 May 1995.
[121] Video, *De revolutie van*, 1991.
[122] Video, *De revolutie van*, 1991
[123] Appendix 3, Bethel Hospital, Delft, Temperature Charts November 1945. Source: H.L. Houtzager en M.A. Verschuyl, 'Delfts Pionierswerk: de Fabricage en Klinische Toepassing van Penicilline', *Medisch Journaal Delft*, 4, (December 1995), p.194.
[124] H.L. Houtzager en M.A. Verschuyl, 'Delfts Pionierswerk', p.194; M. Burns, 'Codename Bacinol', p.87; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.198.

15 November she was given her first intravenous injection of 50,000 units of NG&SF penicillin. As the first temperature chart shows, the next day her temperature was normal, 36.8°C. Her recovery continued and she left hospital on 5 December 1945. She was discharged only twenty days after receiving NG&SF penicillin. This was Maria Geene.

The second patient remains anonymous. She was an eighteen-year-old woman with a similar infection and had been admitted on 26 November 1945 with a temperature of 40.8°C. On that day she received her first penicillin injection of 50,000 units. Intravenous injections continued on 27 and 28 November with 100,000 and 150,000 units respectively. Her infection cleared and her temperature returned to normal. She was discharged from the Bethel hospital on 14 December 1945. Her complete recovery from seriously ill to leaving hospital had taken nineteen days.[125]

Scheurkogel illustrated the effect of this success on the war stressed Dutch company. As he pointed out, at the end of the war:

> As well as uncertainty, daily life was under great pressure. Scarcity of food, fuel and the lack of electricity and gas meant that factory life remained at a very low level of activity. Added to that the isolation of the west of the Netherlands had brought with it a break in the supply of flour. This meant that the bakers had almost no need for yeast. It goes without saying that the good results from the first clinical application with the laboratory scale penicillin gave further plans for action at NG&SF a sharp shot of activity.[126]

NG&SF succeeded in bringing penicillin that had been produced on a technical scale onto the Dutch market in 1946. Before this could be achieved, however, more efficient and effective development methods had to be found.[127]

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[125] H.L. Houtzager en M.A. Verschuyl, 'Delfts Ponierswerk', p.194; M. Burns, 'Codename Bacinol', p.87.
[126] K. Scheurkogel, 'Technische bereiding', p.45.
[127] *De Fabrieksbode*, 15 October 1960, p.269.

Conclusion

In conclusion, it can be seen that on a general as well as medical level, knowledge of the existence of penicillin came with the advance of the Allies. Before the war, NG&SF had a thriving business. Nonetheless, given the restrictions of war and occupation, at the end of the war NG&SF was not in a more favourable position than any other Dutch company to contemplate starting new research. As Scheurkogel points out, during the war NG&SF markets dwindled as they became more restricted to the local market. Yet, this lack of 'work' might have been a stimulus to penicillin research. Secrecy, something imbedded in the NG&SF culture, would have added piquancy. There would have been a feeling of getting 'one over' the occupier. However, nervousness of being found out close to the expected end of the war stopped NG&SF research in August 1944. It was resumed in January 1945, under the extreme restrictions of the *hongerwinter*

While no definite documented evidence has been traced regarding the initial source of information on penicillin reaching NG&SF, an 'authorised' version seems to have evolved. While this thesis questions some aspects of the 'authorised' version, for example *De Vliegende Hollander* versus *De Wervelwind* as a source of information, it does not question the successful research into penicillin in Delft. On the contrary, the aim has been to pay tribute to the success of NG&SF's wartime research.

At the same time, research into the reason for the success of Delft and the failure of others, has brought a fuller version to the fore. It is clear that penicillin research in Delft was initiated by the fusion of the Director of one of the world's best-known culture collection, Westerdijk at the CBS, with an eminent microbiologist, Kluyver of Delft's TH and a talented but fortunate doctor, Querido. When this fusion merged with the skills of the fermentation experts at NG&SF, Struyk, Stheeman, Rombouts and their able assistants, the results were telling. Add to this the determination and leadership of F.G. Waller and we begin to have some idea of why Delft

succeeded where others failed. As Scheurkogel pointed out, at the end of the war, the success of NG&SF's penicillin in its first clinical application, far from stopping laboratory scale production, merely gave further plans a 'sharp shot of activity'.

Chapter 5

1945
The Dutch Health Care System and NV Nederlandsche Gist- en Spiritusfabriek.

In May 1945 the situation the Netherlands was dire. De Jong lists the physical damage brought about by war and occupation. At the point of defeat approximately 260,000 hectares of land was underwater, deliberately flooded by the retreating *Wehrmacht.* The provinces Gelderland, South Holland, Zeeland, North Holland and Utrecht were worst affected. Many of the large cities were virtually destroyed, including Nijmegen, Hengelo, Enschede, The Hague, Arnhem and Oosterbeek.[1] About 120,000 houses had been badly damaged of which almost 90,000 had been classed as irreparable. A further 390,000 houses were regarded as lightly damaged. This meant that of the nine million Dutchmen approximately half a million families had lost their homes.[2]

The ports of Rotterdam and Amsterdam were deliberately sabotaged. Mines and abandoned *Wehrmacht* tanks hampered transport. Damage to canals disrupted internal shipping. Most of the major bridges were badly damaged and road surfaces were in poor condition. The number of lorries and buses in working order was severely reduced, such trams as there were had no electricity. Plundering of rolling stock had left the railway system inoperable. Effectively the only means of transport was by foot or by bicycle, many of which were without tyres.[3]

Money manipulation by the Germans had led to five times as much money in circulation as was required by the economy. This exerted an enormous upward pressure on prices. Everything was scarce and the black market was very active.[4] In addition to the almost 230,000 Dutch citizens who

[1] L. de Jong, *Het Koningrijk*, Deel 10B, pp.1440-1442.
[2] L. de Jong, *Het Koningrijk*, Deel 10B, pp.1442-1443.
[3] L. de Jong, *Het Koningrijk*, Deel 10B, pp.1443-1444.
[4] L. de Jong, *Het Koningrijk*, Deel 10B, pp.1445.

had died, of which 102,000 were of Jewish origin, De Jong calculates that almost 2 million people, that is more that a fifth of the population, were displaced.[5]

The population reflected the mental shock of occupation which had brought with it hardship and privatisation. In Report No. 172, Colonel C.P. Stacey of the liberating First Canadian Army described the Dutch population as a people 'who possess a love of freedom and a strong aversion to any form of regimentation or direction'.[6] However, he submitted that:

> The ensuing struggles of opposing ideologies ... accompanied by the German occupation had produced physical and psychological sufferings which resulted in a slackening of all efforts, in all domains of life, private as well as public.[7]

As a result, many of the 'fine qualities' that had characterised the Dutch 'in normal times' seemed to be 'in temporary eclipse'. The struggle for independence and self-respect had relaxed with the entry of the Allied troops. Indeed, the Medical Officer at the Headquarters of the 2nd Canadian Corp, who had 'known' the Netherlands before its Nazi occupation, summed the situation up in the following words:

> The people are tired – tired to the limit. They lean, and lean rather heavily on any support offered them. .... They have always been independent from all points of view; they do not mind being dependent now ... The Dutch are a fine people, they have been stunned, and only time will bring them back to their own high standards.[8]

The problems facing the reconstruction of the Netherlands were formidable. The aim of this Chapter is to show the various ways in which the Dutch Health Care System (*Gezondheidszorg*), academics, researchers and commercial companies restored contact with each other in an effort to

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[5] L. de Jong, *Het Koningrijk*, Deel 10B, pp.1447.
[6] Canadian Military Headquarters, Historical Section, Report 172, 'Canadian Participation in Civil Affairs / Military Government', Part IV, Belgium and the Netherlands, General Historical Survey, p.62. Source: Website cmhg.forces.gc.ca 21/07/04.
[7] Canadian Military Headquarters, Historical Section, Report 172, p.63.
[8] Canadian Military Headquarters, Historical Section, Report 172, p.64.

come to grips with the development of penicillin. Within this, the pivotal role of NG&SF will be highlighted.

The Dutch Health Service at the end of the war.

At the end of the war, the Dutch Health Care System had a shortage of everything – doctors, nurses, medicines, medical technical apparatus and repair materials. Hospitals were run down and overworked. Eddy Houwaart estimates that war damage had resulted in the loss of 1200 hospitals although, in part, this loss was also due to insufficient maintenance during the financial crisis of the 1930s. On top of that most of the Jewish care centres had disappeared and around 200 Jewish doctors murdered, a severe loss to the medical fraternity.[9]

The beginning of the post-war era brought with it a greater need for medicines than ever before. During the war the health of the population had deteriorated badly, especially in the last year. Exhaustion and lack of food had resulted in a high infant mortality. Illnesses returned which before the war had been successfully suppressed, such as tuberculosis, typhus and diphtheria. In particular the rapid spread of these illnesses in the year 1945-46 gave the health authorities cause for concern. Added to that, the return of thousands of war victims put pressure on the medical system. In the first years of post-war recovery, therefore, the financial requirements for medical care in the Netherlands stayed relatively high and medicines remained scarce. Accordingly, this combination of medical shortages and the high demand for help meant that it took some years before the health of the Dutch population and the Medical Health Service returned to their pre-war levels.[10]

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[9] E. Houwaart, 'Wederopbouw en expansie', Chapter 6 in *Techniek in Nederland in de Twintigste Eeuw.* Vol. IV, *Medische Techniek*, (Zutphen: Walburg Pers / Stichting Historie der Techniek, 2001), p.235.
[10] E. Houwaart, 'Wederopbouw en expansie', p.235.

Dutch Government Interest in Penicillin at the End of the War

In October 1945 the Director of the Rijks Instituut voor de Volksgezondhied (RIV, National Institute for Public Health),[11] W.A. Timmerman, reported to the Minister of Social Affairs about a 'Centrum voor onderzoek voor penicilline en andere antibiotische geneesmiddelen' (Centre for Research on Penicillin and Other Antibiotic Medicines). The report started with the statement:

> Penicillin is an extraordinarily important medicine. There can be no doubt of the role of penicillin in medical treatment. It is, therefore, of importance that this medicine is made available to the Dutch nation. There are two ways in which this could be done, either by importing it or by producing it in this country.[12]

Having drawn the conclusion that penicillin either had to be imported or produced in the Netherlands, he continued with an overview of his recent visit to England but said that he had the strong impression that imports from England could not be counted upon. His reasoning for this was that although there were various factories producing penicillin, the majority, if not all, were working with old methods of production which did not produce large amounts. There was a new factory being built in Liverpool, but even when in full production it was questionable if export to other countries would be possible. Moreover, 'England' would have to provide firstly for her dominions and colonies.[13]

In addressing the situation in the United States, Timmerman reported that he understood from his English contacts that the situation there was very different. American penicillin production made sufficient quantities to allow for export. In fact, American penicillin was available in the Netherlands although the amount was very small, only '900 million units'. In order to give his

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[11] RIV now *Rijksinstituut voor Volksgezondheid en Millieu* (RIVM, National Institute for Public Health and the Environment).
[12] RIV Report U.317/45, 'Centrum voor onderzoek voor penicilline en andere Antibiotische geneesmiddelen', Dr. W.A. Timmerman, October 1945, p.1. Source: Dr. A.J. de Neeling, RIVM, Bilthoven, the Netherlands, November 2003.
[13] RIV Report U.317/45, p.1.

readers an overview of what he meant by this he quoted that, at that point, the treatment of one patient required 'approximately 100 million units'(sic) of penicillin.[14] It seems likely that Timmerman meant 100 thousand units, as this was closer to the amount administered to the first patients who received penicillin.[15] However, even allowing for such an error the amount available came nowhere near to any kind of national requirements.

He put forward the view that this small amount of available penicillin could be divided between a few places in the Netherlands and used only when absolutely necessary, although he estimated that the 900 million units would be used up in less than three months. In order that supplies did not run out, he advocated that enquires be made about ordering in advance from American producers. In order to do so contact would have to be made with American producers as, on the grounds of information available to him, he could not be certain that American supplies were available. If they were, they could be transported from the United States to the Netherlands by boat. Penicillin itself, he reported, did not take up much space and this could be made even less if the packaging was left out. However, with a reference to the requirements of penicillin storage at the time, he stated that 'such a cargo' would have to be kept separate 'in the ship's refrigerated area'[16].

How far penicillin production in Switzerland had come, and if it was available, was not yet known to Timmerman. However, he clearly detailed the 'current price' paid for penicillin as 'f.2.50 for 100,000 units'. He did note that he had been told through his contacts in England that the 'price in America has been reduced to $0.40 (US) per hundred thousand units' although, here too, he was not yet certain of his facts.[17]

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[14] RIV Report U.317/45, p.1.
[15] For example, Maria Geene received 50,000 units and the second patient 50,000; 100,000 and 150,000 units. This thesis, Chapter 4, pp.146
[16] RIV Report U.317/45, p.1.
[17] RIV Report U.317/45, p.1.

In considering how much penicillin would be needed in the Netherlands per year, Timmerman submitted that it would be 'extremely difficult to anticipate since, as usual, demand would increase as soon as supply increases'. He summarised the cost of importing penicillin on the basis of 30,000 patients with a requirement of 100,000 units at $0.40 per 100,000 units, as $120,000. On the other hand, should the price of 100,000 units be 'f.2.50' then the total cost would be approximately $300,000. Added to that, it was his considered opinion that costing on the basis of 30,000 patients was on the low side. Any forward planning for Dutch Public Health, therefore, would have to be made for more patients rather than less. How far this would cause difficulties for Dutch foreign exchange he could not say.[18] While Timmerman was clear about the need for penicillin within the Netherlands, at the end of the war, under the prevailing circumstances, he could only be unclear about projected availability and the cost of import.

Timmerman's report then addressed the second possibility, that of 'making it ourselves'. Here he stated that Dutch production could be done either by the State or by a private firm subsidised, or not, by the State. If the State were to take on the responsibility of penicillin production this would have to come through the National Institute for Public Health as public health lay at the centre of that Institute's tasks. This meant that a whole new section of the Institute would have to be built, solely for the production of penicillin using modern methods. He noted that he had not seen such a factory, but he was sure that it would be very costly to build. He was also sure that the running costs would be high when the large number of workers, who would be needed to run the plant, was taken into consideration. Such a project, he determined, would certainly work at a loss unless the price of the product was kept artificially high either by the State or by restricting import. In his opinion, this would also have political implications and the question remained whether or not the

[18] RIV Report U.317/45, pp.1-2.

Dutch consumer would be prepared to pay such a high price. His advice to the State was to consider obtaining 'this preparation' through other ways.[19] The development of penicillin by the Dutch State in Timmerman's opinion would be too costly.

However, he continued:

> We could consider the alternative, production through a private firm but under supervision. From the beginning the financial considerations for this seem even. Some firms could use existing plant materials. Here I am thinking particularly of the Gist- en Spiritusfabriek but whether it is possible to make that firm viable without subsidy looks unlikely to me.[20]

He clearly felt, therefore, that at the end of the war, NG&SF was not 'viable without subsidy' in the production of Dutch penicillin although he gives no further explanation for this. He further noted that one of the Directors of the Bataafsche Petrol Company[21] (BPC) laboratory in Amsterdam had told him that the method used to make American penicillin had been researched in the laboratories of Shell America and that they (BPC) had all the patents for this in hand. Timmerman had gathered from these comments that the Bataafsche Petrol Company might consider penicillin production.[22] However, whether or not BPC did have access to the American methodology for penicillin production via '*Amerikaansche* Shell' (Shell America) also remained unclear.[23]

Moreover, in any production of Dutch penicillin Timmerman cautioned against building a costly penicillin factory. In his opinion, it was not yet known how long this would be necessary. The chemical synthesis of penicillin, he continued, was shortly awaited in England and definitely in

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[19] RIV Report U.317/45, p.2.
[20] RIV Report U.317/45, p.2.
[21] Later Royal Dutch Shell.
[22] RIV Report U317/45, p.2.
[23] Shell was not involved in the post-war production of penicillin.

America. How far away this really was he could not say. No one was saying anything. As far as he knew, the structural formula was not yet known. Only when this was known could testing start on laboratory scale, and only when this was successful would a halt be called on the 'present' industrial method which, itself, he said, called for 'unusual talents'. What he could say was that it would be some years before synthetic penicillin reached the market. But, he stated that 'surprises should never be excluded and this is also a point that should be taken into consideration'.[24]

Timmerman's report concluded:

> In short it is my opinion that the State should not involve itself in the production of penicillin. If a private enterprise would like to take the initiative then the State has no objection. However, the end product should come under State controls for sterility, working conditions and safety. These controls already exist for other biological medicines under the care of the Rijks Instituut voor de Volkesgesondheid. Any production of penicillin would also have to be tested through this Institute.[25]

In the end, Timmerman's opinion was that 'import is the cheapest way'. However, imported penicillin would also have to be approved by the Institute and delivered by authorised methods of transport. He was of the opinion that pharmaceutical wholesalers would shortly be able to purchase penicillin, from which time 'we would not have to fear' stagnation in delivery. He further concluded that, unlike Belgium where a State decision of '12 April 1945' recommended a State Centre for the production of penicillin, in the Netherlands the desire for State involvement was limited. Nonetheless he 'would press for the setting up of a study centre to research the whole question'. The study of penicillin, he said, was only a first step. Little was known over the biochemistry of moulds and, as new facts came to light, improvements and the isolation of therapeutic micro-organisms would lead to an expansion of the subject matter. However, he stated that: 'This research should be separate from industry ... it should be undertaken by Institute or

[24] RIV Report U317/45, p.2.
[25] RIV Report U317/45, p.3.

University research laboratories' and, in his opinion, the RIV was the best Institution to do such research.[26]

Ultimately Timmerman's report produced no clear proposals on penicillin. What he does is balance the possible cost of importing penicillin with the possible cost of Dutch production. While he recognised that State involvement in this production would be a limiting factor he also questioned the viability of the most likely commercial companies, namely NG&SF and BPC. What is clear is that Timmerman wanted the control of penicillin, nationally produced or imported, under his Institution, the National Institute for Public Health.

The first meeting of the Commission for Antibiotic Medicines was held on 10 January 1946 at the *Gezondheidsraad* in The Hague. Dr. L.C. Kersbergen and Drs. F. van Genderen chaired the meeting. Those in attendance were Dr. C. van den Berg, Director General of Public Health, Prof. Dr. B.C.P. Jansen,[27] Dr. Kruysse, Dr. W. A. Timmerman, A.H. van de Velde and Prof. J. Westerdijk.[28] These people, therefore, were considered to be leading public health figures and/or experts on the possible development of antibiotics in the Netherlands at the time. In fact, Jansen had talked with Penau on his 1943 visit to Westerdijk at the CBS.[29]

The Minutes of this first meeting cover much the same ground as Timmerman's report to the Minister of Social Affairs of October 1945. It set out the task of the Commission as advisor to the Minister in the setting-up of a National Institute to control the quality and supply of penicillin in the Netherlands. The National Institute for Public Health had been chosen as the body to fulfil this

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[26] RIV Report U317/45, p.3.
[27] B.C.P. Jansen was Director of the Dutch National Institute for Nutrition and the first Dutch government official to request a sample of *Penicillium notatum* on 4 June 1942. This thesis, Chapter 2, p.70.
[28] RIV Report, Commissie inzake Antibiotische Geneesmiddelen, Report 10 January 1946, pages not numbered.
[29] This thesis, Chapter 2, p.70.

function. The reason given was that it already had a staff, which included researchers, medical staff, chemists, bacteriologists, pharmacists and all were free from any industrial concerns. The only requirement had been the employment of one biochemist.[30] Timmerman's request, therefore, that his Institute was the best prepared to do research with penicillin had been agreed.

Jansen reported on his visit to America and Canada in order to look at penicillin producing installations in those countries. He had found them open, not at all secretive and pleased to give details of procedure. In Toronto, for example, the first factory he visited let him see the growth of its mould culture in bottles. At this factory the amount of penicillin produced was enough to supply the whole of Canada. The cost of this production was not too high, it worked out at approximately Fl.350,000, and the number of necessary personnel totalled one hundred. However, this company had now gone over to the use of deep tanks, which delivered much more penicillin at less cost and needed only twenty-five personnel. In his visit to America, Jansen had gone to the Merck factory where deep tank fermentation was also used. As in Canada, at Merck all methods concerning the production of penicillin had been explained to him.

However, Jansen observed that:

> If we want to work quickly it was suggested that we make application for licences directly to the firms themselves. This apparently goes much faster than via governmental agencies. Improvements are being made all the time and the feeling is that sulphonamide will become less important. The cost price of penicillin will certainly become lower.[31]

The discussion that followed continued along he lines of Timmerman's Report of October 1945. However, whereas Timmerman had taken no direct policy line, what is clear is that the Committee was unanimous over the State control of penicillin. There was a great deal of concern about the cost to the State in importing penicillin. There was also concern on the cost to the State should it

[30]RIV Report, Commissie inzake Antibiotische Geneesmiddelen, Report 10 January 1946.
[31] RIV Report, Commissie inzake Antibiotische Geneesmiddelen, Report 10 January 1946.

support the commercial production of penicillin in the Netherlands. Added to that, great consideration was given to the expectation that a synthetic route for penicillin production might soon be available. All in all, the financial risks involved in the making of penicillin were considered to be very high.

On the point of commercial production, Timmerman suggested State investment in a commercial factory. Jansen pointed to the success of deep tank methodology and the subsequent reduction of costs. Westerdijk said that Florey had told her that the cost of synthetic penicillin would in fact be more expensive than the biological product. She also reported that nine factories in the Netherlands were busy with penicillin research using cultures that she had supplied. The private sector, therefore, were working towards the production of a Dutch penicillin. Kruysse reported that penicillin was being made at the Gist- en Spiritusfabriek and better methods of production were also being worked upon there.

Jansen said that in his opinion if nine companies were working on penicillin production the State should give some leadership but van den Berg returned to the pros and cons of the discussion. In his opinion:

> We have to be able to make a decision that means we have enough penicillin but there are also risks in production and they must be met by the State ... However, we must not be too quick to decide what to do. ... We must ensure that there is enough penicillin made in this country or that there is enough money for us to import from the production of other countries. ... We should also be talking to the Department of Trade and Industry about whether or not a lead could be taken in a trial to produce penicillin in this country.[32]

For van den Berg, Director General of Public Health, making penicillin accessible to the Dutch population seemed a daunting task. Kruysse, a pharmacist, noted that the factories would be looking for a profit.

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[32] RIV Report, Commissie inzake Antibiotische Geneesmiddelen, Report 10 January 1946.

There was, however, general agreement in the first meeting of the Commission for Antibiotic Medicines that there was a need in the Netherlands for a clear, academic, research programme. One that was both biological and medical but also practical. According to Jansen:

> The coming together of basic academic and industrial research has never been more necessary. In America these two groups work well together and the results are extremely good. We, the academics, need contact with what is practical.[33]

Timmerman agreed with the desire for academic and industrial research to work together, each influencing the other. Westerdijk stressed Fleming's suggestions about moulds, bacteria and their products and the need to know more, the need for more research. As far as contact with industry was concerned, Westerdijk stated that she had never had a problem; on the contrary her experience had always been very positive. Timmerman looked forward to future contact with commercial companies. According to van den Berg there would shortly be a meeting between the Health Council and TNO at the Ministry of Social Affairs which would include the Department of Trade and Industry.[34] As early as January 1946, therefore, the Ministry of Social Affairs was planning discussion with the Department of Trade and Industry on the subject of possible penicillin supplies and production.

Finally van de Velde broached the topic of the *Geneesmiddelenwet* in conjunction with new antibiotic medicines. Timmerman hoped that the Government would control any new substances brought onto the market. Westerdijk stated that, in her opinion it was still possible that new penicillins would be produced. In fact she had many cultures that were good producers of penicillin-like substances, but, she noted, this 'production... is still the work of experts'.[35]

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[33] RIV Report, Commissie inzake Antibiotische Geneesmiddelen, Report 10 January 1946.
[34] RIV Report, Commissie inzake Antibiotische Geneesmiddelen, Report 10 January 1946.
[35] RIV Report,, Commissie inzake Antibiotische Geneesmiddelen, Report 10 January 1946.

On 12 February 1946 the Commission for Antibiotic Medicines met again. Regarding the production of penicillin in the Netherlands, three possible contenders were named: the Gist- en Spiritusfabriek in Delft; Brocapharm;[36] and, TNO. The reasons for this choice were, firstly, that Brocapharm had previously had some success in the production of Expansine, even although it had been proven to be too toxic; and, secondly, that the Chairman of TNO had confirmed the establishment of an organic laboratory within his organisation which could research antibiotic medicines. No reason is given for the inclusion of NG&SF in the Commission's list of possible penicillin producers.

However, the Commission also felt that more research in the field of antibiotics still remained to be done. It was not their wish to 'just follow the English and American methods of producing penicillin'. But the question of who should be liable for the costs of such research remained unanswered. In fact, the Commission's directive was plain for all to see. It was that the development of Dutch penicillin should be overseen by the State but not funded by the State.

What is apparent is the Commission's complete lack of commercial acumen. The constant enthusiasm for the Dutch Civil Service and academics to join with industry reflects the point that the post-war era brought the State, academics and commercial interests together in 'Teamwork' and 'Big Science'.[37] However, at this point it has to be noted that the American Teamwork enjoyed during the war years had in fact fallen away. In post-war America old company rivalries had returned.

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[36] Brocapharm was a subsidiary of Brocades, Stheeman & Pharmacia. It was the wholesale arm of BS&P. Personal Communication John Burns June 2005.

[37] This thesis, Chapter 1, p.29.

An example of the return of American rivalry in the international market is seen in a letter to the Dutch National Institute for Public Health from the State Department for Medicines and Medical Supplies of 11 October 1946. In this letter the Director of this *Rijksbureau* listed the American companies that produced penicillin with their prices. The Companies total nineteen. Of the nineteen, Park Davis & Co, Upjohn Company and Merck & Co share the same price, Fl. 6.31 for 200,000 units of penicillin. E.R. Squibb & Sons is the lowest at Fl. 3.77 per 200,000 units. No reason is given for the differences in prices, but the difference between the highest and lowest is almost Fl.3 per 200,000 units, one that would sway any purchaser with financial considerations.[38]

Further, the letter names five companies that could shortly supply the Netherlands with penicillin. These were: Upjohn Company, Hoffman-La Roche, Wyeth International Ltd., Bristol Myers Co. and Cutter Laboratories. However, the *detailprijs* (retail price) for their penicillin was unknown and no decision on the import of penicillin had yet been taken. [39] For the Dutch State, therefore, financial consideration remained paramount in the supply of penicillin.

Dutch Commercial Interest in Penicillin at the End of the War.

While Dutch State organizations were considering the question of State involvement in the production of penicillin and the involvement of multi-faceted scientific research with commercial companies, Dutch commercial companies were also considering their market position. In this, the possibility of producing penicillin on a commercial basis was being considered both individually and in joint ventures. For example, from the Central Archive of NG&SF a report from W.H. van Leeuwen shows that as early as August 1945 NG&SF had entered into discussion about penicillin production with another Dutch company, namely Organon.

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[38] RIV, Letter from Rijksbureau voor Genees- en Verbandmiddelen to RIV, 11 October 1946.
[39] RIV, Letter from Rijksbureau voor Genees- en Verbandmiddelen to RIV, 11 October 1946.

Organon had its origins in the meat product company van Zwanenberg. When insulin was discovered in 1921 the Managing Director, Saal van Zwanenberg, realised that he could extract insulin from the pancreas glands of pigs, which he was already processing. He established a new company, Organon, to do this. Organon also specialised in other natural hormones such as corticosterone and oestrogen. As such, it was a company that had broad experience in the medical and pharmaceutical fields. During the war it had been expropriated by Schering-Kahlbaum of Berlin and came under German control. A German supervisor replaced the Jewish van Zwanenbergs at the head of the company. At the end of the war Schering-Kahlbaum became part of the East German sector and was plundered by the Russians. For the van Zwanenbergs, this allowed the return of Organon to its pre-war management whose task was the re-establishment of their company.[40]

On 5 November 1945 van Leeuwen. wrote to F.G. Waller that he had coincidently met with Mr Tausk, a Director of N.V. Organon, at a symposium in Nijmegen in August. In the course of conversation Tausk had said to van Leeuwen that he would like to meet to discuss cooperation on the penicillin front. This meeting had since taken place in Oss, at the headquarters of Organon. In an overview of the 'General Situation' he (Tausk) reported that since the end of the war Organon had been in contact with, among others, 'CIBA and Geigy' in Switzerland. Before the war they had had frequent contact with the Swiss Professor Reichstein. Reichstein had discovered the Vitamin C process and had sold his patents to Hoffmann but he still had contact with Ciba. Tausk was going to Switzerland on 16 November and hoped to re-establish contact with Reichstein, Ciba and other chemical firms.[41] As has been shown, Ciba was one of the main contributors to the

[40] W. Wennekes, *De aartsvaders. Grondleggers van het Nederlandse bedrijfsleven*, 8th druk, (Amsterdam: Olympus, 2000), pp.479-500.
[41] GB:CA, W.H. van Leeuwen Archive, Correspondence van Leeuwen – F.G. Waller, 5 November 1945.

dissemination of information on penicillin during the war with the publication of A. Wettstein's article, 'Penicillin', in the Swiss Medical Journal of 10 June 1944.[42]

In discussion over possible cooperation in the penicillin area, Tausk began by giving van Leeuwen a presentation on what Organon knew about penicillin, and what they had done to date. He had visited the penicillin factory of the Wellcome Research Foundation in England, which he described as an Institute of the Burroughs Wellcome Pharmaceutical concern. According to Tausk, the directors of this Institute were not at all secretive about their penicillin work and showed him the whole factory. They operated with bottle cultures and used 50,000 milk bottles per day, but everything was automated. The last phase was vacuum drying, which they did at under zero degrees during which the penicillin concentrate became a dry powder. Tausk said that the illustrations from the English brochure called 'Penicillin' were probably taken from this factory.[43] There is no indication in van Leeuwen's report what was meant by the 'English brochure called Penicillin' or why it should be a familiar concept to Tausk, van Leeuwen or F.G. Waller.

Tausk had gone on to discuss with van Leeuwen all the factory details involved in the production of penicillin. He said that he was in a position to obtain any further information necessary. He had had a conversation with Professor Heilbron, an important organic chemist in England, and told van Leeuwen that, in Heilbron's opinion, it would be simpler to produce penicillin via mould culture than to synthesise it. In fact Heilbron wondered if synthesis would ever be possible. Heilbron had also discussed with Tausk the possibility of transferring the penicillin production process to Holland but had said that, before any business could be undertaken, an official approach would have to take place between the British and the Dutch governments.

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[42] This thesis, Chapter 3, pp.95-96.
[43] GB:CA, W.H. van Leeuwen Archive, Correspondence van Leeuwen – F.G. Waller, 5 November 1945.

Tausk told van Leeuwen that Organon had heard of penicillin for the first time in mid-1942. Information had come to them via Germany. They had started an investigation with Professor Julius at Utrecht University but, because of the German supervisor, it had been kept in strict secrecy. They had obtained various *Penicillium* strains from the CBS and had reached the point where they had produced a potent product but could not be certain whether or not it was penicillin. This uncertainty arose in the first place from the fact that they had not used *Penicillium notatum* but another strain that officially was not able to produce penicillin. There were also small differences between this product and the American product, namely the absorption at different pH's on one particular absorbent. Although he does not name the *Penicillium* strain used, Tausk claimed that the extraction and purifying procedure were very simple and their product was relatively pure. Tausk referred to Organon's international experience in the commercial and marketing fields, which would be perfectly appropriate for the promotion of penicillin. He also said that their pharmacological laboratories would be able to investigate the activities of future penicillin products, and to do clinical testing of new antibiotic products.[44]

Summing up for van Leeuwen, Tausk highlighted three assets that Organon would bring into a possible cooperation. Firstly, a wide knowledge of what was happening abroad; secondly, the experience of Prof. Julius at Utrecht University; and thirdly, an established commercial organisation and research laboratories. It was Tausk's desire to coordinate fundamental research in the penicillin area and, in order to obtain production processes, he would be prepared to work in cooperation with the Dutch government.[45] Organon's wartime experience in their research with *Penicillium* strains obtained through the CBS appears to have a striking familiarity with that of NG&SF and Bacinol. It would be anticipated that the offer of the experience of those based at Organon in the pharmaceutical sphere would be appealing to those at NG&SF.

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[44] GB:CA, W.H. van Leeuwen Archive, Correspondence van Leeuwen – F.G. Waller, 5 November 1945.
[45] GB:CA, W.H. van Leeuwen Archive, Correspondence van Leeuwen – F.G. Waller, 5 November 1945.

What happened was that van Leeuwen had replied that NG&SF also had a penicillin-like product. It behaved exactly like American penicillin and had been applied with great success on several occasions. He stated that NG&SF produced its penicillin-like product both in surface culture, in bottles, and in deep culture. They also had a relatively simple extraction process. Van Leeuwen further stated that as far as commercial exploitation was concerned, while NG&SF did not have a commercial organisation that could be compared to that of Organon, his feeling was that penicillin was a self-promoting product. He had, therefore, no doubts that NG&SF could exploit it successfully themselves.[46]

As far as cooperation in research was concerned, van Leeuwen said that NG&SF felt that it would be very difficult to coordinate the activities of several research laboratories. Although the IG (Farben) approach of joint ventures with different industries could lead to an efficient method, in general terms van Leeuwen doubted that this approach would work in the development of the chemical industry in the Netherlands. He was also of the opinion that unless it was strictly necessary he would avoid government involvement.

In his report, van Leeuwen told Waller that his overall impression had been that Tausk was surprised how far NG&SF were with their research. Tausk had admitted that he too found cooperation with other groups difficult, and, given the choice, he (Tausk) would rather not involve the government.

The rest of the discussion had concentrated on the possible cooperation in penicillin production between Organon and Delft. Tausk had emphasised that it was not his intention to take over

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[46] GB:CA, W.H. van Leeuwen Archive, Correspondence van Leeuwen – F.G. Waller, 5 November 1945.

NG&SF but he felt that their cooperation would be in the best interests of the Netherlands. The production of penicillin by various mutually competitive companies was unattractive to him from a business point of view. In Tausk's opinion NG&SF could produce penicillin and Organon market it. For this a separate 'Company' would be established, into which both parties would pool their interests. Research could be done jointly. Organon would provide the work already done by Prof. Julius and NG&SF their research. Patents for the new company could be obtained via Organon's patent organisation. Involvement by the government would only be desirable for the gaining of foreign patents.

When van Leeuwen had raised the question of possibly taking other partners into the proposed new Company, such as Brocades & Stheeman, who had also approached NG&SF with the desire to share fundamental research, Tausk had frowned. He was not impressed with Brocades & Stheeman and a three way division of the shares was unattractive to him. Also, Brocades & Stheeman and Organon were direct competitors in the pharmaceutical world. There would, therefore, be difficulties in sharing information. Van Leeuwen then broached the subject of joint ventures with other Dutch companies such as Philips. Tausk had replied that the Directors of Philips were difficult to do business with but also, again, admitted that Philips was a direct competitor of Organon in the manufacture of vitamin D3. The meeting between Tausk and van Leeuwen had ended with a walk through the Oss factory.[47]

In the history of the development of penicillin in the Netherlands, this report confirms that NG&SF was not the only company researching with *Penicillium* strains during the war years. In particular the research of Brocades Stheeman & Pharmacia with *Penicillium expansum* has been noted earlier.[48]

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[47] GB:CA, W.H. van Leeuwen Archive, Correspondence van Leeuwen – F.G. Waller, 5 November 1945.
[48] This thesis, Chapter 3, pp.84-88.

Nonetheless, at the end of the war, this report reflects a desire for joint ventures in the production of penicillin in the Netherlands. However, while the attitude previously shown from the Dutch State could be described at 'ivory towerism', at least two commercial companies, NG&SF and Organon, preferred little, if any, State involvement. In the production and marketing of penicillin, commercial companies preferred to keep to themselves.

Following van Leeuwen's report much written discussion took place between the Directors of NG&SF on the possibility of joint venture in the production of penicillin. For example, on 28 February 1946, R.A. Jellema, who had been involved with the management of NG&SF penicillin since January 1946, circulated a report on 'Gist-Organon' to W.H. van Leeuwen, H.F. Waller and F.G. Waller. The topic covered the proposed cooperation with Organon. In Jellema's opinion the expected contribution of Delft had been undervalued in two particular ways. Firstly, the leading position that Delft held in the microbiological world had not been given enough recognition and, secondly, that the results that Delft had already achieved had been underestimated by Organon.[49]

Regular reporting within NG&SF on the pros and cons of a joint venture between NG&SF and Organon continued until April 1946. These documents reflect an increasingly polarised stance. Finally, on 19 April 1946 Tausk wrote to the Directors of NG&SF. He stated that, after deep consideration, his Board of Directors had decided that the concept of Organon only selling penicillin and not taking any part in research or manufacture was totally unacceptable. It had never been the intention of Organon to sell a product for which they had no responsibility in quality control. Nor had it been the intention to be part of an organisation in which their role was reduced to that of a wholesaler. In his opinion, NG&SF saw too many disadvantages and too few

[49] GB:CA, W.H. van Leeuwen Archive, Correspondence F.G. Waller – van Leeuwen, 27 February 1945; R.A. Jellema – van Leeuwen, 28 February 1946.

advantages in a joint venture. It would, therefore, be better if both parties found their own way in the field of antibiotics. On 25 April 1946 the Directors of NG&SF, W.H. van Leeuwen, F.G Waller and H.G. Waller, replied to the Directors of N.V. Organon. They formally accepted the decision of the Organon Board.[50]

Conclusion.

On liberation the difficulties facing the Dutch population are aptly brought to the fore, both by their Canadian liberators and conditions in the Public Health sector. At the end of the war there was a pressing need for penicillin as a standard medicine, from a reliable market source with a fixed price. However, in the supply of penicillin State financial concerns remained paramount. There was a desire for State involvement. But there was a tendency towards 'ivory towerism' and a lack of commercial acumen. There was a desire to emulate the 'Big Science' and 'Teamwork' emitting at the end of the war from the United States. Although cash-strapped, the State wanted involvement in the development of penicillin of Dutch penicillin, but as controller.

'Big Science' and 'Teamwork' might have become the bywords for Government research but proposed post-war joint ventures appeared to lack lustre in the Dutch business world. Organon's demands remained too high for NG&SF management. At NG&SF, Organon was considered to 'lack the required expertise'. For both, there was little appeal in working with other Dutch companies such as Brocades Stheeman or Philips. For Organon, these companies remained 'rivals'; at NG&SF cooperation with several others was perceived as 'too difficult to operate'. In the end, as in America, secrecy, old rivalries and market protection prevailed.

[50] GB:CA, W.H. van Leeuwen Archive, Correspondence van Leeuwen – Tausk, February – April 1946.

Chapter 6

1945
Reintegration with Allied Wartime Research: Facing the Backlog.

With liberation in May 1945 NG&SF were able to verify their antibacterial substance, Bacinol, as penicillin. However, as has been shown, publications on the production of penicillin in both Britain and America were under an Allied embargo from 1941 until the end of the war.[1] During the war, there was an enormous build up of information on penicillin research and production facilities by the Allies but not all of it had been published. At the end of the war an avalanche of information about penicillin appeared in academic journals and commercial brochures. In academic and commercial terms the backlog facing the Netherlands, regarding the development of penicillin, was enormous.

The backlog is underscored by two publications. First, the *British Medical Bulletin* of 1944, which surveyed articles published on penicillin between 1929 and 1943. The reason given for doing so was that interest in penicillin was worldwide 'but wartime disturbances' had added to the difficulty in some countries of obtaining access to the relevant literature. Consequently, this special number of the *Bulletin* had been given over entirely to a survey of penicillin from the date of its discovery until the end of 1943, 'when clinical trials on a more adequate scale became possible'.[2] Prof. L.P. Garrod, Fleming, Florey and Chain had written special contributions. In total this *Bulletin* contained abstracts of 241 articles and an extensive bibliography on penicillin. It is contained in the archive of the Rijksinstituut voor Volksgesondheid en Milieu. Although there is no evidence about the date this *Bulletin* was received at the RIV, when it did it would have alerted those with an interest in penicillin research to the task that lay ahead.

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[1] I. Pieroth, 'Penicillin', p.29.
[2] *British Medical Bulletin*, 2, No. 1, 1944, p.2. Source: RIVM Archive.

It should, also, be noted that this *Bulletin* was one of the principal sources for the reviews on current British and American penicillin research contained in the *Schweizerische Medizinische Wochenschrift* of 10 June 1944. This latter was the journal obtained by Querido in July/August 1944 and photocopied at NG&SF.[3]

The second publication underscoring the backlog covers information from the United States. It is Merck's 1945 Company Brochure. Entitled 'Penicillin' this publication included an 'Annotated Bibliography' and stated in its introduction, 'So rapid are the developments in this field that no publication can hope to be completely up to date by the time it has gone through to press'.[4] It contained 521 reviews on publications about penicillin. The Director of Research at Merck, R.T. Major, sent it to Kluyver at the TH, Delft, in January 1946. Given his relationship as NG&SF advisor, there can be no doubt that researchers at NG&SF would also have had access to it as they strove to bring their antibacterial product, Bacinol, onto the market.

Chapter 5 of this thesis has shown that there was a desire in the Netherlands to 'catch-up' in the development of penicillin both academically and commercially at the end of the war. However, while the Dutch National Institute for Public Health considered the pros and cons of State involvement, commercial companies such as Organon and NG&SF looked towards commercial ventures. Organon did not enter the penicillin market, NG&SF did. By 1950 NG&SF was a world market leader in the production of bulk penicillin. In order to reach this point, NG&SF had to face the backlog of information. Accordingly, at the end of the war, the manner in which up-to-date information on penicillin came to NG&SF will be explored.

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[3] This thesis, Chapter 4, p.127; Chapter 3, p.104.
[4] KA, Penicillin Reprints Box.

Facing the Backlog.

The Kluyver Archive confirms the reintegration of Dutch academic Institutions in the international arena at the end of the war. It also illustrates the desire to engage with what had happened in the Allied countries. However, a series of letters between Kluyver and the Librarian of the TH in Delft, dated between January and December 1946, reflect the fact that this was no easy task. These letters contain many references to the remit of the *Commissie Blauw* (Blauw Commission). During the war Blauw had been based in London. His remit from the Government-in-exile had been to purchase academic books and journals for distribution to Dutch libraries, universities and colleges at the end of the war. Given the post-war transport difficulties and the administrative problems of re-establishing a national government it is not surprising that this distribution took a frustratingly long time. It was February 1946 before the TH Librarian could write to Kluyver to say that he had received notice from the KNAW in Amsterdam that the publications bought by the Blauw Commission had arrived. He reported that the KNAW had also discussed the fact that the American Library Association was prepared to deliver back numbers of certain publications free, with the proviso that the subscription be continued. Owing to the Dutch foreign exchange problems, however, the KNAW had had to decline.[5]

The relative dearth of information on penicillin in the Netherlands at the end of the war can also be gleaned from local correspondence. For example, on 20 September1945 Kluyver received a letter from an associate, W.L. Veer, from Oss. Veer apologised for the fact that when he visited Delft in June he did not have time to visit Kluyver. He had heard from Rombouts 'of NG&SF' that Kluyver's yeast culture collection had managed to survive the 'infamous winter', and he hoped very much that the TH Laboratory would soon be running on all cylinders again. Unfortunately, Veer's experience was that new Anglo American literature came at very irregular

[5] KA, Catalogue 199085, Folder 1, Letters A-C, Librarian TH to Kluyver, January to December 1946.

intervals and he added his disappointment that exact data about penicillin were not yet known.[6] In particular, this disappointment serves to highlight the frustration of having to wait until knowledge in the form of publications came from outside the Netherlands to those waiting within. However, not all waited. At the end of the war, given the chance, those academics who could, went in search of Anglo American literature.

Medical Catch-up: A. Querido at Leiden University Hospital.

For example, in the second-half of 1945 Querido not only returned to NG&SF as a part-time advisor, he also returned to Leiden Uiversity Hospital. In his capacity as a medical doctor, Querido had accompanied the *ziektransport* (transport of those who were ill) by train from Theresienstadt to Pilsen in the American Zone. From there, deloused by DDT, he was flown back to Eindhoven. From Eindhoven he made his way to Leiden where, in June 1945, he was met with 'open arms'. Hans Goslings, a good friend and colleague, had 'reserved' a position for him in the Klinisch-bacteriologisch Laboratorium (Clinical Bacteriological Laboratory).[7]

In December 1945 Leiden University Press (LUP) published the first edition of a book entitled *Recent Medical Science 1940-1945*. This was followed by a second edition in January 1946.[8] It contained a series of articles taken mainly from the *British Medical Bulletin* that had been published during the years 1944 and 1945. Members of the Leiden medical faculty had chosen the articles for publication on the basis of interest expected from general practitioners, specialists and research workers. The aim of the book was to fill in 'as far as possible the gap in our knowledge caused by the war'. The conclusion of each article contained a detailed bibliography so that readers could consult the original texts 'when they become available'.[9] Thanks for help in

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[6] KA, Catalogue 1990089, Folder 2, Letters S-Z, W.L. Veer to Kluyver 20 September 1945.
[7] A. Querido, *Andries Querido*, p.96
[8] *Recent Medical Science 1940-1945*, 2nd ed, January 1946, (Leiden: Universitaire Pers Leiden, 1946).
[9] *Recent Medical*, Preface, pages not numbered.

publication is given to the British Council, Netherlands Branch, and their medical department in London; to the Royal Society of Medicine for permission to reprint the articles; to Prof. L.P. Garrod for putting his lecture on penicillin at Leiden's disposal; and, to the War Office for their contribution 'to our material on penicillin'. The Preface closed, noting 'how great has been the sympathy and readiness ... of our British colleagues' to help in the 'rehabilitation of medical knowledge in the Netherlands'.[10] Also, acknowledged is the input of Querido.

The book contains 31 articles. Only three are devoted to penicillin. The first is by Fleming on 'The Discovery of Penicillin'. It is fairly short, only four and a half pages in length, but gives a concise and instructive review of his 1929 research. He gives no bibliography.[11] The second is by L.P. Garrod on 'The Therapeutic Use of Penicillin'. This article is very informative and gives a short account of 'what penicillin is, how it must be handled, and how it should be used'.[12] It is in fact a copy of a lecture he had given in France after its liberation in 1944 and, although he pointed to the production of penicillin 'now on an immensely greater scale' he did warn that quantities were still limited to the fighting forces. He hoped that it would 'be placed freely on the market' soon after the war was over. As such this article offered an insight not only into the medical application of penicillin but also opened up the urgency of marketing for the civilian sector.

The last article, 'The Use of Penicillin',[13] is a publication from the Army Medical Department Bulletin published by the War Office in June 1944. Although, again, a relatively short publication this article contains details on the standardised units of penicillin in tablet form; the special properties required for 'Stability'; 'Solubility, Absorption and Excretion'; 'Antibacterial action'; 'Methods of Administration'; how to 'Handle the Drug'; possible 'Reactions'; the 'Duration of

[10] *Recent Medical*, Preface, pages not numbered.
[11] *Recent Medical*, Article 28, p.309.
[12] *Recen tMedical*, Article 29, pp.314-321.
[13] *Recent Medical*, Article No. 30, pp.322-328.

Treatment and Criteria of Cure'; and, concluded that if these guidelines were followed there should be no 'failure'.[14] At this point, however, it should be noted that this was not the only military medical document to influence the development of penicillin in the Netherlands, as will later be shown.

Although short, the last two articles in particular can be seen to form the basis of concise contemporary information on penicillin published in Britain. Meant as an introduction for Dutch general practitioners, specialists and research workers, both would have been sufficient for any party interested in the development of penicillin to obtain a firm understanding of advances made during the war years. Also, the fact that the 2nd edition was printed so close to the 1st is an indication of its value in the Dutch academic world. It would also have been invaluable to those considering possible marketing opportunities, like those at NG&SF.

Academic Catch-up: A.J. Kluyver at the TH, Delft.

At the end of the war Kluyver's correspondence reflects the first tentative steps of reunion with academic colleagues, former students and friends. The emotion contained therein offers an insight into the feelings expressed at the end of the war. It also clearly portrays the difficulties NG&SF faced in the further development of penicillin.

For example, one of the first post-war letters Kluyver received is dated 16 May 1945. The sender is Marjory Stephenson of the Sir William Dunn Institute, Biochemistry Laboratory, Cambridge. A respected microbiologist, she was the first woman to be appointed Fellow of the Royal Society and a member of the first Committee of the Society for General Microbiology, founded early in 1945.[15] In May 1945 Stephenson wrote to Kluyver:

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[14] *Recent Medical*, Article No. 30, pp. 322-328.

[15] Alexander Fleming was the first President of the Society for General Microbiology.

> Now that Holland is liberated I cannot remain longer without trying to communicate with you. Please reply soon and allay my anxiety if you can. Like most and many of my continental friends you have been in my mind these years. Also, if you have been able to work we should like reprints. I have some ready to send but at present everything goes by air and I cannot send very much....[16]

Her letter continued, passing on information in an effort to bring Kluyver up-to-date with what had happened to other associates during the war years.

On 7 June 1945 Kluyver replied:

> It was a very great delight to receive your letter of 16 May... I was especially happy because it meant such good news both of you and the many others to whom my thoughts had wandered during these five years of desolation. We Dutchmen owe a great debt to Great Britain and we realize that numerous of your compatriots have given their lives in order to save our Western civilization from the dreadful menace of the Nazis. This was more than a phase. I speak from experience of five years of slavery. I am not only a wiser and a sadder man than the one you met last time but also a lighter and an older man. I have lost 37 kilos in body weight and the years passed in the territory occupied by Germany count double. But before dealing further with my experiences I would like to express my great satisfaction to all those who have been able to continue with their work.
> I was afraid that ammunitions factories, home guard, relief work or even active service would have claimed all the scientists. That this is not so is of course due to the fact that your government has rightly recognized the paramount importance of scientific research for the final victory. Penicillin, DDT and undoubtedly many other things that are unknown to me are there to testify.[17]

He continued by drawing attention to the devastating effects of five years of German occupation. He thanked her for collecting and sending the reprints because the Netherlands was 'a very poor nation now'. He was most doubtful whether or not the Government would be able to reserve part of its credit for the payment of subscriptions to foreign journals, as everything was in short supply. Reconstruction, he said, would take a long time.

On a personal note, he said that in contrast to several of his friends, his family was still alive. Referring to the enforced service of young Dutch men pressed into work in Germany, he said that

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[16] KA, Catalogue 1990089, Folder 2, Letters S-Z, M Stephenson to Kluyver, 16 May 1945.
[17] KA, Catalogue 1990089, Folder 2, Letters S-Z, Kluyver to M Stephenson 7 June 1945.

his eldest son had just come home after 'two years of German slavery' and described the last six months of occupation as:

> cold and hungry ... but owing to the very liberal English and American support after our liberation we are very quickly recovering.[18]

Another privilege, he said, was that his laboratory was still intact. Several other laboratories had been badly looted but he had managed to hide some of the 'most precious parts' of his instruments.[19] However, for the last two years of the war he had had no students and academic work had practically stopped. A final blow to his academic work was the fact that 'since last autumn we have had little gas and electricity'.[20] He continued that:

> At the moment the situation has not yet changed and the prospects for a quick improvement are far from bright. Nonetheless we trust that at some time we will recover. Tokens of sympathy from friends abroad, like your letter, are very helpful in this respect.[21]

Kluyver's next letter to Marjory Stephenson said that he very much appreciated the invitation from Society for General Microbiology to attend their forthcoming meeting on 19 and 20 December 1945 in London. On 12 December 1945 Stephenson replied that she was delighted he would be able to attend. She would be pleased to put him up in Cambridge. Her letter to Kluyver ends with the underlined statement, 'do not bring any rations'.[22]

Both Kluyver and Westerdijk attended the London Meeting. Kluyver presented a paper. However, the difficulties in arranging travel to such academic meetings at the end of the war is illustrated in a series of correspondence between Kluyver and R. St. John Brookes of the National Collection of Type Cultures, Elstree, Hertfordshire. At the time, St John Brookes was Secretary to the Committee of the Society for General Microbiology. The cost of travel to the meeting for Kluyver

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[18] KA, Catalogue 1990089, Folder 2, Letters S-Z, Kluyver to M Stephenson 7 June 1945
[19] KA, Catalogue 1990089, Folder 2, Letters S-Z, Kluyver to M Stephenson 7 June 1945.
[20] KA, Catalogue 1990089, Folder 2, Letters S-Z, Kluyver to M Stephenson 7 June 1945.
[21] KA, Catalogue 1990089, Folder 2, Letters S-Z, Kluyver to M Stephenson 7 June 1945.
[22] KA, Catalogue 1990089, Folder 2, Letters S-Z, M Stephenson to Kluyver 12 December 1945.

and Westerdijk was met by the Society. It was paid through a representative of the British Council stationed at the British Embassy in The Hague.

On a personal note, Kluyver wrote to St John Brookes on 26 November 1945 that it had been very complex but he had been successful in obtaining the required 'permits and visas'. British currency was not freely available for Dutch citizens but, through the Dutch Government office in London, he had been able to arrange a daily allowance of '£3'. He recounted his brother-in-law's experience of difficulties with accommodation due to demobilization and asked if the Society could find him a 'cheap hotel with a small bedroom'. St John-Brookes replied that their friend and colleague A.C. Thaysen of the Chemical Research Laboratory in Teddington would be delighted to 'put him up'.[23]

Another series of letters with pre-war contacts let us see that as early as September 1945 Kluyver was catching up on information on the development of penicillin. For example, on 10 September 1945 H.G. Thornton of the Rothamstead Experimental Station, Harpenden, Hants., wrote to Kluyver. He began by saying that he had been very anxious about Kluyver and continued:

> In Britain there is the greatest sympathy for the Dutch people and admiration for their bravery both during the Nazi occupation and during the very hard times through which we are all now passing. We have been much more fortunate than you, we have been able to continue our work at Rothamstead without serious disturbance although my own house has twice been damaged by flying bombs. I hope it might be possible for you to visit us sometime in the not too distant future. You will always be most welcome. I enclose a few reprints of our work here. Have you done any work on penicillin? I have heard that you have strains of *Penicillium notatum.* [24]

[23] KA, Catalogue 1990276, Folder not numbered, Leters A-L, R St John Brooks to Kluyver 30 November 1945.
[24] KA, Catalogue 1990089, Folder 2, Letters S-Z, HG Thornton to Kluyver 10 September 1945.

On 18 September 1945 Kluyver replied. He thanked Thornton for his letter and the reprints. He commiserated on the flying bombs but was pleased that research had continued in Britain. However, in his last sentence Kluyver wrote:

> Owing to some industrial connections I have been interested in penicillin but in my laboratory we have no strains of *Penicillium notatum*.[25]

At the end of the war, therefore, Kluyver was, as ever, secretive of his advisorship to NG&SF. While happy to exchange academic information he was not prepared to commit himself to more than a passing knowledge of NG&SF's commercial research with penicillin.

At the same time, a series of letters between Kluyver and Thaysen indicate that in the immediate post-war months Kluyver's contacts were working on his behalf. On 25 September Kluyver wrote to Thaysen:

> Miss Morris was kind enough to inform me that she was preparing some cultures for me which she would send later. May I infer that this communication refers to the strains of Penicillin *notatum* that you kindly offered to me during your visit? I would greatly welcome such a present.[26]

On 5 October, Thaysen replied:

> I have arranged with Miss Morris this morning to send you the strains of *Penicillium notatum* which we have got here and which include the latest ones from the US growing under submerged conditions.[27]

It is not yet clear when or why Thaysen visited Kluyver so shortly after the war. However, these letters illustrate that by October 1945, barely six months from the end of the war, Kluyver had access not only to contemporary British *Penicillium* strains but also to the 'latest ones' from the United States. There can be no doubt that such knowledge would be shared and discussed with Waller's team at NG&SF.

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[25] KA, Catalogue 1990089, Folder 2, Letters S-Z, Kluyver to HG Thornton 18 September 1945.
[26] KA, Catalogue 1990089, Folder 2, Letters S-Z, Kluyver to AC Thaysen 25 September 1945.
[27] KA, Catalogue 1990089, Folder 2, Letters S-Z, AC Thaysen to Kluyver 5 October 1945.

From August 1945 Kluyver also rekindled his correspondence with friends and colleagues in the United States. For example, 13 August 1945 started a series of correspondence between Kluyver and R.L. Starkey of the State of New Jersey Agricultural Experimentation Station in New Brunswick. Starkey had been a researcher at Rutgers University under Waksman. This correspondence contains letters in which Starkey recalled the pleasure of his sabbatical year in Holland with Kluyver. His concern for Kluyver and those at the TH is plain, as he 'has heard nothing from them'. He had sent some packages that included the vitamin tablets, Vigram, and he hoped these might help to make up for food deficiencies. He detailed the research that had taken place in his department on 'microbial fat synthesis' during the war years and brought Kluyver up to date on the current circumstances of two of Kluyver's former students, now resident in the United States. 'Dr. Hoogerheide', he said, was no longer working at Squibb but had moved to PABST in Milwaukee 'about a year ago' and H.F. Phaaff had received his Doctors degree at the University of California. He ended with the news that Waksman and his students had isolated a large number of antibiotic substances, one of which offered promise as it had properties similar to that of penicillin and would be useful for control of a number of diseases not affected by penicillin – 'it is called Streptomycin'.[28] As early as August 1945, therefore, Kluyver was being brought up-to-date with what had happened, not only in scientific research within his circle but also, as Starkey's letter illustrates, with former pupils and personal friends.

Kluyver replied to Starkey on 12 November 1945 in a letter that illustrates the pressure Dutch researchers had been put under during the years of occupation. He began by discussing the work Starkey had done and said that, in the first years of the war, microbial fat synthesis for industrial applications had also been studied at the TU but since they did not want to give indirect support to the German war effort it all had to be kept secret.[29]

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[28] KA, Catalogue 1990092, Folder 4, Letters S-Z, RL Starkey to Kluyver 8 October 1945.
[29] KA, Catalogue 1990092, Folder 4, Letters S-Z, Kluyver to RL Starkey 12 November 1945.

The rest of this letter reflects not only the emotion of the time but also of the high price paid by Dutch society during their years of occupation:

> We are of course acquainted with the phenomenal success of penicillin... The fame of Dr Waksman's Streptomycin has also reached us. If rumours about its usefulness against tuberculosis are confirmed it may be something of the significance of the atom bomb. There may be some exaggeration in this dictum but I am deeply impressed with the ravages which tuberculosis has brought about during the last years in our population, and this in a country that before the war had the lowest tuberculosis death rate in the world. This reminds me of the fact that our mortality statistics for the years of the war have just been published. It is somewhat surprising to see that the percentage of death rate has been three times that in Great Britain and Northern Ireland. Here in Holland it was chiefly civilians who paid the toll.[30]

He described the winter of 1944/45 as 'a well organised famine' and continued:

> Since the Liberation we have made a fresh start but traffic is far from normal, all larger bridges have been blown up and our railway carriages and locomotives have been stolen... Recovery is slow... In some respects progress is satisfactory. Nearly all the flooded areas have been recovered. The worst is that so many factories have been looted. Both raw materials and machinery had been dragged to Germany and our benevolent liberators will not allow us to fetch our property back. We are therefore a very poor people and our restricted foreign credit must be used for the purchase of locomotives etc. ... Nowadays we are a nation of beggars. Realising this our Government has temporarily abolished all import duties on gifts that we receive from outside... The gifts you sent have been most welcome. The coffee and the tea are a joy for my whole family and, as for the cigarettes, you know me so well you could at least imagine my happiness.[31]

Considering the financial restrictions of the Dutch at the time, not being allowed by the liberators to reclaim that which had been forcibly taken must have been galling.

On 29 August 1945 Kluyver resumed his pre-war correspondence with his former pupil J.C. Hoogerheide. Hoogerheide must have been one of the first post-war correspondents from America as, in this letter, Kluyver thanked him for the parcel he had sent and especially the 'coffee, tea and soap but most of all for the cigarettes'. Reflecting stringent rationing, Kluyver stated that since the

[30] KA, Catalogue 1990092, Folder 4, Letters S-Z, Kluyver to RL Starkey 12 November 1945
[31] KA, Catalogue 1990092, Folder 4, Letters S-Z, Kluyver to RL Starkey 12 November 1945

day of liberation he had only received a total of forty cigarettes from the official distribution.[32] He asked Hoogerheide for reprints and stated his curiosity about the antibiotic H1, which had appeared so promising.[33]

In October 1945 Hoogerheide replied. As an expatriate Dutchman working in the United States, his understanding of Kluyver's experience is evident. His own family, he said, had 'lost everything'. They were trying to get visas to go to America. 'H1', he reported, had proven to be identical to the *Tyrothricin* of Dubos and, although it had been developed independently, Dubos had 'priority'.[34] H1 had been used during the war on a limited scale for infected wounds but 'correctly... gave way to penicillin'.[35]

He continued by telling Kluyver of Florey's visit to the United States in 1941 during which it had been Florey's aim to interest people like Coghill and the American drug industry in penicillin production. Although at the time no one was sure of its therapeutic potential, Merck and Squibb had been prepared to investigate further. Hoogerheide had:

> On the recommendation of Waksman, been offered the leadership of a team at Squibb to produce sufficient penicillin to test its therapeutic potential. Dr. Foster, a former pupil of Waksman, at Merck and my (Hoogerheide's) laboratory were the first, with an infinite number of difficulties, to produce sufficient penicillin to be tested in patients.
> When this proved successful everyone became interested in penicillin and research switched to large-scale production methods. During the first two years surface culture was used but after this production was switched to deep culture in tanks.
> Although Squibb is not the largest producer of penicillin they were the first to be able to supply the army.
> The penicillin project was one that had no precedent in the history of medical research and it gave me great satisfaction to have been a part of it, although, as my

[32] According to one of his wartime students, Ant Kaars-Sypesteijn, Kluyver was a habitual smoker. During the war he grew tobacco in the TH Botanical Garden. Personal Communication.
[33] KA, Catalogue 1990276, Folder not numbered, Letters A-L, Kluyver to JC Hoogerheide 29 August 1945.
[34] Dubos role in the development of antibiotics is referred to earlier. This thesis, Chapter 2, p.35.
[35] KA, Catalogue 1990276, Folder not numbered, Letters A-L JC Hoogerheide to Kluyver, 1 October 1945.

> contribution was entirely practical you will not find my name in the history books.[36]

On 17 November 1945 Kluyver replied congratulating Hoogerheide. He noted with pride that one of his graduates had been prominent in the development of penicillin.[37] However, again bearing in mind the secrecy surrounding his NG&SF advisorship, he does not mentioned the work done during the war years with penicillin by Hoogerheide's alumni at NG&SF.[38]

These letters are only a few examples of many similar letters Kluyver received and sent to his friends, colleagues and former students in both Britain and the United States at the end of the war. In particular they show the economic hardship experienced by Dutch society at the time, but they also show the determination to rebuild knowledge of the research and development that had taken place during their occupied 'isolation'. At the same time they reflect the willingness of friends, colleagues and former students in Britain and the United States to help.

For example, during the war years H.A. Barker, of the University of California at Berkeley, who had spent a sabbatical year in Delft, had arranged through his offices for the build up of a 'Delft Library Fund'. By the end of the war this fund had reached 'well over $100'. Contributions had come from prominent names in microbiological research of the time, such as Peterson, French, Hungate, and Buchanan. At the end of the war, in addition to buying reprints for Kluyver through the 'Fund', Barker also arranged that fellow academics send reprints of material they had published during the war years directly to Delft.[39]

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[36]KA, Catalogue 1990276, Folder not numbered, Letters A-L, JC Hoogerheide to Kluyver, 1 October 1945.
[37]KA, Catalogue 1990276, Folder not numbered, Letters A-L, Kluyver to JC Hoogerheide, 17 November 1945.
[38] J.C. Hoogerheide joined KNG&SF staff in 1955. Source: B. Elema, *Opkomst*, p.114.
[39]KA, Catalogue 1990085, Folder 1, Letters A-C, HA Barker to and from Kluyver, January to November 1946.

At this point the Kluyver Archive shows what can only be called an avalanche of information sent directly to Kluyver. Many contained information on contemporary American research and development of penicillin. An example of the way in which such information reached Kluyver is given by a letter of 19 November 1945 in which, at the suggestion of Kluyver's former pupil, C.B. van Niel of the Hopkins Marine Station, Pacific Grove, California, J. Martin, Director of Research for Commercial Solvents Corporation in Terre Haute, Indiana, enclosed two reprints. One was a 'general article dealing with large scale preparation of penicillin' the other was a copy of the Commercial Solvents booklet entitled 'Penicillin and the Present Day Concept of its Clinical Applicability'. Other company reprints, Martin reported, would be sent to Kluyver by the individual authors.[40]

Merck, as we have seen, provided Kluyver with their 1945 Company Brochure. They also provided Merck Brochures for 1943 and 1942, as well as reprints from the work that had taken place in their laboratory during the war years and samples of synthetic vitamins. On 9 January 1946, in the first of a series of letters, R.T. Major, Director of Research and Development, told Kluyver that he had heard of his need through an associate and friend, Roger Stanier, who had spoken with Kluyver at the recent Society for General Microbiology meeting in London. He, himself, had been 'much interested' in Kluyver's publications in the field of microbiology 'for a good many years'.[41]

Similarly, in November 1945, at the request of C.B. van Niel, A.F. Langlykke, the Head of Fermentation Division at the Northern Regional Research Laboratory, wrote to Kluyver:

> We are forwarding to you reprints of the technical contributions of this division. It is indeed a pleasure to provide you with this material and we shall be happy to supply you with further reprints in the future at your request. We are all happy to

[40]KA, Catalogue 1990090, Folder 2, Letters M-Z, J. Martin to Kluyver, 19 November 1945.
[41]KA, Catalogue 1990090, Folder 2, Letters M-Z, RT Major to Kluyver, 9 January 1946.

> know that you have survived past difficulties and are once more engaged in active microbiological work.[42]

Kluyver's reply of 2 January 1946 reflects his eagerness to catch-up. However, it also reflects a sense, for Kluyver especially, that Dutch research had a mountainous task in any attempt to re-enter the scientific community:

> May I thank you heartily for your kind letter of 19 November and the very valuable set of reprints of the technical contributions of the fermentation division. Since we have been cut off so long from all scientific progress in the United States it will not need further substantiation that the information these very interesting publications gave us has meant a great deal to us. I will of course be greatly obliged to you if you will put my name on your mailing list for future publications. I cannot reciprocate your kindness in a suitable way. Our work has been too badly interrupted but if there are any older publications from my laboratory which for some reason or other are of interest to you I hope you will let me know and I shall do my utmost to send them to you.[43]

Whilst here we can glean a hint of depression at being so far behind contemporary research, this letter marks the beginning of a series of correspondence between Kluyver and the NRRL that lasted well into 1946 and beyond. For example, on 7 June 1946 Andrew J Moyer of NRRL sent reprints authored by Coghill and himself dealing with the production of penicillin; and, on 29 October 1946, Kluyver acknowledged receipt of the 'very interesting' NRRL paper by Rapier and Fennell on 'The Production of Penicillin X in Submerged Cultures'.[44] Again, undoubtedly this information would have been shared with NG&SF.

At the end of the war Kluyver's letters illustrate the academic bareness in life under Nazi occupation. They also illustrate the difficulties in trying to re-establish normal life and the awareness in the Netherlands that they had to win back knowledge. Not only had the Netherlands to recover from rationing of food; the ravages of the hunger-winter in a 'well organized famine'; and, the plundering of raw materials - they also had to recover from a famine of information.

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[42]KA, Catalogue 1990090, Folder 1, Letters J-L, AF Langlykke to Kluyver, 19 November 1945.
[43] KA, Catalogue 1990090, Folder 1, Letters J-L, Kluyver to AF Langlykke, 2 January 1946.
[44] KA, Catalogue 1990090, Folder 2, Letters M-Z, Kluyver to AJ Moyer 7 June 1946.

There was, however, no money. There could be no immediate government funding. Material that had been obtained during the war had to go through laborious administrative channels. There was, as happened in France, Germany and Japan, no Allied expertise entering the country. However, as we have seen, endeavours to compensate for this lack of information took many forms. Reprints of scientific publications detailing wartime advances were received through friends and colleagues in the wider scientific world. For Kluyver, this can be seen to take off after he attended the London Meeting for the Society of General Microbiology in December 1945. Many American reprints reached Kluyver after January 1946. Earlier than that, however, NG&SF were also anxious to update their information on the development of penicillin. Here too the influence of Kluyver and Querido played its part.

Kluyver – NG&SF

As early as October 1945 the Nederlandsche Gist- en Spiritusfabriek sent one of their Chemical Engineers, C.W.F. Spiers, to the United States. Spiers had first hand experience of penicillin production in Delft. His name appears as a recipient in Stheeman's NG&SF R&D Report 750 regarding the first experiments with penicillin.[45] On his visit to the US Spiers took with him samples of the first penicillin made by NG&SF. The typewritten labels on two small flacons held in the NG&SF archive contain the words 'Dr. Spiers. 23rd October 1945'.[46]

During his visit to the US, Spier's task was to inspect research laboratories and commercial producers involved with the development of American penicillin. In order to do so, as well as samples of NG&SF penicillin, Spiers took with him a letter of introduction from Kluyver. It is dated 19 October 1945 and reads:

[45] This thesis, Chapter 4, p.143.
[46] M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', Figure 6.

> My Dear Friend,
> I hope you will allow me to introduce to you my fellow countryman Dr. C.W.F. Spiers. Dr Spiers is a consulting engineer connected with the well known yeast concern Nederlandsche Gist- en Spiritusfabriek in Delft. He is, in the said capacity, making a tour of the United States in order to get an impression of recent industrial developments. I should much appreciate it if you would kindly give Dr Spiers some assistance, for instance, by giving him an introduction to places of interest to him.

This introductory letter is one of many. There is no list of whom Spiers planned to visit but identical copies of this letter have been found in the Kluyver Archive addressed to all of Kluyver's American contacts named in this thesis, for example, Barker, Hoogerheide, van Niel, Phaaff and Starkey. However, there are many others. On 6 November 1945, F.W. Tanner, Head of the Department of Bacteriology at the University of Illinois, wrote to Kluyver expressing his relief that Kluyver was still alive and reported that he had 'enjoyed Dr. Spiers from the Gistfabriek' when he visited. Moreover, his (Tanner's) son 'who is in the US Department of Agriculture Research Laboratory in Peoria' took him (Spiers) there for the day. In his reply Kluyver thanked Tanner, but his reply also lets us see that Spiers was reporting back to Kluyver when he said Dr Spiers had found his visit 'very agreeable' and that:

> I hope to see him before long. From his letters I know that he has greatly profited from his various visits. I understand that he is especially indebted to your son for all this promising research worker did on his behalf.[47]

The length of time Spiers spent in the United States collating information on recent industrial developments with penicillin is unknown but the fact that his visit lasted at least eight months can be gleaned from Kluyver. For example, on 6 June 1946 Starkey wrote to Kluyver on the content of two meetings, firstly, the American Chemical Society and, secondly, The Society of American Bacteriologists. At the meeting for Bacteriologists in Detroit, Starkey said that he had 'had the good fortune to meet Dr. Spiers of the Yeast Plant at Deft', and that there had been 'subsequent visits to our laboratory in New Brunswick. He (Spiers) seems to have had the opportunity to see

[47] KA, Catalogue 1990092, Folder 4, Letters S-Z, Kluyver to FW Tanner, 6 November 1946.

many things during his stay in the United States but informed me that he expects to return shortly to Holland'.[48]

Unfortunately, no correspondence or reports by Spiers have been found in either the Kluyver or the NG&SF Archives. Nonetheless, that Spiers initiated the first penicillin contacts for NG&SF in the United States through Kluyver's network is further illustrated by Kluyver's correspondence. On 18 October 1946 Kluyver wrote to Hoogerheide that 'Mr Waller of the Nederlandsche Gist- en Spiritusfabriek would like to talk to you in connection with the discussion you had had with Dr. Spiers in Milwaukee'.[49]

Kluyver's active interest in penicillin in combination with his work as an advisor for NG&SF is again seen in a letter dated 9 January 1946 when Kluyver wrote to Raistrick at the London School of Hygiene and Tropical Medicine. He apologised that he had not manage to see Raistrick during his recent visit to London but thanked him for giving 'Dr. Querido of Leiden' the various strains of *Penicillium notatum.* Querido had forwarded them to him.[50] Although Kluyver does not mention NG&SF's interest in penicillin it is clear that he was working on their behalf, not only in the United States, but also in Britain.

In a further series of letters between January and June 1946 Kluyver asked the British Medical Research Council in London for reprints of twenty publications.[51] These included articles such as 'Penicillin: a Study in Cooperation'and 'The Chemistry of Penicillin'. [52] On 21 January 1946, he corresponded with the National Institute for Medical Research, Hampstead, London, in which he

[48] KA, Catalogue 1990092, Folder 4, Letters S-Z, RL Starkey to Kluyver, 6 June 1946.
[49] KA, Catalogue 1990085, Folder 2, Letters D-H, Kluyver to JC Hoogerheide, 18 October 1946.
[50] KA, Catalogue 1990092, Folder 3, Letters R-S, Kluyver to H Raistrick, 9 January 1946.
[51] KA Catalogue 1990090, Folder 2, Letters M-Z, Kluyver to MRC, January to June 1946.
[52] *Nature*, 29 December 1945, p.6 and p.761; *Nature*, 29 December 1945, p.766.

thanked the Institute for 'making publications available' and ordered copies of eight publications from the Medical Research Council, List 44.1, July to December 1945.[53] Most are on penicillin.

Finally, the connection with Kluyver as gatherer on information on recent research and development with penicillin in Britain and the United States, is reflected in a series of correspondence between Kluyver and St. John Brookes. On 1 March 1946 Kluyver asked St John Brookes for cultures of *Staphylococcus aureus* 'used in the standardized tests for Penicillin'. He said he thought here were two of them. One used in England, 'no. R6571' in the National Collection of Type Cultures, and the other, he thought was American. He also wanted a culture of *Bacillus subtilis* which was also used in penicillin testing.[54] On 8 March 1946 St John Brookes replied:

> With regard to the strains we sent you recently, number 6571A (Heatley) is certainly the Oxford 'strain' used for testing penicillin. Your assumption regarding the other two is probably correct but the information we actually have is as follows:
> Number 6718 Staphylococcus *aureus*, FDA number 219, ATCCC number 6538, US Food and Drug Administration reputes to have a special advantage in penicillin assay work. Received April 1944.
> Number 6816 Baccillus *subtilis*, Glaxo 417, Penicillinase producing strain from Glaxo Ltd, Greenford, Middlesex.
> Reference Nature 1944, 154, p.236.[55]

The speed, therefore, at which Kluyver engaged with the research and development of penicillin is plain to see. By 29 April 1946, almost exactly a year from the end of the war, Kluyver could write to Jackson Foster in Austin, Texas, that, thanks to the generosity of his many friends 'our thirst for literature has been largely quenched'.[56] In July 1946 he wrote to C.E. Clifton of Stanford University, California, that the Dutch recovery had been very time consuming and that much time and energy had been devoted to trying to restore former conditions. He thanked all of his

[53] KA Catalogue 1990090, Folder 2, Letters M-Z, Kluyver to MRC, January to June 1946.
[54] KA Catalogue 1990090, Folder 2, Letters M-Z, Kluyver to J St. John Brooks, January to August 1946.
[55] KA Catalogue 1990090, Folder 2, Letters M-Z, J St. John Brooks to Kluyver, January to August 1946.
[56] KA, Catalogue 1990085, Folder 2, Letters D-H, Kluyver to JW Foster, 29 April 1946.

American friends for their contribution to that recovery process and added that they were 'finally in the position of knowing what we should know'.[57]

That Kluyver shared this knowledge with those at NG&SF is also plain to see. In a letter dated 16 February 1946 NG&SF Library Department returned to Kluyver 'at the request of K. Scheurkogel the publications on Penicillin and related substances'. They added that the publication by J.W. Foster and H.B. Woodruff, 'Microbiological Aspects of Penicillin: VI. Procedures for the Cup Assay for Penicillin' contained in the *Journal of Bacteriology*, 47, 43 (1944) is not included, but that it would be returned 'as soon as possible'. NG&SF library also asked if they could borrow 'a number of these publications again' and included a list of other publications they would like to borrow from him. This list included publications by Waksman, Foster, Woodruff, Raper of NRRL, and, the Commercial Solvent Corporation's company booklet on the development of penicillin.[58] All had played prominent roles in the research and development of American penicillin, and, as we have seen, all sent reprints and publications directly to Kluyver shortly after the war ended.

From the time of liberation, therefore, Kluyver can be seen to continue to play an important role in the development of penicillin with those at the Nederlandsche Gist- en Spiritusfabriek. This is all the more remarkable as pre-war, as evinced by his publications, Kluyver was interested in all aspects of bacteriology with the exception of medical microbiology. His post-war interest in penicillin, therefore, could only have stemmed from the work that had taken place at NG&SF during the war years.

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[57] KA, Catalogue 1990085, Folder 1, Letters A-C, Kluyver to CE Clifton, 14 January 1946.
[58] KA, Catalogue 1990085, Folder 2, Letters D-H, NG&SF to Kluyver, 16 February 1946.

Querido – NG&SF

Like Kluyver, Querido worked hard on behalf of NG&SF at the end of the war. As nutrition expert at Leiden his task was to explore the advances in vitamin production that had been made during the war. In order to do so he had been invited to visit London by J.C. Drummond, the then British Minister for Food. Querido had had contact in pre-war days with Drummond when he (Drummond) had been Professor of Biochemistry of University College London.[59] Indeed, Drummond was one of the first foreign scientists to visit the Netherlands at the end of the war. After liberation, his 'food teams' swung immediately into action in the Netherlands, saving many of the seriously under-nourished *hongerwinter* victims.[60]

Taking advantage of Querido's invitation, F.G. Waller asked him to buy research literature for NG&SF. He also asked him to find out the price and availability of chemicals NG&SF needed but which, at the end of the war, were not available in the Netherlands. On 4 September 1945, Waller wrote to Querido, in note form, of a discussion they had had the previous day. In it he introduced Querido to NG&SF's London agent, Mr Paton, whom he had asked to help Querido:

> in the buying of scientific books which could be of importance to our company and which we will finance ... We have a limit of £70 and we leave the choice of books to you.[61]

Before the war, NG&SF had had subscriptions to a number of scientific journals. However, from 1940 they had not been able to renew their subscriptions. Waller thought that is was possible that all of the 1940 publications would have been kept for them, but he did not think that this would be the case for scientific journals published between 1941-1945. He asked Querido, therefore, to

[59] A. Querido, *Andries Querido*, p.98.
[60] KA, Catalogue 1990049, Folder 1, Letters A-K, Kluyver to KR Butlin, 27 August 1952.
[61] GB:CA, F.G. Waller Jnr. Archive, Correspondence Waller – A. Querido, 4 September 1945.

check antiquarian shops for back copies. From 1945 NG&SF would revert to arranging subscriptions via Mr Paton.

The list given to Querido included: *Biochemical Journal; Industrial Chemist; Journal of Chemical Society; Chemical Abstracts; Journal of the Institute of Brewing; Nature;* and, *Nutrition Abstracts.* Waller also said that he 'would very much appreciate it if' he could obtain copies of the list of articles that had been made by Dr. Spiers 'as soon as possible'.[62] Should the purchased literature be too big for Querido to bring back, Mr Paton had agreed to post it on.

Part of Waller's list dealt specifically with 'Penicillin'. Here, Waller asked Querido to obtain a strain of the original *Penicillium notatum* and a growth culture of the original *Staphylococcus aureus* that Fleming had 'used'. In fact he wanted everything Querido could find out about the testing of penicillin 'especially the way it can be determined whether or not a particular preparation contains pyrogens' and information on the 'ammonium salt of penicillin'.[63]

The list continued by requesting information on the recent developments in chemical and bioantiseptics; vitamin B complex; flour with added vitamins for bread making; and, food taste enhancers, in particular Marmite. Waller closed by saying that he hoped the list was not too long and that 'there is certainly plenty to fill your time'.[64]

On 30 October 1945 Querido replied to Waller and gave a short report on his activities in England. He said that he had found it difficult to get the requested literature as nothing had been saved for continental subscriptions. By working through the book trade he had managed to get

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[62] GB:CA, F.G. Waller Jnr. Archive, Correspondence Waller – A. Querido, 4 September 1945.
[63] GB:CA, F.G. Waller Jnr. Archive, Correspondence Waller – A. Querido, 4 September 1945.
[64] GB:CA, F.G. Waller Jnr. Archive, Correspondence Waller – A. Querido, 4 September 1945.

back copies of *Nutritional Abstracts and Reviews* and some of the *Journal of the Chemical Society*. These were underway. He had also managed to get some *Biochemical Journal*, but not a complete set, and a very few copies of *Nature*. He had placed a subscription for *Nature*, which would run until 30 September 1946. He also listed the books he had bought and sent an itemized bill for £19.16.6d. Copies of the articles asked for by Dr Spiers he had already given to Waller by hand.[65] Querido's report reflects what must have been the frustration of occupied territories at the end of the war. Counter to their attempt to reintegrate into the area of research and development, nothing had been saved for continental subscriptions. Consequently, literature was difficult to obtain.

However, on the task of 'Penicillin' Querido stated:

> I received the original surface and submerged strains of *Penicillium notatum* from Prof. Raistrick and have given them by hand to Prof. Kluyver. The staphylococcus strain for analysis has also been given to you.
> The information about comparisons for penicillin as carried out by the National Institute for Medical Research I have given to you in the form of a, not yet published, manuscript and a letter.
> The test for toxicity and pyrogenicity I have already given to you. I have a copy of the British penicillin standard in my refrigerator in Leiden.
> I did not hear anything about the ammonium salt of penicillin. I have written a letter to you about the structure of penicillin.[66]

He also stated that 'Wooley, Sure, McCay, Elvenhem and McHenry of the Rockefeller Institute' would send of copies of all their publications from 1940 to 1945 as would Merck. From this he deduced that 'we will have the most recent information on vitamin-B complex and any new antibiotics'.[67]

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[65] GB:CA, F.G. Waller Jnr. Archive, Correspondence A. Querido – Waller, 30 October 1945.
[66] GB:CA, F.G. Waller Jnr. Archive, Correspondence A. Querido – Waller, 30 October 1945.
[67] GB:CA, F.G. Waller Jnr. Archive, Correspondence A. Querido – Waller, 30 October 1945.

On 13 September 1945, Randolph T. Major, Director of Merck & Co., sent publications which had been produced in the Merck Research Laboratories during the years 1940-1945'.[68] Also, on 14 September 1945, D.W. Wooley of the Rockefeller Institute for Medical Research wrote to Waller that he was pleased to send reprints of Rockefeller publications since 1940, which were available. He ended, 'I trust they reach you in good time'.[69] Like Kluyver, therefore, Querido's advisorship to NG&SF proved invaluable in accessing information on penicillin in the early post-war years.

Catch-up: Nederlandsche Gist- en Spiritusfabriek.

At the end of the war, the interest of NG&SF in the development of penicillin is plain. This is clear from information retrieved from both of their advisors, Querido and Kluyver. However, although willing to continue with the research and development of penicillin, the number of obstacles to be overcome must have been daunting. As stated previously, as early as November 1945, discussion between van Leeuwen of NG&SF and Tausk of Organon had ventured into the possibility of a joint venture in the development of Dutch penicillin. By April 1946 these negotiations had fallen by the wayside. Nonetheless, the NG&SF archives show that the end of the war brought an active desire to catch-up, in both the academic and commercial sense, with research on penicillin that had taken place during the war.

From his European tour of June 1946, Selman A. Waksman visited Amsterdam following his attendance at the first French-speaking Biochemical Conference since the outbreak of the war. He and his wife had arrived in Amsterdam by train late in the afternoon and had had a visit that evening from 'our old friend Professor Kluyver accompanied by his wife, and by Dr. (sic) and Mrs. Waller of the alcohol distillery of Delft'. Waller, Waksman said, was 'interested in the

[68] GB:CA, F.G. Waller Jnr. Archive, Correspondence R.T. Major – Waller, 13 September 1945.
[69] GB:CA, F.G. Waller Jnr. Archive, Correspondence D.W. Wooley – Waller, 14 September 1945.

manufacture of antibiotics'. Waksman recounted that he had not seen Kluyver since they parted at the Microbiological Conference in New York seven years earlier. He listened to the hardships experienced by the Netherlands during the German occupation, which he found 'very depressing'. Waksman asked Kluyver to come to the United States to learn what had been done in the field of microbiology during the war years but Kluyver had answered: 'Perhaps later, when I will be able not only to take but have something to give in return'. Together Waksman, Kluyver and Waller talked 'until far into the night ... about antibiotics, microbiology, and the problems of the world at large'.[70]

More evidence of the way the very practical way Waller used Kluyver's network is shown in a series of letters starting 18 January 1946 when Kluyver corresponded with W.H. Peterson of the College of Agriculture, University of Wisconsin. During the war Peterson had been involved with the analysis of American penicillin. At the end of the war he had sent Kluyver reprints of his work. On 8 November 1946 Kluyver wrote:

> My former colleague Dr. J.C. Hoogerheide, who has been visiting me, and by now has returned to the US has taken with him some samples of the Penicillin produced by the Nederlandsche Gist- en Spiritusfabriek here in Delft. He told me that he would show you these samples and that possibly you might be willing to have them analysed on their penicillin contents. If you could give some attention to this point we should be very much obliged to you. We are hopeful that in these preparations Penicillin G will prevail.[71]

On 3 December 1946 Peterson replied to Kluyver that he has received the samples of NG&SF penicillin from Hoogerheide. He was happy to announce that there were high values for Penicillin G. He also said that he would send the abridged details of the microbiological methods used.[72] A delighted Kluyver replied to Peterson on 4 February 1947 thanking him. The results, he said,

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[70] S.A. Waksman, *My Life*, pp.237-238.
[71] KA, Catalogue 1990090, Folder 2, Letters M-Z, Kluyver to WH Peterson, 8 November 1946.
[72] KA, Catalogue 1990090, Folder 2, Letters M-Z, WH Peterson to Kluyver, 3 December 1946.

'were very satisfactory and the producers of this first Dutch preparation are very happy to have a confirmation from an authoritative source that their product was practically all Penicillin G'.[73]

It should also be noted that, in this series of correspondence written documentation exists of the microbiological method used by Peterson. Added to that, he sent a sample of his test organism to Kluyver. This would certainly have been passed from Kluyver to NG&SF, who would then be in a position to analyse their material using one of the most up-to-date, academically sound, American methodologies.

Again, Kluyver's willingness to help Waller is shown to even greater advantage when in November 1946 he met Sir Alexander Fleming in Paris. Both had attended the Paris Congress of the 50th Anniversary of the death of Louis Pasteur. Although there is no archival evidence that this was at Waller's request, Kluyver must have asked Fleming if he would analyse samples of the NG&SF material. In a letter of 24 December 1946, Fleming wrote to Kluyver that he had sent the sample of penicillin that Kluyver had given him in Paris to the Glaxo Laboratories for analysis 'as I told you I would'. Fleming was now passing on the results. According to Glaxo, both chemical and microbiological analysis had shown that the average total content of the penicillin sample was '136,000 international units'. Fleming further stated that, 'this penicillin is at least as good as most penicillin either here or in America, and from the last figure it looks as though you give a very generous measure with 136,000 as opposed to (the average) 100,000'.[74]

On 2 January 1947 Kluyver replied that he seemed indeed to have given Fleming a very generous bottle. He had just heard from NG&SF that an assay of a number of vials made by Dr. H. Welsh of the Food and Drug Administration at Washington DC, showed the average content per vial was

[73] KA, Catalogue 1990136, Folder 3, Letters M-P, Kluyver to WH Peterson, 4 February 1947.
[74] KA, Catalogue 1990091, Folder 2, Letters D-H, A Fleming to Kluyver, 24 December 1946.

101,500 international units. Kluyver added that Glaxo Laboratories had used a chemical assay with which he was not familiar. He asked Fleming if he would mediate for him and, provided there were no industrial secrets involved, would he prevail upon the Glaxo Laboratories to send him (Kluyver) the methodology. On 13 January 1947, Glaxo sent their methodology. On 17 January 1947 Kluyver thanked Fleming for acting on his behalf.[75] There being no industrial secrets, he would have shared this with Waller.

Conclusion.

At the end of the war Kluyver's letters serve to illustrate the academic bareness of scientific life under occupation. They also illustrate the difficulties of trying to re-establish some kind of normality after five years of occupation. Kluyver poignantly describes these five years as 'desolation' and 'slavery' during which his country was 'looted'. The backlog was enormous. Not only had they to recover from the 'well organized famine' of food and the plundering of raw materials, they also had to recover from a famine of information. There was, however, no money. As the RIV archive has shown, no immediate government funding was forthcoming. Nevertheless, there was a desire to proceed, to catch-up.

At a time when the Dutch administration floundered in obtaining up-to-date information, it was the unofficial channels of friends and colleagues who were faster in filling the gaps of academic publications. The archive communications of Kluyver illustrate that, at the end of the war, his contacts provided what was literally an avalanche of information about penicillin. This came mainly from the United States, not only from academic researchers, but also from commercial producers, like Merck. It was, too, his British contacts that enabled new information on *Penicillium* to reach Delft.

[75] KA, Catalogue 1990091, Folder 2, Letters D-H, Kluyver to A Fleming, 17 January 1947.

Querido's invitation to visit London provided Waller the opportunity to access British sources. While subscriptions had not been held open for continental orders during the war, Querido's visit enabled Waller to re-establish his British contacts. It also enabled new *Penicillium* strains to be brought to Delft, through contact with Raistrick.

There can be no doubt that, at the end of the war, Waller benefited enormously from the influence of his advisors, Kluyver and Querido. In particular, Kluyver's network fed Waller's need for reliable information on penicillin development and the most up-to-date production methods, through experts such as Peterson and Fleming. Such information would have been pivotal in Waller's decision to further develop NG&SF penicillin.

Chapter 7

The Road to Mass Production, 1945-1946.

In the development of penicillin in America, J.C. Hoogerheide states that by 1944 the major problems of production were solved and 'the battle was won'.[1] However, in order get to that point commercial decisions had had to be made regarding the expansion of production facilities and investment in larger fermenters. These expansions required huge investment with the added risk that penicillin might be synthesized chemically, which would make the expensive fermentation equipment obsolete. In America most pharmaceutical companies, such as Squibb, Pfizer, Abbott, Lilly and Upjohn, took the risk. Merck, on the advice of its chemical staff, did not. They opted for the expected economical synthetic process. For Britain, Hobby states that, it was November 1945 before large-scale production units had been completed or were under construction at Allen & Hanbury, Boots Pure Drug Company, Distillers Company, Glaxo Laboratories, Imperial Chemical Industries (ICI), Kemball Bishop Ltd., the Royal Navy Medical School and the Wellcome Foundation.[2] However, like Merck, ICI were later to cease the production of penicillin by fermentation procedures and both lost a vital market.

In the Netherlands, only six months after liberation, *De Fabrieksbode*, presented the wider circle of NG&SF employees with the concept of 'penicillin'. On 3 November 1945 it printed an article, which asked 'Wat is Penicilline?' (What is Penicillin?). It contained information on Fleming's original research and introduced Florey's initial interest with penicillin in 1938.[3] This article was continued in the *Fabrieksbode* of 24 November 1945. The second publication covered the work of the Oxford Team; of American involvement; of the wartime success in the development of

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[1] J.C. Hoogerheide,'The Penicillin Legend Remembered', *La Chimica e l'industria*, 62, 5, (1980), pp.440-445.
[2] G. Hobby, *Penicillin*, p.139.
[3] *De Fabrieksbode*, 3 November 1945, pages not numbered.

penicillin; of the illnesses penicillin could cure; and, of the method of injection. However, the *Fabrieksbode* also made it clear that the demand for penicillin remained high and more research had to be done in the search for a purer, easier to administer product.[4] The source of this information was given as '*Kijk*', a newspaper printed by the *Amerikaanschen Voorlichtingsdienst* (American Information Service).[5]

However, barely nine months later, 10 August 1946, the banner of the *Fabrieksbode* heralded 'Penicilline ons nieuwe product' (Penicillin Our New Product). This article began with comment on wartime as a time of loss of life, but also a time of great steps forward for mankind. It described how the wartime development of radar technology 'now' helped air and sea vessels to 'see' in fog and offered even more possibilities in the future; how the atom bomb had opened visions for more sources of energy, which would end dependence on coal resources; and, the development of penicillin, an exceptional medicine which appealed 'directly to our human instincts'.[6]

In order to explain more about NG&SF's new product, F.G. Waller had been asked by the *Fabrieksbode* to describe for the workforce the history of penicillin; how he had first heard of the success of penicillin during the war; and, how NG&SF came to be involved in its production. Recounting the story of Fleming, Florey and the research carried out during the war years by the Allies, Waller went on to relay the now familiar steps in the development of penicillin at Delft - that he had first heard about penicillin during the occupation via clandestine radio and some journal articles. As the area of research with sterile cultures was well known to NG&SF, in

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[4] *De Fabrieksbode*, 24 November 1945, pages not numbered.
[5] '*Kijk*' was published as a temporary newspaper until the Dutch press was allowed to return on the basis that their wartime activities had been screened and no misdemeanour had been found. It ran two articles which included penicillin. The first was No 16 'De vorderingen der geneeskunde' (Advances in medicine) and No. 24, 'Wat is Penicilline?' (What is Penicillin?), no date of publication is given. Source: NIOD.
[6] *De Fabrieksbode*, 32, 10 August 1946, pages not numbered, Front Page.

January 1944 'they' decided to start their own investigations. By September 1944 'we' had a product, although impure. However, the severe conditions of the hunger winter limited research. In May 1945 a sample of American penicillin was received which stimulated and reactivated research at Delft. In October 1945 NG&SF had both a purer product and enough penicillin stock to perform the first 'clinical trial'. It was successful. It was at this point the decision was made to take Delft's penicillin from the laboratory to 'Factory Scale'. [7]

To scale-up production many technical problems had to be solved but according to Waller, 'we were stimulated by American publications which confirmed for us that the way we had proceeded and were proceeding was correct'. As one success was achieved more successes followed and more experience gained in factory scale production. 'This month', August 1946, he reported, 'our product has come onto the market. It is as good as the American product. It will be delivered to patients through the State Department for Medicines'. He ended with the observation that this event 'is of importance for the whole of the Dutch population'. Penicillin was now made at a Dutch factory and sold under the label of a Dutch company, NG&SF. This achievement, he noted, was the result of 'academic research, technical knowledge and managerial initiative'. But he also noted that it was the work of a 'very small groups of chemists and engineers of whom the Gistfabriek is very proud'.[8]

In this article Waller stated that the first clinical trial was done in October 1945. This timing differs chronologically from the earlier statement in this thesis, which coupled the first clinical application of NG&SF penicillin to two temperature charts.[9] These charts are of the two patients who received Bacinol intravenously in Delft Bethel Hospital in November 1945. It could be,

[7] *De Fabrieksbode*, 10 August 1946.
[8] *De Fabrieksbode*, 10 August 1946.
[9] Appendix 3.

however, that Waller was in fact referring to the previously mentioned *in vivo* animal tests done by Rombouts.[10]

Waller's report was published in the *Fabrieksbode* of August 1946. This was just over a year from the end of the war. To get to this point, however, NG&SF management had taken decisions which they knew would alter the course of their Company. The move was from a yeast fermentation base to a pharmaceutical one.

According to Elema, a positive motivating factor in this shift from yeast to pharmaceutical had been that, because of the drastic condition of the Dutch economy, the Government more than welcomed the Dutch production of this important new medicine. On the negative side was the fact that in the United States and Britain so much was already known about penicillin, not only in the areas of microbiology, biochemistry and chemical research, but also in its large-scale production.[11] Elema's observations, therefore, highlight an obvious question. How, at a time of post-war economic crisis, could NG&SF consider investing in the development and production of penicillin by fermentation?

As the RIV archive has shown, the State was loath to give financial help to commercial companies, preferring to supervise the production of penicillin. The van Leeuwen archive has illustrated that NG&SF was loath to accept State involvement or joint ventures. NG&SF preferred to remain an independent commercial company. Perhaps the drive for NG&SF to produce penicillin came from purely commercial reasons, to make a profit from a much-wanted drug. As has been shown, van Leeuwen considered penicillin to be a 'self-promoting product'.[12] A

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[10] This thesis, Chapter 4, p.136.
[11] B.Elema, *Opkomst*, p.39.
[12] This thesis, Chapter 5, p.166.

commercial market already existed. On the other hand, Waller's article highlighted the pressing need in the Dutch national health sector. Perhaps the spur to develop NG&SF penicillin was their desire to make the medicine that spoke 'directly to our human instincts'.[13] Perhaps it was a mix of the two.

Gerard Mensinga, one of the first involved in the large-scale production of penicillin at NG&SF, recalled that 'they' had no idea of the profitability of penicillin. He maintains that 'their interest was purely scientific'. This, he said, was typical of NG&SF. They were an 'engineers' company, they enjoyed the challenge. However, he added that Mr Diamant, who was responsible for the financial side of the company, had the motto: 'Produce what you can sell'. Reflecting the theses of Blom and Lagrou and the national wish to move 'forward', Mensinga endorsed the feeling at NG&SF at the end of the war as one of wanting to move on. Everyone, he said, wanted to do his or her best for the reconstruction of the Netherlands. As a company, NG&SF wanted to stand-alone. They wanted to do it themselves.[14] Nonetheless, what is clear from the British and American experience, financing such an investment needed money.

NG&SF: Financial position at the end of the war.

The Annual Report for 1945 offers a unique insight to the financial position of NG&SF at the end of the war. The Report opened with a mark of respect for those employees who died during the war. It was pleased to report, however, that the majority of the younger workers who had been taken as modern *'slavenarbeid'* (slave workers) to Germany had arrived back in Delft shortly after liberation, safe and well. Also, both the Delft and Bruges factories had been spared war damage.[15]

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[13] This thesis, this Chapter, p.200.
[14] Personal Communication. G. Mensinga 22 April 2005.
[15] GB:R&D, NG&SF Annual Report 1945, pages not numbered.

It continued that during the war the company had managed to stay working although the last six months had been difficult. This was partly due to the scarcity of materials, and partly because it was difficult to keep machinery going that was so run down it was constantly in need of repair. Also, NG&SF personnel had consciously continued to work in the face of propaganda organisations like the *Arbeidsfront*[16] (Labour Front) and the lowering of morale that accompanied never-ending shortages. Nonetheless, NG&SF had continued to meet the yeast requirements of both the Netherlands and Belgium. The company was also pleased to report that they had been able add a little to the food rations allowance of their employees.[17]

The Report describes the wartime products Gistex and Aromex as supplements for the break in meat and fats available to the population. This had led to the Gist becoming an important supplier of protein rich substitutes. The chemical department continued to work with butanol and acetone products for the paint industry. It also worked with the *Rijksbureaus*, in an attempt to solve national shortages. These varied activities had required great input from the research, technical and commercial staff but compensated a good deal for the fall in work from the main, yeast and alcohol, sources of income. The result was that NG&SF had come through the war years in a fairly stable financial position.[18]

In looking at the financial situation for 1945, the Report illustrates that until June 1945 Delft had recorded a significant loss. However, a financial upturn was expected as since liberation the increase in bread ration portions meant that the demand for yeast was steadily increasing. Moreover, from 1 October 1945 spirit production had resumed its pre-war value. [19]

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[16] Consistent with Nazi policy the *Arbeidsfront* was an attempt to integrate all workers unions into one.
[17] GB:R&D, NG&SF Annual Report 1945, pages not numbered.
[18] GB:R&D, NG&SF Annual Report 1945.
[19] GB:R&D, NG&SF Annual Report 1945.

Addressing the exploitation costs of the Delft factory directly, the Report went on to say that a sum of Fl.600,000 had been added to the *Reserve voor Vernieuwing* (Renovation Reserve). This made a total reserve of Fl. 2,400,000. It was expected that in future years more would have to be set aside for plant repair and renewal in order to compensate for the five year wartime backlog when little, if anything, had been done. Such investment was necessary in order to keep scientific knowledge and technical expertise at the desired standard. A new *hoogedruk-ketelhuis* (high pressure boiler-house), which was badly needed at the Delft factory, had been commissioned.

The 1945 Annual Report shows a steady return to work and reflected that the company was financially secure, although share profits were substantially lower than their pre-war levels. The shareholders profit was 6% for *prioriteits-aandeelen* (priority shares) and 5% for *gewoon aandeelen* (ordinary shares).[20] Nonetheless, for a country facing severe economic challenges both the steady return to work for NG&SF personnel, coupled with a shareholders profit, illustrate what must have been seen as a positive economic future.

The economic recovery of NG&SF continued in 1946. The Annual Report shows that the dividends for both priority and ordinary shares were set at 6%. Further, that their dry yeast product, Engedura, was once again the Dutch market leader and also in demand abroad. Additionally, in order to satisfy the post-war needs of the building and paint industries, the solvents section was working to full capacity. Here, too, there was increasing international demand. As a result, production for the export market was in the process of being expanded. Following an increase in ration allowance, better results had been recorded in the distillery section, and a return to export for this product looked realistic.[21]

[20] GB:R&D, NG&SF Annual Report 1945.
[21] GB:R&D, NG&SF Annual Report 1946, pages not numbered.

In the development of penicillin, the 1946 Directors Report shows that NG&SF brought a limited amount of penicillin onto the market in the second half of that year. It gave a résumé of research with penicillin since 1944, and pointed to the possibility of producing 'this antibiotic medicine'. It stated that the last months of the war had slowed NG&SF's penicillin research, however, immediately after the war ended research had been resumed and a factory production method for penicillin had been successfully created. 'Shortly', it stated, 'a new Department will be initiated in order to supply Dutch penicillin needs'. From the success of 'our laboratory research' and following the building of 'our own factory methodology' NG&SF could, 'without the help of foreign currency investment for the leasing of foreign procedures', bring Dutch penicillin, which was 'fully medically approved', onto the market. The Report further stated that in spite of shortages of materials, which were seriously holding back research, it was the NG&SF's intention to continue in this area.[22]

The continuation of research with NG&SF penicillin.

The extent of ongoing research with penicillin at NG&SF can be gleaned from a report of Rombouts dated 4 July 1946. It was sent only to F.G. Waller. This report illustrates both the diversity of the research and what had been achieved between September 1945 and April 1946 in the development of NG&SF penicillin. Taking part in these experiments with Rombouts were Klokgieters, Stheeman and, from October 1945, W. Berends. According to Rombouts much time had been spent on determining the strength of penicillin solutions that came from NG&SF samples. On the topic of standardisation, his report showed that as early as November 1945 the Delft Unit was compared to the Oxford Unit using the official British Standard Tables that Querido had brought back from England. He also referred to 'Clinical Trials' that had taken place

[22] GB:R&D, NG&SF Annual Report 1946.

on 3 October 1945 and concluded that the success of these experiments indicated that further 'Clinical Studies' could be undertaken.[23]

At this point it can be noted that Rombouts report verifies Waller's statement, which placed NG&SF first clinical trials in October 1945. While in contemporary terminology clinical trials refer to tests in humans, in Rombouts terminology 'Clinical Trials' could have been the injection of NG&SF penicillin into animals, namely rabbits. In modern terminology they would probably be considered as pyrogenicity tests in animals.[24]

According to Rombouts pyrogen testing had been conducted according to English recommendations since the end of March 1946, but from May 1946 his pyrogenicity testing complied with the new American guidelines. From January 1946, as well as pyrogenicity control, NG&SF penicillin was tested for toxicity. Each test used five mice weighing 20g and each mouse was injected intravenously with 1,000 Oxford Units dissolved in ½ ml distilled water. From the beginning of June 1946 this dose was increased to 4,000 Oxford Units, which brought this testing in line with the American guidelines.

Testing NG&SF penicillin for stability was also quickly established. The first stability studies were started in November 1945. These studies gradually increased the temperature at which NG&SF penicillin was kept in order to control melting and discolouration. Rombouts noted that even the discoloured product produced no pyrogenicity.[25] In essence, in this Report, Rombouts laid out what became the standard product controls for NG&SF penicillin.

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[23] GB:CA, NG&SF Report No. 1024, J.E. Rombouts, Vacantie-rapport 1946, 4 July 1946.
[24] GB:CA, NG&SF Report No. 1024, 4 July 1946.
[25] GB:CA, NG&SF Report No. 1024, 4 July 1946.

Increasing penicillin production.

In discussing the scaling up of NG&SF penicillin production, Elema points to the fact that, at the end of the war, the production of penicillin meant that more academic and technical staff were urgently required. For example, as reported in the 1946 Annual Report, Elema points to the new *Afdeling Antibiotica* (Antibiotics Department) established in January 1946, led by Scheurkogel.[26] Scheurkogel had specialised in technical microbiology under Kluyver at the TH in 1929. He first worked for the Gist in 1934 but went on to NV Verenigde Industrie Rotterdam where, by 1942, he was Deputy Director. He returned to NG&SF as Coordinator of Penicillin Production. His task was to set up the penicillin sector of the company.[27]

In his article in the *Chemische Weekblad*,[28] Scheurkogel confirmed that the early development of NG&SF penicillin started with 'surface' cultures in milk bottles that had been sterilized. However, he reported that this was cumbersome and time consuming. Moreover, new technical information was being published and large differences in work methods could be seen. According to Scheurkogel:

> It goes without saying that in a fermentation plant, where workers are used to biological processes taking place in large tanks, that the submerged culture production would be preferred by those in Delft. They quickly sought new working processes with their own tried and tested fermentation techniques in large scale submerged production.[29]

Perhaps surprisingly to those at NG&SF, some of the contemporary publications on work methods in the production of penicillin referred back to a pre-war publication of their mentor and

[26] B.Elema, *Opkomst*, p.40.
[27] *De Fabrieksbode*, 8 January 1971.
[28] K. Scheurkogel, 'Technische bereiding', pp.69-72.
[29] K. Scheurkogel, 'Technische bereiding', pp.69-72.

advisor, Kluyver. In these studies he had made use of a vessel that became known as Kluyver's *kolfje* or flask (Appendix 4a).[30]

According to Hoogerheide, Kluyver's studies had not been intended to develop a technical process for deep culture production, but when the pressure was on to produce more and more penicillin then the studies from Kluyver's laboratory unmistakably pointed the way to the possible development of a deep culture technique. At NRRL an extensive screening programme had been set up to find strains that would produce penicillin when grown submerged based on Kluyver's flask;[31] Waksman used Kluyver's submerged technique of agitation and aeration,[32] as did Foster at Merck.[33] At NG&SF, a critical role in the success of Delft's penicillin began when Struyk took the decision to stop growing penicillin moulds in open culture and to start growing it like yeast, in deep vats.[34] Accordingly, Factory Foreman, Verkennis, was asked to free some of the metal tanks normally used for in-depth yeast culturing at the factory pilot plant, F3, for work with penicillin.[35]

Struyk's Research Report, of 10 August 1946, 'Bereiding van Bacinol – Orienteerende proeven met submerged cultures' (Preparation of Bacinol – Exploratory tests with submerged cultures), started by explaining the reason for the report as:

> Although shaken cultures from *Erlanmeyers* (conical flasks) produce good results it appears to us that we could increase production of Bacinol by using submerged cultures. Added to that, this would fit better in our factory procedures.[36]

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[30] Source: KA; Personal Communication L. Robertson, December 2003.
[31] J.C. Hoogerheide, 'The Penicillin Legend', pp.440-445.
[32] W.R. Strohl, *et al*, 'The History of Natural Products Research at Merck & Co., Inc.', *ASM*, 51, 1, (January/February 2001), pp.5-19.
[33] J.W. Foster, H.B. Woodruff and L.E. McDaniel, 'Microbiological Aspects of Penicillin. IV Production of Penicillin in Submerged Cultures of Penicillium', *Journal of Bacteriology*, 51, (4 April 1946), p.465.
[34] *De Fabrieksbode*, 29 September, 1978, p.87.
[35] *De Fabrieksbode*, 29 September, 1978, p.87.
[36] GB:CA, NG&SF Report 419, A.P. Struyk, 'Bereiding van bacinol – orienteerende proeven met submerged cultures', 10 August 1946.

For the exploratory tests, 'appropriate apparatus' had to be found. Initially, the same growth medium as for the shaken culture was used. However, Struyk intended that some variations would be made in the growth medium and any effect monitored. Also, variations to the amount of air in the tank would be introduced. In addition to P6, *Penicillium baculatum* Westling, other cultures of other moulds would be included in the tests.[37]

On the point of 'appropriate apparatus' surprisingly Struyk chose not to use Kluyver's *kolfje*. Instead, he used a *B-buizen* or B-flasks. In explaining this decision Struyk reported that Kluyver's *aeratiekolven* (aeration flask) had been considered to see if it 'was appropriate for our task'. However, this turned out not to be the case. His reason for this was that the mycelia bound to the porous bottom and after 2 to 3 days the air supply was blocked. He then turned to the *B-buizen* that NG&SF used in *proefgistingen* (test fermentations). These were made of glass and had a 'pointed base', which meant that the mycelia could not bind to the base. Struyk provided a schematic figure of the B-flask beside his written description. (Appendix 4b).

Struyk continued his report with a list of the cultures used and the growth medium. The cultures he numbered and listed as:

P6 *Penicillium baculatum* Westling
P11 *Penicillium griseo-roseum* Dierks (received from SOMER)
P28 *Penicillium notatum*, culture 1249 (received from SOMER)
P33 *Penicillium notatum*, culture Fleming (received from THAYSEN)
P34 *Penicillium notatum*, culture 332 (received from THAYSEN)
P35 *Penicillium chrysogenum* (received from THAYSEN)

Why Struyk capitalised his source names has to do with the writing style of the time, but when we look at these sources and we can again see the influence of Kluyver in NG&SF's research.

[37] GB:CA, NG&SF Report 419, 10 August 1946.

Thaysen was a British contact of Kluyver. In 1945, Thaysen had passed *Penicillium* cultures to Kluyver.[38]

Struyk continued his report with a description of the medium used, the temperature, time, and resulting suspension. However, at this point, 10 August 1946, Struyk indicated that he was still using his own Delft Units to determine his results and pointed the reader to the previous research report of '12 November 1945' in which he had charted the difference between Delft Units and Oxford Unit.[39] The results of his tests he described as very moderate but concluded that:

> The testing of Bacinol production in submerged culture. ... using B-buizen . ... has given results which were well worth the effort. It is certainly worthwhile taking this research further.[40]

The recipients of this report were F.G. Waller and K. Scheurkogel.

The following day, in Report 420, Struyk, with the assistance of W. Soudijn and L.P. Lagendijk, informed Waller and Scheurkogel that, using the '*B-buizen*' as their aeration container, 'a good mould culture and very highly improved quantities of penicillin' had been produced.[41] Using an existing NG&SF fermentation technique, therefore, Struyk had developed a submerged culture fermentation technique that 'highly improved' the production of their own penicillin.

Struyk's research then expanded into finding additives for an improved medium for the new fermentation technique. Again, the use made of the scientific reprints sent at the end of the war is aptly illustrated at the start of Struyk's report. His background literature is listed as:

1. Nature, 156, p766, 1945. Chemistry of Penicillin.
2. K.B. Raper, D.F. Alexander and R.D. Coghill, J. Bact., 48, p639, 1944.

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[38] This thesis, Chapter 6, p.179.
[39] Contained in R&D Report 1024, J.E. Rombouts 4 July 1946.
[40] GB:CA, NG&SF Report 419, 10 August 1946.
[41] GB:CA, NG&SF Report 420, A.P. Struyk, 'Bereiding van bacinol – proeven met submerged cultures', 11 August 1946

The publication 'Chemistry of Penicillin' contained a summary of the research resulting from the teamwork of seventeen British and twenty-one American Government institutes and commercial companies.[42] Also, following the research of Raper, Alexander and Coghill at NRRL, Struyk chose to experiment with the medium 'Corn-steep Liquor', a by-product of the maize industry. At the time, corn-steep 'exactly the same' as the American version was available in the Netherlands. It could be found at Honigs Maizena Fabriek in Koog aan de Zaan. Kluyver had ordered some, on 26 February 1946, ostensibly for the TH.[43]

As well as corn-steep, for further comparison Struyk added lactose preparations from Schering, Brocades, the North Holland Sugar Factory and the North Holland Milk and Sugar Factory. However, the individualism of Struyk's research can be further seen from the fact that he also used one of NG&SF's own growth mediums. It was the '*graanbeslag van F2*', the grain base normally used in plant F2.

Struyk continued Report 420 by listing the mould cultures he used for comparison with NG&SF P6 *Penicillium baculatum*. These were:

> *Penicillium notatum* (received from QUERIDO)
> *Penicillium chrysogenum* NRRL 2000 (also known as X1612).

These *Penicillium* strains once again reflect the influence of NG&SF advisors. As has been shown, in October 1945 Querido had gone to London. On Waller's behalf, he had bought a series of publications and had received strains of *Penicillium notatum* cultures from Raistrick. These he had brought back and, as arranged, given to Kluyver and Struyk.[44] Also, at the end of the war,

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[42] B. Elema, *Opkomst*, p.41.
[43] KA, Catalogue 1990092, Folder 2, Letters A-D, V van den Olden to Honigs Maizena Fabriek, 26 February 1946.
[44] KA, Catalogue 1990089, Folder 1, Letters A-R, AJ Querido to Kluyver, 31 October1945.

Thaysen had sent Kluyver the 'latest ... from the US growing under submerged conditions'.[45] By 1946, Westerdijk at the CBS, [46] had received strains, not only from the National Type Culture Collection in England, but also from Raper at NRRL.[47] Clearly all three advisors continued to add to the in-depth research in progress with penicillin at Delft.

Struyk's confidence and diligence in this very new field of research is illustrated in his Report 420 of 11 August 1946. It is a twenty-two-page document, which contains six pages of tables. Yet, from his experimentation with the new British and American *Penicillium* strains Struyk concluded that there was no reason to give *Penicillium notatum* (culture 832) or *Penicillium chrysogenum* NRRL 2000 preference over P6, *Penicillium baculatum*.[48] From the outset, therefore, penicillin produced from NG&SF's own culture strain continued to be as good as that from Britain and America.

Nonetheless, the ongoing problems that had to be solved in the production of NG&SF penicillin are clearly illustrated by Struyk's report to Waller and Scheurkogel in December 1946.[49] This report, number 1036, was concerned with the difficulty in clearing infection from the B-flasks following contamination of growth cultures, and the need for better sterilization techniques. In trying to eliminate such infections various methods had been used, such as shorter use of the growth medium and a change of filters every two days instead of three, but the conclusion had been drawn that a completely new filter system was needed.

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[45] KA, Catalogue 1990089, Folder 2, Letters S-Z, AC Thaysen to Kluyver, 5 October 1945.
[46] Johanna Westerdijk became an NG&SF advisor in 1946. Source: *Fabrieksbode*, 16 December 1961, p.373.
[47] KA, Catalogue 1990350, CBS Annual Report 1946, List of *Penicillium*.
[48] GB:CA, NG&SF Report 420, 11 August 1946; M. Burns, 'Codename Bacinol', p.86, M. Burns and P.W.M. van Dijck, 'The Penicillin Production Process', p.196, M. Burns, J.W. Bennett and P.W.M. van Dijck, 'Code Name Bacinol', p.30.
[49] GB:CA, NG&SF Report 1036, A.P. Struyk, 'Weekrapport van 8 t/m 14 December 1946', 6 January 1947.

In order to test the filter new system, parallel testing of the B-flasks had been used. The batch chosen was B-428 to B-443. In 'test 436' Struyk had used a different anti-foaming agent which 'according to American literature is used in their laboratory testing'.[50] In his experiments to improve NG&SF technology in the production of penicillin, therefore, Struyk continued to crosscheck his results with methodology coming from the United States.

Deep Fermentation: Production using submerged culture.

Like their British and American counterparts, the Delft team were faced with new problems in the mass production of penicillin. In order to enter the commercial market these had to be quickly overcome. A new 'upscaling team' was created under the leadership of J.M. Jongbloed. It included J.P. van den Berg, C.H. Elzenga, G. Mensinga, H. Mostert and A.H. Saltet. They were called '*bedrijfs assistenten*', company assistants.[51]

The first industrial scale production of NG&SF penicillin took place on 15 May 1946. As recalled by Jan van den Berg, F.G. Waller himself inoculated the first fermenter using innoculum (fungus) grown in a conical flask, the top of which had been sterilised by flaming. Previous to this all fermentations had taken place in R&D, mostly in milk bottles. The first fermenter had a content of 150 litres and was known as an *Ensinkketel* (Ensink tank). Upscaling to 15, 60 and 300 Hectolitres (Hl) soon followed.[52]

The room they used was a small area in M.A. Scheffer's part of the fermentation plant. As one of the new penicillin production employees, H. Mostert pointed out:

> We had to solve problems on a daily basis. We had to keep the vat sterile but we had to keep the mix moving. The first time we tried we didn't have an *impeler* (a

[50] GB:CA, NG&SF Report 1036, A.P. Struyk, 6 January 1947,
[51] Personal Communication. Jan van den Berg, 20 April 2005.
[52] Personal Communication. Jan van den Berg, 20 April 2005.

> mixer). We hadn't thought about that. Nobody had ever been involved in anything like this before.[53]

As Saltet explained:

> The 15 Hl stainless steel fermentation tank and the small inoculating tank had, long before the war, been bought for other tasks. We let the mixture simmer for three days. When it was ripe we started the extraction process. It was a job that brought its own tension with it... We weren't sure about our task and neither were the management... that was why we had the instruction that either Scheurkogel or de Horn had to be present when we started the extraction.[54]

Former Gist Brocades Chairman, E.W. ter Horst added:

> I was employed by my father-in-law, H.F. Waller, in May 1945 especially for the production of penicillin. Don't forget up until then we had only had experience with the fermentation of bakers yeast. That happens fairly quickly and on top of that bakers yeast is not all that sensitive to infection. Now... all at once we had to give the penicillin fermentation process ten times as much time and had a mould that was very sensitive to infection. Everything we did was new.[55]

In the submerged fermentation of penicillin the contents of the tank had to be aerated for the duration of the fermentation process, but it had also to be kept sterile. This meant that the air being forced into the tank from outside had to be sterile. The penicillin tanks, therefore, had to be hermetically sealed against contamination by other micro-organisms.[56] Dust particles were a problem. They were filtered out, but this meant that dust and dirt stayed behind on the filter. The filters were also used to sieve out the residue that gathered at the bottom of the tank. This meant that they stayed in contact with the mix inside the tank. From this, the mash that fed the mould culture could be contaminated. In order to overcome this problem the technical staff first used glass wool. Filters made from glass wool were sterilised with steam for an hour before the fermentation process began. However, for each fermentation process the glass wool had to be re-sterilised and the end result was that it melted. The technicians had to find another method. Steam sealing was unsuccessful, air sealing came next but proved too time consuming. The team then

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[53] Mr. Mostert Personal Communication December 1999; M. Burns, 'Codename Bacinol', p.81.
[54] *De Fabrieksbode*, 29 September 1978, p.87.
[55] *De Fabrieksbode*, 2 May 1995, pages not numbered.
[56] *De Fabrieksbode*, 13 October 1978, p.91; M. Burns, 'Codename Bacinol', p.80.

invented a system of 'double steam sealing' whereby at the point of exit the residue from the mash had to pass through two filter layers. These filters were separated from each other by a dip in the pipe. Each filter was sterilised by a layer of steam. This meant that contamination was hindered, as it would have to pass through two, separate, layers of steam.[57]

That there was an air of excitement among those first involved with the production of penicillin at the NG&SF becomes self-evident with the statement that they 'worked for days deep into the night'.[58] According to H.M. de Horn, a Chemical Engineer who had worked in NG&SF Chemical Technical Service since 1934:

> The Gist was a family concern. They knew their business and how to keep trade secrets. We knew about fermentation. Fermentation plants have to be kept going twenty-four hours of the day. Mr. Waller often joined us on the night shift. He was known to us as 'Mr. F.G.'. He was the driving strength behind us. Every day we had meetings. There were only seven or eight of us. We always had a list of suggestions, a list of things to do. What we decided one day, we tried out the next. Producing Bacinol was not a duty, it was a pleasure but also exciting. We wanted to succeed.[59]

Technically much of that achieved by the Delft team remained improvisation. At the time, post-war restraints meant the adaptation of apparatus and material already used for normal Gistfabriek work or it had to be borrowed. For example, the first sieve used in penicillin production at the NG&SF came from the local sugar factory. To compensate for the lack of a centrifuge the food company Nutricia donated one, until de Horn invented what they called the 'Hornex'. The Hornex was a counter-current system in the form of a carousel; a continuous method for concentrating and purifying the penicillin fluid. At the time the feeling was that more robust apparatus could be made later. What was important was higher penicillin yield.[60]

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[57] *De Fabrieksbode*, 29 September 1978, p.87; M. Burns, 'Codename Bacinol', p.81.
[58] *De Fabrieksbode*, 29 September 1978, p.87.
[59] H.M. de Horn, Personal Communication November / December 1999.
[60] *De Fabrieksbode*, 29 September 1978, p.87; M. Burns, 'Codename Bacinol', p.82.

Before the penicillin could be used it had to be 'dried'. Again an internal solution was found when the skill of 'freeze drying' was applied. This was a technique they learned from the blood transfusion service in Amsterdam.[61]

The results of the initial NG&SF in-depth experiments were so good that F.G. Waller decided to order a new fermentation tank for the production of penicillin. It was made with stainless steel, then a very expensive new material. While little was known about stainless steel at the time, what was known was that stainless steel containers would not react with their contents. It was also more easily cleaned than most other materials.[62] The order to make the fermenter went to Reineveld's machine factory in Delft, an established supplier of apparatus to the Gistfabriek.[63] The first fermentor specifically for the production of Dutch penicillin, therefore, was one that required new skills outside as well as inside the factory.

The Leidsche Apparaten Fabriek (LAF).[64]

At the end of the war, the Leidsche Machinefabriek (Leiden Machine Factory), a company that specialised in stainless steel products, was in urgent need of re-investment. Again, F.G.Waller took the initiative. As an article in *Over en Weer*, the LAF company newspaper explains:

> After liberation the Gistfabriek needed to renew a lot of their equipment. Although they had experienced little physical damage during the war, the lack of wartime raw resources had meant that almost everything needed either immediate attention or replacing. At the time the Dutch apparatus industry was overloaded with urgent orders, especially those in the metal industry and F.G. Waller grew impatient. In 1947 NG&SF bought the Leidsche Machinefabriek and renamed it the Leidsche Apparaten Fabriek[65].

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[61] *De Fabrieksbode,* 13 October 1978, p.91
[62] *De Fabrieksbode*, 29 September 1978, p.87; M. Burns, 'Codename Bacinol', p.81.
[63] *De Fabrieksbode*, 29 September 1978, p.87; M. Burns, 'Codename Bacinol', p.81.
[64] Leidsche Apparaten Fabriek literally translates as Leiden Apparatus Factory.
[65] *Over en Weer*, July 1968, No. 1, p.18-19; Personal Communication, P. Fritz, February/March 2000.

In so doing Waller ensured that the fifty man personnel of the LAF, all of whom had experience with stainless steel, brought their talents to NG&SF. As an independent company, the LAF received its own industrial supplies of stainless steel. However, as owner of the LAF, NG&SF secured a regular source of stainless steel for themselves. In its first year of production the LAF met 50-75% of NG&SF's apparatus requirements.[66]

The project to buy the LAF was financed with money gained from NG&SF's base products. As the Annual Report for 1947 illustrates, underpinning a 6% priority shareholders profit and a 7% ordinary shareholders profit lay increased yeast production, production for the paint industries and increased alcohol production. These increases came, not only from supplying the Dutch market, but also from an increase in exports. In 1947 NG&SF also successfully launched a product pointed to the dietary needs of the time, *Vitamine Gistvlokken* (Vitamin Yeast Flakes). It was a new, dried yeast base, vitamin B-complex that had been medically approved as a dietary supplement. The 1947 Annual Report also shows that the new Penicillin Department, although still in its initial stages, had shown that it would shortly be able to fulfil the penicillin needs of the Netherlands, and that the quality of NG&SF penicillin met with overall approval. Consequently, NG&SF expected an increase in demand for their penicillin and production would be expanded as soon as possible. A very welcome expansion had been the acquisition of the Leidsche Apparaten Fabriek workplace in Leiden, which added substantially to NG&SF's workshop capacity.[67]

According to Elzenga, the purchase of LAF was not such a success. NG&SF gained unnecessary personnel and, in reality, not many fermenters came from Leiden. At the time, most of the fermenters for the large-scale production of penicillin came from other parts of the factory, where

[66] *Over en Weer*, July 1968, No. 1, p.18-19; Personal Communication P. Fritz.
[67] GB:R&D, Annual Report 1947, pages not numbered.

they had been used in the production of other products. The years of 'recovery' were stimulating, 'but you had to take what you could get from the *Rijksbureaus*, there was little choice'.[68]

Nonetheless, at a time of national shortage in all spheres of life, NG&SF was successfully re-establishing its traditional commercial base of yeast fermentation, both at home and abroad. Not only that, but its research and development departments brought new products, such as the medically approved Vitamin Yeast Flakes, for an expanding market. In particular, the establishment of the Leiden Apparatus Factory shows a determination to continue with the expansion of penicillin production.

Penicillin Production.

As has been shown, chronologically, Delft entered the penicillin market in 1946. In the United States and the United Kingdom, penicillin had been in meaningful production since 1942 and certainly by 1943. In the intervening years figures for penicillin production, especially in the United States, had soared. For example, the US 1943 production of 21,192 billion units had risen to 1,663,385 billion units in 1944 and to 6,852,000 in 1945.[69]

In 1946 and 1947 figures for the production of NG&SF penicillin are illustrated in Appendix 5.[70] As can be seen in 1946 production on a commercial scale was very limited. However, between 1946 and 1947 there is a significant increase. In fact, it was enough to cover the whole of the Dutch requirement. How was this achieved?

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[68] Personal Communication C.H. Elzenga, 29 April 2005.
[69] R.W. Herion, 'History of penicillin', p.235.
[70] This table and diagram have been made up from figures contained in NG&SF Penicillin Reports 1946-1949.

Commercial Interest

NG&SF was not without fermentation experience but there were other difficulties that had to be solved before the Dutch market could be reached. For example, in an interview for the *Fabrieksbode* in April 1970, Scheurkogel looked back on the first penicillin sales and distribution. According to Scheurkogel:

> The sale of the first 1,000 flacons per month, each of 100,000 units, started in June 1946 was not much of a problem. At the time we had one fermentation tank of 15 hectolitres. One fermentation process took about a week. If everything went according to plan, even with the very low yield of that time, we had 1,000 flacons every 3½ weeks.
> We talked to the Rijksbureau voor Geneesmiddelen first. As the import of penicillin was very limited due to the lack of dollars in post-war Netherlands we were, with our own penicillin in our own country, welcomed with open arms.[71]

Nonetheless, his description of the beginning of production of Delft's penicillin reveals a daunting and financially risky task.

An official distribution system was developed with the *Rijksbureax* whereby eight hospitals had Government *toewijzingsbonnen* (allocation vouchers) for the 1,000 flacons NG&SF produced per month. The first months were certainly difficult. If a fermentation did not work then it was extremely difficult to make up the backlog and 'we were quite happy if a few hospitals did not send their allocation vouchers at the beginning of the month.' After about a year penicillin production was markedly increased when the first 60-hectolitre tank was commissioned. The consequence of this was that all of Dutch hospital allocation requests could be supplied. After the first 60 Hl tank, five others were commissioned and soon all Dutch hospital doctors could be allocated NG&SF penicillin. In the meantime, the sales situation changed. In the place of direct delivery from the factory to the eight hospitals, a sales system gradually developed which

[71] *De Fabrieksbode*, 24 April 1970, p.79.

involved wholesalers and pharmacists. Also, to keep doctors supplied with information a medical representative was employed.[72]

While Scheurkogel points to an active interest by Dutch hospital internists, medical wholesalers and pharmacists, Elema contends that, although the Dutch Government welcomed the production of this new medicine, Dutch doctors approached the product from a very conservative and reserved standpoint. This was because it had to be injected by a medical practitioner every four hours; a time consuming process.[73]

Clinical Trials.

Coinciding with Scheurkogel's report of the sale of the first 1,000 bottles of penicillin in June 1946, the first Clinical Trials with Delft penicillin had its roots in an exploratory discussion of 31 May 1946. This took place between NG&SF Chairman, van Leeuwen, and Dr Jacob Mulder of the Internal Medicine Department at Leiden University Hospital. Initial contact had been established via Querido. At the meeting Mulder confirmed his interest in penicillin and his wish to investigate it further. It was agreed that as soon as packaging for NG&SF penicillin was ready Mulder would be sent a sample. On 26 June 1946 Querido took a box of 10 flacons, each of 100,000 units, in NG&SF official packaging from Delft to Leiden. On 3 July 1946 discussion took place between van Leeuwen and Mulder in which Mulder said he would be pleased to test NG&SF's weekly production and to look at it, *in vivo*, in patients. The haste for the first results is shown in the agreement that Mulder would telephone his findings only two days later, on 'Friday 5 July at 9 o'clock'. [74]

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[72] *De Fabrieksbode*, 24 April 1970.
[73] B. Elema, *Opkomst*. pp.39-40.
[74] GB:CA, W.H. van Leeuwen Archive, Correspondence van Leeuwen – J. Mulder, May 1946.

It was agreed that each week Querido would supply Mulder with 10 flacons and that Mulder would design a fixed investigation scheme. Specifically, the scheme would investigate pyrogenicity, penicillin blood levels and local irritation. It was also agreed that a standard manner of reporting back to NG&SF, and 'all the documentation that this would bring' would be set up. In return Mulder, an influenza specialist, looked forward to building up a stock of penicillin for use by Leiden University Hospital in the expected post-war flu epidemic.[75]

Appendix 6 contains a translation of the original clinical report on the first batch of NG&SF penicillin to be tested at Leiden. These tests show the manner in which Mulder quickly formalised his style of reporting.

The first test is dated 5 July 1946. The format was typed on officially headed, A4 paper but was filled in by hand. The preparation used is given as '*eerste zending. W. ochtend*' (First delivery. Wednesday morning). The name of the patient was protected. The diagnosis was '*maagca*' (*maagcarcinoma*, stomach cancer). The report related to the intramuscular injection of 50,000 units of Delft penicillin. No subjective feeling after the intramuscular injection was noted and the pain on injection was given as 'not more than that for the injection of any other preparation'. There were no extraordinary reactions to the injection. The temperature of the patient and the penicillin titre of the blood serum remained stable, that meant the sample was not pyrogenic.

The second test is a continuation of the first. In this test the same patient was given 5,000 units but this time intravenously. Again the temperature is monitored; it showed little increase. In the third test, again 50,000 units were delivered intramuscularly. Temperature change was monitored

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[75] GB:CA, W.H. van Leeuwen Archive, Correspondence van Leeuwen – J. Mulder, May 1946.

for six hours after injection, but remained remarkably stable. This first report was signed by Mulder. He concluded that 'no side effects' had been found. In effect, this study combines pyrogenicity and toxicity tests in a patient in whom penicillin would not have been therapeutically effective.

Thereafter a more formal manner of reporting emerges. The results are typed onto a form and indicate administrative assistance. The date and batch number of the penicillin preparation is given, as is a diagnosis. Initials identify the name of the patient. Batch 12, dated 6 July 1946 was administered to three patients. Again intramuscular and intravenous injections were used, but not both in the same patient. The first patient, diagnosed as suffering from '*Koch Pulmonem d.d. Besnier Boeck*' (sarcoidosis), received 50,000 units of NG&SF penicillin by intramuscular injection. The second, diagnosed as '*Ro-bestralingspatient*' (X-ray patient), received 5,000 units intravenously. The third patient, diagnosed as '*maligne granuloom.*' (malignant granuloma, probably Hodgkins Disease), was given 50,000 units intravenously. The conclusion to these tests state 'no pyrogenicity' and that the 'blood level curve was normal'. These reports bear the signature of J. Mulder and W.R.O. Goslings. As will later be shown, both Mulder and Goslings continued their professional interest in NG&SF penicillin.

However, from this Report it can also be noted that the second and third patients, like the first, did not have an infection. One was an X-ray patient and the other had a form of blood cancer. The question has to be asked, therefore, if these first penicillin trials were purely random testing, a blind test or volunteers? What is clear is that in the first clinical trials performed at Leiden University Hospital, penicillin tests were performed in a precise and ordered manner. They were signed and countersigned by two medical doctors and the results carefully monitored. It is also of interest to note that, at the time, one batch of penicillin could be released following one Clinical

Trial, which recorded a maximum of three tests per batch on three different patients with three different illnesses.

A fuller overview of the first Clinical Trials with NG&SF penicillin conducted at Leiden University Hospital is given in Appendix 7. Later pyrogenicity tests were standardized and conducted at NG&SF with rabbits. At the time, however, the fact that such tests had taken place in human patients would have offered the Dutch public and the Dutch medical fraternity, a degree of certainty and trust in the application of this new medicine.

Production / Marketing

It is a truism of modern pharmaceutical life that a medicine, however effective, does not sell itself. In general there is a sense of caution in the medical world that has to be overcome before a new medicine is accepted. While van Leeuwen reflected the view that penicillin was a 'self-promoting product', the early experiences of NG&SF in the marketing of NG&SF penicillin clearly show that even the 'wonder drug' was no exception to the rule of caution.

The first Monthly Penicillin Report for NG&SF penicillin was produced at the end of August 1946. It is a typed list of the first, seven, hospitals to use Delft's penicillin. They are: Academisch Ziekenhuis, Leiden; Academisch Ziekenhuis, Groningen; Academisch Ziekenhuis, Utrecht; Johannes de Deo Ziekenhuis, The Hague; Wilhelmina Gasthuis, Amsterdam; St. Jacobus Stichting, Wassenaar; Binnen Gasthuis, Amsterdam. Also included was the Gemeente Apotheek, Den Haag, (Local Authority Pharmacy, The Hague). All had used a Government *aankoopvergunning* (permission to buy).

The first production figures for NG&SF penicillin, taken from the Penicillin Monthly Reports for 1946 are listed below:[76]

Month 1946	Ampoules Supplied
August	820
September	900
October	1100
November	1000
December	800

The Report of November 1946 offers a good overview of the first months of penicillin production. In this report R.A. Jellema told W.H. van Leeuwen and F.G. Waller that, a total of 1100 ampoules of Delft penicillin had been delivered that month. Of this almost 900 went to the seven hospitals listed above; 100 had gone to the Bethel Hospital in Delft; 100 to St. Jacobus Stichting, Wassenaar; 6 ampoules had been given to Dr. Boekwinkel for clinical tests; 5 ampoules had been given to Dr. den Dooren de Jong for bacteriological testing; and, 10 ampoules given to Prof. Kluyver to be sent to Dr. Hoogerheide in America.[77]

He further reported that, Onze Lieve Vrouw Gasthuis in Amsterdam, the eighth hospital on NG&SF's allocation list, did not use NG&SF penicillin because the price was too high. Visits had been made to the University Hospital in Leiden and Johannes de Deo Ziekenhuis in The Hague regarding enquiries about ampoules of double and triple strength.[78]

[76] GB:CA, R.A. Jellema Archive, NG&SF Penicilin Monthly Reports, November 1946.
[77] GB:CA, R.A. Jellema Archive, NG&SF Penicillin Monthly Reports, November 1946.
[78] GB:CA, R.A. Jellema Archive, NG&SF Penicillin Monthly Reports, November 1946.

In the Penicillin Report of December 1946, St. Jacobus Stichting, Wassenaar, ordered less that their *vergunning* (State allocation permit) allowed because they were 'using up old, imported, penicillin'. However, that the reputation of NG&SF penicillin continued to increase is reported by instances such as that of Dr. Nix of Voorburg who, when admitted to hospital with a lung infection, had expressed the clear wish that he wanted to be treated only with Delft penicillin. Also, as Professor Mulder at Leiden University Hospital would only use Delft penicillin, the allocation from Leiden had risen from 600 to 1,500 ampoules. The 'outstanding' quality of NG&SF's penicillin steadily continued to earn its reputation.[79]

However, in January 1947, Jellema pointed out that deliveries had fallen. This was because, of the 8 hospitals that originally received their allowance from NG&SF, three had definitely stopped, namely Onze Lieve Vrouw Gasthuis, Amsterdam; Wilhelmina Gasthuis, Amsterdam; and, Utrecht University Hospital. In total 750 ampoules of Delft penicillin had been supplied, 700 with *vergunning*. The Gast- Ziekenhuis in Dordrecht had asked for only 50 ampoules, half of its monthly allocation. 28 ampoules had been supplied without *vergunning*, 10 of which were in reply to an urgent request from Leerdam Ziekenhuis. 100 ampoules had been given to Dr Querido; 90 for clinical tests and 10 for delivery to Monheim. However, he added, the reduction in price already initiated would have a favourable effect on sales.[80]

Jellema recommended that the new lower price be well publicised to stop further cancellations. In his view, the problem was to fix the price at a level that did not increase demand too greatly but which would maintain goodwill. He recommended Fl.3.50 as the better price. Further, in order to publicise NG&SF penicillin, Scheurkogel, had given 32 ampoules to GPs free of charge and, with

[79] GB:CA, R.A. Jellema Archive, NG&SF Penicillin Monthly Reports, December 1946
[80] GB:CA, R.A. Jellema Archive, NG&SF Penicillin Monthly Reports, January 1947.

the permission of F.G. Waller, 2 ampoules had been delivered to the Bacteriologisch Laboratorium of Unilever in Rotterdam for research into analytical methods.

However, an example of the State control of penicillin is made clear by the Rijksbureau voor Volksgezondheid who had informed Jellema that in view of the decision of the University Hospital Utrecht not to make use of its monthly allocation, the *Rijksbureau* had reduced the amount NG&SF was allowed to produce to 900 ampoules per month. Nonetheless, Mr Knop of the *Rijksbureau* had assured Scheurkogel that as soon as NG&SF's product played a larger part in the allocation of penicillin, the amount they would be allowed to produce would be increased. It was the *Rijksbureau*'s intention that the amount of imported penicillin stay constant. This meant that increases in the allocation for Dutch hospitals would automatically be directed towards Delft. In this way, the amount Delft was delivering to hospitals would, naturally, increase.[81]

One interpretation of this could be that the Dutch government was willing to keep foreign imports of penicillin at a low level in order to give Dutch penicillin the advantage by promoting NG&SF penicillin. On the other hand their perilous foreign exchange situation would have left little alternative. Added to that, the quality of NG&SF penicillin was regarded as 'outstanding'. At the right price, it was more than equal to its foreign competitors.

Conclusion

As research with penicillin progressed at NG&SF, research with P6 continued to show that NG&SF's *Penicillium baculatum* could match that of the *Penicillium* strains from Britain and America. Added to that, for the scale-up of penicillin production, they could use their own, existing, fermentation techniques and methodology.

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[81] GB:CA, R.A. Jellema Archive, NG&SF Penicillin Monthly Reports, January 1947.

Nonetheless, the history of the early years of production and marketing of penicillin saw NG&SF confronted with major problems. Firstly, production itself was fairly precarious. The amounts of penicillin produced per month were relatively small and there was clearly great uncertainty as to the quantity that could be produced on a regular basis. Yet, again, the first steps to relieve production problems were taken 'in house' by Waller's technical staff. Also, at a time of national shortages, the purchase of the LAF secured future stainless steel fermenters for the sole purpose of large-scale penicillin production.

Surprisingly, another factor to be overcome in the initial supplies of NG&SF penicillin was that of medical reservation. It was apparent to all concerned that measures would have to be taken to counteract this. To an extent the first Clinical Trials at Leiden, as well as establishing that there was no pyrogenicity or irritation, were a step towards countering any conservative doubts.

From the outset, however, NG&SF were encouraged by the State but also confronted with State intervention. The Rijksbureau voor Volksgezondheid clearly controlled the supply of penicillin within the Netherlands. Hospitals were allowed to purchase penicillin by a system of State allocation vouchers. Price too played its part. Dutch hospitals were obviously strapped for cash. This had an effect on the amount of penicillin they could afford to order.

On the other hand, in an attempt to control foreign exchange, the State restricted imports of penicillin. Dutch hospitals were automatically directed towards Delft; but it was to penicillin produced to a high standard at a keen market price. Accordingly, during the years 1945-1947, the road to mass production of NG&SF penicillin broadened the traditional, yeast based, activities. Slowly but surely NG&SF developed a pharmaceutical branch.

Chapter 8

Dutch Penicillin at NV Nederlandsche Gist- en Spiritusfabriek, 1946-1950.

Walter Laqueur states that in the reconstruction of the Netherlands the problems faced by the Dutch government were, broadly speaking, similar to the other governments and political parties all over Europe. They were: the transition from war to peace; the purge of collaborators; the re-introduction of democratic institutions; and, the reconstruction of national economy.[1] Houwaart points out that, in the Netherlands after the war reconstruction was paramount, so too was the reintegration of research, development and production. Medically the emphasis was on the quality of life, and in the health service there was a shift in approach from the private to the public. However, given the combination of shortages of medicines and the high demand for help, it is not surprising that it took some years before the health of the Dutch population and the Medical Health Service returned to their pre-war levels.[2]

Under the influence of reconstruction, the call was for preventative medicines. The Dutch medical authorities were suddenly faced with the new Anglo-American therapeutic medicines, penicillin and streptomycin. Also, during the war years, vitamin and hormone preparations had been improved and surgeons and anaesthetists had new anaesthetics. There were new blood transfusion techniques; a flexible gastroscope; new forms of heart research and electrocardiograms; new biochemical research methods; and, mass x-ray systems.[3] Reconstruction of the Dutch Health Service, therefore, required massive intellectual and financial input.

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[1] W. Laqueur, *The Rebirth of Europe*, (New York, Chicago, San Francisco: Holt Rhinehart, 1970), p.43.
[2] E. Houwaart, 'Wederopbouw en expansie', p235.
[3] E. Houwaart, 'Wederopbouw en expansie', pp.242-242.

Moreover, the end of the war brought a fundamental change in medical culture. Before the war the Dutch medical system had taken its lead from the German model but at the end of the war German medical authorities no longer existed. It seemed natural therefore, for those involved in the Dutch medical system to look more to their liberators, the Anglo-Saxon medical world. According to Houwaart, this was partly because some Dutch doctors had lived in Britain during the war years and had become familiar with the way the British medical system operated. It was also partly because Dutch doctors were allowed make study trips to the United States, at the cost of the Dutch Government, in order to learn and bring back up-to-date medical techniques.[4]

As Houwaart notes, the new Anglo-American methodology meant 'teamwork'. It meant moving away from the hierarchical pre-war system where the patient deferred to the doctor, to one in which each patient required the services of a team of experts, in consultation with each other and the patient. An example of the new interdisciplinary methodology was reflected in the Department of Internal Medicine of Leiden University Hospital. From 1946, this Department was under the direction of the Professor Jacob Mulder. At the invitation of the Rockefeller Foundation, Mulder sent students to the United States to study new methods in cardiology, gastroenterology and endocrinology. These study trips marked the beginning of wider diagnostic study at Leiden.[5] Mulder, as has been shown, was also influential in the first clinical trials with NG&SF penicillin.[6]

The Medical Brains Trust.

Elema states that, initially many Dutch doctors approached penicillin from a very conservative and reserved standpoint because it had to be injected by a medical practitioner at regular intervals

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[4] E. Houwaart, 'Wederopbouw en expansie', pp. 242-243.
[5] E. Houwaart,'Wederopbouw en expansie', p242-243.
[6] This thesis, Chapter 7, pp.221-224.

on a daily basis which was very time consuming. There were also questions of bacteria building up resistance to penicillin.[7] However, the weekly Dutch Journal of Medicine, the NTvG, shows that from the 2 articles published on penicillin in 1945, 49 articles relating to penicillin and its uses were published in 1946; 52 in 1947; and, 48 in 1948. This is roughly one a week. This was brought back to 38 in 1949 and 19 by 1950,[8] however, it is clear that at the end of the war the call for information over and guidance in the use of penicillin by the Dutch medical profession was substantial. In 1946, in order to promote NG&SF penicillin and to pass on information regarding the use of penicillin, NG&SF established the Medical Brains Trust (MBT).

The Trust included Waller, Kluyver, Querido and Willem Goslings. Willem Goslings had returned to the Netherlands in 1945 from North Sumatra. He joined the Department of Internal Medicine at Leiden where his brother Hans was employed. As noted earlier, Hans Goslings had kept Querido's place in the Department open so that he (Querido) could return to Leiden. Querido recommended Willem Goslings to NG&SF as an advisor for their Antibiotic Department.[9] As has been shown, Goslings was also involved in the first clinical trials with Mulder.[10] Another newcomer to the MBT was Louis E. den Dooren de Jong, a graduate of Delft's TH and colleague of Kluyver.[11] At the time den Dooren de Jong was Head of the Bacteriological Laboratory for Rotterdam West. As and when necessary, the MBT was joined by representatives from both the research and commercial departments of NG&SF.

The task of the MBT was to answer incoming medical questions; keep literature on penicillin available and up to date; decide which paths new research should take; and, act as a general

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[7] B.Elema, *Opkomst*, p.40.
[8] www ntvg.nl databank search results 30/07/2005.
[9] A. Querido, *Andries Querido*, p.117.
[10] This thesis, Chapter 7, p.223.
[11] B. Elema, *Opkomst*, p.40.

information centre on all enquiries about penicillin. Initially, the MBT met frequently, and there was much contact between them and NG&SF's research department. Ultimately, this exchange of thoughts and ideas brought valuable medical, pharmaceutical and commercial results into effect.[12]

The precise date of the establishment of the MBT remains unknown. Querido says that it existed for about five years. He recalled meetings, with Kluyver in the Chair, as an evening of exciting and stimulating discussion.[13] As yet, no trace of the content of the MBT meetings has been found in NG&SF archives. However, the Kluyver Archive offers an insight into the early meetings through copies of the Index to the Medical Brains Trust Minutes. For example, the Index for 1946-1947 is split into two sections. The first section is entitled 'Authors', the second 'Subjects'. The alphabetical 'Author' section refers to only thirty-three articles. With the exception of one French and two Dutch publications, all are in the English language, which confirms the post-war trend towards the new *lingua franca*, English.

The 'Subjects' section of the 1946-47 Index, however, shows the scope of penicillin research and development at NG&SF. This section covers twelve A4 pages and illustrates a meticulous, alphabetical, cross sectioning of the topics covered. Sources are given as 'PD' (Delft), 'PL' (Leiden), 'PDJ' (den Dooren de Jong) and 'R' (reference).[14] The versatility of topics in this Index is striking, but the topic 'penicillin' alone covers almost four of the twelve pages. Yet, again, the 1948 Index to Minutes of the MBT meetings illustrates the speed at which information on penicillin had been gathered by NG&SF. By 1948 the 'Authors' section had grown from thirty-three articles to six A4 pages but the 'Subjects' remained at twelve pages. By 1949 these Sections had grown to sixteen and twenty-seven pages respectively.

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[12] B. Elema, *Opkomst*, p.49-50.
[13] A. Querido, *Andries Querido*, p.117.
[14] PD means *proef te Delft* (Delft study); PL means *proef te Leiden* (Leiden study); PDJ means *proef Dr Den Dooren de Jong* (study by den Dooren de Jong); and, "R" stands for *referaat*, (reference).

Digesta Antibiotica.

Part of the reason for the setting up of the Medical Brains Trust was to stimulate articles for publication in order to inform the wider Dutch medical community of the new 'wonder drug', penicillin, and its usage. To this end NG&SF set up *Digesta Antibiotica* (DA, Antibiotic Digest). Although published by NG&SF's *Medisch-Wetenschappelijke Dienst* (Medical Scientific Service), initially the task of editorship fell to Goslings. The first DA article was printed in 1947. The authors of this first article are identified by the initials 'W.G. and A.Q.', i.e. Goslings and Querido. It is entitled 'Penicilline als chemotherapeuticum' (Penicillin as a Chemotherapeutic Agent). In this fifteen-page article the history of the development of penicillin from Fleming, Florey and Chain to Coghill was traced, as was the inclusion of the American pharmaceutical industry and the upscaling of penicillin to large-scale production. It compared the original strain, *Penicillium notatum*, with the new strain, *Penicillium chrysogenum*, and showed the change in production method from 'surface' to 'submerged'. It stated that the purification of penicillin had come far enough to allow the production of penicillin in crystalline form and that there were four types of penicillin, known in America in letter form as F, G, X and K but in Britain by the Roman numerals I, II, III, and IV. A comparison of the strengths and weaknesses of the four types was made. This was followed by an explanation of how penicillin works; how it could be used; its pharmacological properties; and, its therapeutic potential. The authors submitted that, while a large amount of printed material on penicillin was available, they would provide a short list of eleven publications for those who would like to read further.[15] From this first DA publication, a confidence and strength of understanding of the new drug penicillin is clear.

[15] *Digesta Antibiotica*, 1, 1947, N.V. Nederlandsche Gist- en Spiritusfabriek, Delft, 1947. Source: TU Library, Delft. Original source: Kluyver Archive.

As Goslings and Querido indicated, the amount of literature accessed to allow this publication had meant severe summarising of many written sources. Their literature list had, however, been deliberately reduced. Of the eleven publications listed, only five were in English. One was Fleming's 1945 publication *Penicillin: its practical application* and three were American, by W.E. Herrell; C.S. Keefer and D.G. Anderson; and, J. Kolmer.[16] One was Swiss German, by W. Grűninger (Luzern), another was Swiss French by F. Bustinza-Lachiondo (Neuchatel) and a third was the Swiss *Revue médicale* (Swiss Medical Review).[17] Three were in French, the first authored by C. Levaditi; the second by R. Martin *et al*; and, the third J. Monnier.[18] The influence of Levaditi and Martin on the development of French penicillin has been previously noted. As has that of Levaditi as a source of information in the Netherlands.[19]

However, of particular interest to this thesis is the source entitled *Penicillin therapy and control in 21 Army Group.*[20] This report was published in May 1945 under the direction of the Director of Medical Services for the 21st Army Group. Printed and bound by the Stationery Service of the British Army of the Rhine, it is 365 pages in length and consists of 60 Chapters, albeit only a few pages per chapter. It is introduced by Brigadier A.E. Porritt, Consulting Surgeon of the 21 Army Group. According to Porritt, this publication on penicillin is 'a fitting tribute to the very considerable amount of practical work and scientific research put in by those concerned under

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[16] A. Fleming, *Penicillin: its practical application*, (London: 1946); W.E. Herrell, *Penicillin and other antibiotic substances*, (Philadelphia: 1946); C.S. Keefer and D.G. Anderson, *Penicillin in the treatment of infections*, (New York: 1945); J. Kolmer, *Penicillin therapy, including tryothricin and other antibiotic therapy*, (New York: 1945).

[17] W. Grűninger, *Penicillin*, (Luzern: 1946); F. Bustinza-Lachiondo, *Les antibiotiques antimicroblems et la pénicilline*, (Neuchatel: 1945); *Revue médicale de la Suisse romande*, Numéro consacré à la pénicilline, 65, 1945, pp.657-768,

[18] C. Levaditi, *La pénicilline et ses applications thérapeutiques*, (Paris: 1945); R. Martin, F. Nitti, B. Sureau et J. Berrod, *La pénicilline et ses applications cliniques*, (Paris: 1945); J. Monnier, *Pénicilline: toutes ses applications thérapeutiques*, (Paris, 1946).

[19] This thesis, Chapter 2, pp.56-57; Chapter 3, p.102; Chapter 4, p.130.

[20] Director of Medical Services, 21 Army Group, *Penicillin therapy and control in 21 Army Group*, (British Army of the Rhine: Stationery Service, 1945).

active service conditions'.[21] He continued that 'it will be seen .... that a large volume of work has been encompassed in a relatively short time' and expressed his hope that the results recorded in this publication 'prove of value for immediate application (of penicillin) to civilian life and for stimulation of further research'. At the outset, however, he underscored the fact that the 21st Army Group had been 'undeniably fortunate' in the supplies of penicillin made available to them which 'for the past five months ... have been to all intents and purposes unlimited'.[22]

Although short, the Chapters of this report chronicle an incredible amount of information. They relate to records made on the use of penicillin by British and Canadian hospitals of the 21st Army Group. Most are practical in nature. They report on a wide variety of treatments; investigations into the use of penicillin; and, methods of penicillin application. One deals with the stability of penicillin under 'field' conditions, when frequently the manufacturers' recommended storage conditions, such as refrigeration, were unobtainable. In particular, Porritt highlights the highly successful, widespread use of 'parenteral'[23] penicillin at the most forward surgical levels 'as this was a new conception at the time of the invasion of Normandy'.[24] The invasion of Normandy had started in June 1944. Published a year later, the Chapters of this publication in fact amount to reports on the battlefront use of penicillin, in what can only be considered one of the largest clinical trials ever held.

An adapted summary of the surgical results and the use of penicillin from D-Day to VE-Day in table form is given in Appendix 8. As a source of information published in the first DA, this publication by the 21st Army Group would have been an invaluable reference, not only for Dutch doctors, but also for those at NG&SF.

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[21] Director of Medical Services, 21 Army Group, *Penicillin*, Introduction, pages not numbered.
[22] Director of Medical Services, 21 Army Group, *Penicillin*, Introduction, pages not numbered.
[23] Dosing route other than oral. Generally taken to mean by injection.
[24] Director of Medical Services, 21 Army Group, *Penicillin*, Introduction, pages not numbered.

From 1947 the bibliographies of the *Digesta Antibiotica* further illustrate wide use of both British and American literature. The 1947 DA covered four topics: penicillin in preventative medicine; the use of penicillin in the clinical laboratory; the treatment of gonorrhoea with penicillin; and, an announcement from NG&SF's Antibiotic Department on penicillin inhalation therapy. In 1948 six articles were published. Mulder authored the first article on the use of antibiotics in lung infections and Goslings authored two, one highlighting bacterial resistance to penicillin and the other on penicillin therapy in scarlet fever. N. Lubsen wrote on the use of streptomycin in tuberculosis and E. Lopes Cardozo of Gouda described a new penicillin therapy using aerosol.[25] The last article is an unauthored publication of two procedures by which penicillin ointments could be made.[26] These articles are very much smaller in length than those of 1947. All consist of two to three pages. What is striking, however, are the lengths of their bibliographies. All cite extensive coverage of American and British post-war scientific publications.

The ongoing expansion of the MBT can be seen from the Waller Archive. This contains Minutes of the 50th Meeting of the Medical Brains Trust, which took place on 15 February 1949. Those in attendance were Waller, Kluyver, Querido, Goslings, den Dooren de Jong and Mulder with a mix of old and new NG&SF penicillin team members, namely Stheeman, Scheurkogel, Jellema, Berends, J.L. Terpstra, H. Schaareman and P.J. van der Laan. As well as discussing possible articles for *Digesta Antibiotica* these minutes reflect a very wide grasp of the contemporary use of penicillin not only in humans but also in the new NG&SF commercial venture of the time, veterinary development.[27] By 1949, therefore, not only could NG&SF cover the penicillin needs of the Dutch civilian population, they were on the verge of expanding into animal health.

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[25] Lubsen was also a contributor to the Dutch Medical Journal, NTvG. This thesis, Chapter 3, p.96.
[26] *Digesta Antibiotica*, 1947-1950.
[27] *Digesta Antibiotica*, 1947-1950.

Such up-to-date discussion and reporting on antibiotics continued in the *Digesta Antibiotica* until 1966, when it ceased. At the time it was under the triple editorship of Mulder, Goslings and Querido.[28]

The Ongoing Influence of NG&SF Advisors 1947-1950.

Mulder's full inclusion to NG&SF's Medical Brains Trust came in February 1949. It was partly to compensate for the temporary loss of Goslings and Querido. Both were preparing trips abroad, Goslings returned to Indonesia and Querido, at the invitation of the Rockefeller Foundation, started one year research fellowship in the Massachusetts General Hospital, Boston.[29] Both had, however, agreed to stay on as NG&SF advisors and to remain in the Trust. In particular, Querido had agreed to keep NG&SF informed of what he found in the areas he knew to be of interest to them.[30]

For NG&SF, the benefit of Querido's study year in the US was immediate. On 29 March 1949, his first day in Boston, Querido wrote to Waller that he had travelled via New York and had attended a Congress given by the American College of Physicians. He had also visited a Science Exhibition which was 'all about antibiotics'. In this letter Querido stated that he would send the brochures he had picked up and data on penicillin production. He also had some new and interesting small products to send. One was a small penicillin flacon containing 1cc of procaine penicillin; a second was a needle attached to a cartridge called the Tubex Hypodermic Syringe for administering penicillin G in oil; the third was 'Pennettes' which were pastilles in the form of chewing gum, each pastille contained 10,000 units of penicillin; and, the fourth were small

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[28] *Digesta Antibiotica*, 1947-1950; 1959-1966.
[29] A. Querido, *Andries Querido*, pp.120-127.
[30] GB:CA F.G. Waller Jnr. Archive, Correspondence Waller - A. Querido February/March, 1949.

tablets, each of which contained 50,000 units, for oral therapy in children. This last he described as 'a small but practical idea'. Four years after his post-war visit to London, Querido still acted as a provider for NG&SF as he supplied the latest information on the academic research and development of penicillin. In furnishing such contemporary ideas he was, in effect, acting as Waller's medical eyes and ears.

Kluyver also continued to prove his worth to Waller and NG&SF. In March 1949, in what Kluyver referred to as his *blitzkrieg* trip to the US, he introduced Waller and Berends to his American 'network'. Given Kluyver's academic reputation this network, naturally, contained all the authoritative figures working on penicillin. The Kluyver Archive contains an alphabetic list of the people and institutions they visited.[31] Where he was unable to do this personally he used his circle of friends. For example, on 28 March 1949 Kluyver wrote to Peterson at Wisconsin thanking him:

> For the wonderful reception which I, Waller and Berends received when we visited Wisconsin during our journey. We learned all about antibiotics and all aspects of the work you (Peterson) are doing on penicillin.[32]

There was also a visit in which Peterson played the role of introducer. On 26 February 1949 he wrote to an old friend and colleague, Richard W. Jackson of the Fermentation Division, Northern Regional Research Laboratory, Peoria:

> Professor A.J. Kluyver of the University of Delft, Holland, and Mr F.G. Waller and Mr W. Berends, Nederlandsche Gist- en Spiritusfabriek, Delft, Holland, would like to visit the Northern Region Laboratory on Tuesday 1 March. I know of course that they would be welcome but as an old friend of Professor Kluyver I would like to say a word of introduction on their behalf. Of course I know that Professor Kluyver needs no introduction and if you have not already met him I am sure you will enjoy a visit from him as much as we have.[33]

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[31] KA, Catalogue 1990239, Folder 3, Untitled, 1949.
[32] KA, Catalogue 1990093, Folder 2, Letters N-S, Kluyver to WH Peterson, 28 March 1949.
[33] KA, Catalogue 1990239, Folder 3, Untitled, WH Peterson to RW Jackson, 26 February 1949.

On the home front, Mulder continued to actively influence the development of penicillin within the Netherlands. For example, in June 1949 Scheurkogel, via Waller, requested that Mulder provide an economic argument for presentation to the *Ziekenfonds* (Health Service), regarding the use of NG&SF's new sustained release penicillin preparation, Depocillin, as opposed to ordinary penicillin. Scheurkogel was of the opinion that the argument that 'it means less work for the nursing staff and less pain for the patient' would be insufficient. Before contacting the Inspectorate, Scheurkogel wanted to use as an example the possibility of ' penicillin application ... outside the hospital which, in turn, would give the economic argument of 'less days spent in hospital'.[34]

Mulder replied to Waller on 1 August 1949. On Leiden University Hospital headed paper he addressed the subject: 'Procaine penicillin (Depocillin) versus ordinary penicillin in the clinic'. In a passage just over half a page in length Mulder indicated that procaine penicillin meant less work for the nursing staff and doctors which, owing to the shortage of nursing staff, in his opinion was a huge advantage. However, he also stated that other advantages should not be underestimated. In the first instance injecting procaine penicillin was simpler that injecting ordinary penicillin, this meant that there were fewer complications. Also, after a penicillin sensitivity check in the hospital, some patients could be treated at home, which meant less hospital time. According to Mulder, it could not be denied that, a preparation which was painless to administer and given only twice a day was better than a preparation that had to be injected eight times a day and involved some pain. He further noted that some of these eight injections had to take place during the night, thus diminishing the advantage of undisturbed sleep for a quicker recovery. Accordingly, the reduction of nursing staff and better results were very much the advantages of NG&SF new product Depocillin over ordinary penicillin.[35]

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[34] GB:CA, F.G. Waller Jnr. Archive, Correspondence Waller - J. Mulder, June 1949.
[35] GB:CA, F.G. Waller Jnr. Archive, Correspondence Waller - J. Mulder, August 1949.

At this point, Mulder's advisorship can be seen to reflect Houwaart's observation of specialist influence in the reconstruction of the Dutch National Health Service and the consultation between the State, the medical community and commercial enterprise.[36] It also shows that Waller and Scheurkogel used their medical advisors as a means of influencing government bodies.

NG&SF Company Finances 1947-1950.

According to ter Horst, after the war the Dutch Government protected NG&SF penicillin by putting a high import tax on external penicillin. This import tax lasted for three years. With competition reduced, the production of penicillin at NG&SF had the chance to grow. As a result, after the war, penicillin became the cornerstone of the Company's products.[37]

The 1948 NG&SF Annual Report explains the contemporary situation regarding the production of penicillin. According to this Report, the scarcity of foreign exchange at the end of the war meant that in the first years after liberation the supply of penicillin had been limited by the Dutch Government to hospitals only. However, in 1948 penicillin was released from this restriction and could be supplied on doctor's prescription. This meant that NG&SF could increase production to satisfy the wider market. Ultimately, this extended to fill the medical needs of the whole of the Netherlands. The increase in capacity also meant the possibility of exporting penicillin in the future. Serious study of other antibiotics had also taken place and, accordingly, a plan to modernize both fermenters and research apparatus was set in motion.[38]

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[36] E. Houwaart, 'Wederopbouw en expansie', pp.235-242.
[37] *De Fabrieksbode*, 2 May 1995, Pages not numbered; M. Burns, 'Codename Bacinol', p.88.
[38] GB:R&D, NG&SF Annual Report 1948.

In 1949 the Annual Report shows a drop in profit in the Yeast Division due to a drop in demand for bread products; the staple which had been so essential during the previous years of acute rationing. Much thought had been given to the expansion of penicillin production. Demand for penicillin was steadily increasing and in the last months of 1949 NG&SF successfully brought Depocillin, onto the market. However, the production of penicillin demanded further investment. In part this was to compensate for the shortages in materials at the end of the war, when use had been made of what was available. Although sufficient for the time, these temporary measures were now in need of expansion and modernisation.[39]

Antibiotic Department 1947-1950:

Production.

The continuous increase in penicillin production at NG&SF is reflected in the archive of the Antibiotics Department. In February 1947 the Monthly Reports show another drop in NG&SF's price and a subsequent increase in penicillin sales. In March 1947 the Reports highlight the publication of the first number of NG&SF *Digesta Antibiotica*, following which the Medical Scientific Service had received very positive feedback from within the medical profession.[40]

In fact, as seen in Appendix 5, the Monthly Reports of the Antibiotics Department for the rest of 1947 illustrate a pattern of consistent growth. There are large increases in deliveries, more hospitals visits and a wider distribution of free samples. From April 1947 deliveries were no longer noted in ampoules but in 'Million Units' and reporting on the new Veterinary Service added. In the same month it was reported that interviews for Medical Representative was being actively pursued. Mr Marlestein took up that post in May 1947. The production of penicillin

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[39] GB:R&D, NG&SF Annual Report 1949.
[40] GB:CA, R.A. Jellema Archive, NG&SF Penicillin Monthly Reports, March 1947.

steadily increased: August 239mu (million units); September 285mu; October 316mu; November 327mu; and, December 412 million units.[41] The year ended with a record turnover.

In 1948, the Monthly Reports show continued expansion at Delft. In August 1948, Jellema's report to van Leeuwen, Waller and Scheurkogel confirmed monthly increases in production; another price reduction; and, initial contact over the possible distribution of NG&SF penicillin with eleven out of a total of thirteen Dutch pharmaceutical wholesalers. However, the proposed distribution of penicillin via wholesalers, when compared to that delivered directly from NG&SF, was not considered to be to Delft's advantage. Deliveries via wholesalers meant that there would be an increase in the price, as the wholesalers had their own profit margin to meet. In August 1948 this amounted to 10 cents per 100,000 units. Also, in terms of market share, NG&SF considered only three of the possible thirteen wholesalers large enough to distribute NG&SF penicillin, namely Brocades-Stheeman who had 20% of the pharmaceutical market; ACF with 25%; and Onderling Pharmaceutisch Groothandel, Utrecht, at 45%. Nonetheless the report of August 1948 stated that 'another record month' had been achieved and that NG&SF was supplying '2/3rds of all Dutch use'.[42]

In order to further stimulate sales of NG&SF penicillin, special deals with reduction in price for bulk delivery to hospitals started in September 1948. In October 1948 NG&SF delivered a total 11,114.4 million units of penicillin. The total monthly requirement for all of the Netherlands had been estimated to be between 10,000 and 12,000 million units. The achievement of October 1948, therefore, meant, that NG&SF penicillin production equalled the total national requirement. From 1 November 1948 the *Rijksbureau* allowed General Practitioners to prescribe penicillin, and

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[41] GB:CA, R.A. Jellema Archive, NG&SF Penicillin Monthly Reports, April, May, September, October, December,1947.
[42] GB:CA, R.A. Jellema Archive, NG&SF Penicillin Monthly Reports, August 1948.

pharmaceutical wholesalers were permitted to supply penicillin directly to hospitals, doctors, pharmacists and veterinarians as well as to the Rijksmagazijn van Geneesmiddelen (State Depository for Medicines).[43]

As far as the export of penicillin was concerned the Penicillin Report of October 1948 showed that the first order for 1,000 million units was ready for use by the Dutch army in Indonesia; that samples had been sent to Romania; that a meeting had been organised in Brussels with regard to entering the Belgian market; and, a price list for NG&SF penicillin had been sent to Spain. Through business relations, contact had been made with Turkey and Egypt, where importers of medicines for both countries were well placed to buy Dutch penicillin. October 1948 also saw the production of a new, thermostable penicillin. The year ended with the last report looking forward to an equally good 1949 in the production of NG&SF penicillin.

The Monthly Reports on penicillin for 1949 illustrate that the expected increase in the production of Delft penicillin took place. The major increase in NG&SF sales figures starts from the moment penicillin could be obtained through General Practitioner prescription. There was also a large increase in the use of veterinary penicillin. Tablet preparations were considered, as were dental preparations. 'Depot' preparations on the basis of procaine penicillin appeared for the first time in January 1949.[44] One was to be marketed under the name Retarcilline, as it was felt that the preferred name Depocillin would clash with Upjohn's Depo-Penicillin. However, this situation changed and the proposed new preparation retained the name Depocillin. The advantage of Depocillin was that its sustained release allowed for the administration of fewer doses. However, before Depocillin could be brought onto the market a new type of bottle had to be created.[45]

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[43]GB:CA, R.A. Jellema Archive, NG&SF Penicillin Monthly Reports, September, October, November, 1948.

[44] 'Depot' means sustained release.

[45] GB:CA, R.A. Jellema Archive, NG&SF Penicillin Monthly Reports, January 1949.

Commerce.

On the commercial side, February 1949, saw the employment of a second Medical Representative, A.L. de Ruyter, in the Antibiotics Department. This was three years after the first. Mid-April of 1949 saw the introduction of penicillin in tubes for veterinary use, and during the year copies of *Digesta Antibiotics* were sent to Indonesia for distribution to Indonesian doctors. C. Kamerbeek, who had formerly been employed by the Dutch Pharmaceutical Trading Association, joined NG&SF as Head of the new Commercial Department. In April 1949 a penicillin 'inhaler model' was introduced. L.M. Rientsma, a company employee, had constructed it. Clinical trials started with another new antibiotic product based on penicillin, namely Bicilline.[46] This was the combination of two penicillins, a standard penicillin for immediate release into the body with a sustained release penicillin for longer lasting effect.

The report of August 1949 contained a table for the deliveries of penicillin to hospitals. It also described a visit from a group of Hospital Administrators. At the end of the visit the Administrators had declared that the informative way in which NG&SF explained their penicillin production put the communication skills of other pharmaceutical companies, such as Organon and Unilever, in the shadow.[47]

However, from this point, a much more commercial feel can be seen in the 1949 Penicillin Monthly Reports. Reporting on deliveries to hospitals stop and samples are no longer given to individuals. There is more on the supply of bulk production and price protection. Depocillin was

[46] GB:CA, R.A. Jellema Archive, NG&SF Penicillin Monthly Reports, April 1949.
[47] GB:CA, R.A. Jellema Archive, NG&SF Penicillin Monthly Reports, August 1949.

launched in September 1949 and from October the Monthly Reports were split into two categories, 'Therm' and 'Depo'[48]

NG&SF Penicillin Export 1947-1950.

Scheurkogel says that, it was thanks to continuing research and the use of much larger fermentation tanks that the point was reached early in 1949 when all Dutch doctors and hospitals could be supplied with all of their penicillin requirements by NG&SF. From then on the company began to build up reserve stocks. It was at this point the decision was taken to start exporting.[49] In fact, they had been receiving requests for penicillin from abroad since March 1947.

For example, on 31 March 1947 Jellema had received a letter from the Amsterdam Head Office of NV Handelsvereeniging offering to be an export agent for NG&SF in Java, Sumatra, Borneo and the Far East. At the time, the Handelsvereeniging had stated that they realised penicillin was in short supply in the Dutch national market, but it was in even shorter supply in Indonesia. They hoped that NG&SF would be able to reserve some of their penicillin for export. On 10 April 1947 Jellema, with regret, had refused this request, as NG&SF penicillin production was not yet sufficient to consider export.

It was December 1948 before Jellema could introduce the availability of NG&SF penicillin for export. In a letter of 18 December 1948 he wrote to the Department of Health in Batavia that he was pleased to announce NG&SF, in conjunction with the company Rathkamp, would be introducing penicillin in Indonesia. He gave a brief history of the development of penicillin at NG&SF, and stated that the production situation was such that they could cover any further increase in the Dutch market. This meant that NG&SF had sufficient penicillin to make export a

[48] 'Therm': thermostable, stable to high temperatures; 'Depo': long acting.
[49] K. Scheurkogel, 'Technische bereiding', pp.69-72.

real possibility. Consequently, from 22 December 1948, Rathkamp would be able to deliver NG&SF penicillin on a regular basis. He then described NG&SF's contact with the Dutch medical world via *Digesta Antibiotica*, and said that it was their intention to do the same in Indonesia.[50]

As this letter is the first commercially based 'sales' letter found in Jellema's archive, the choice of Indonesia might be seen as strange. Before the war Indonesia had been a Dutch colony. During the war it was occupied by Japan. At the end of the war the Netherlands fought but failed to retain Indonesia as a colony. In fact, at the end of the war, the 'Indonesian question' brought havoc to Dutch politics. It seems odd, therefore, that NG&SF made such a bid for the Indonesian market. Perhaps it is a reflection of the affinity that remained for Indonesia and its loss. Perhaps NG&SF felt more comfortable with a 'known' market. It was also, as the letter from the Handlsvereeniging shows, an as yet unexploited market. In Indonesia, penicillin was in short supply.

However, according to Scheurkogel, at the time, NG&SF realised that it was neither sensible nor even feasible to maintain its own export organisation with many agents in many lands. They therefore sought a suitable partner, and turned again to NV Organon. The attraction of returning to a partnership with Organon was that Organon was already active in the pharmaceutical market with vitamins and hormones. NG&SF, therefore, would have access to the workings of an experienced export group, locally, in Oss, as well as a network of agents in other countries. This export cooperation began in 1950 and lasted for about ten years. It was then mutually disbanded when, as a consequence of increased international competition, the export apparatus in Oss

[50] GB:CA, R.A. Jellema Archive, Correspondence Jellema - Department of Health, Batavia, 18 Dec. 1948.

became too expensive for NG&SF to sustain. By that time, however, Delft had gained so much experience in exporting that they could continue on their own.[51]

NG&SF Expansion.

The *Fabrieksbode* offers an insight into the rapidly expanded assortment of NG&SF penicillin products had to offer. In addition to the first flacons with 100,000 units of sodium penicillin there were soon flacons with higher concentrations. Bicillin, as has been shown, rapidly followed the first depot preparation, Depocillin. Whenever the medical world had a need for combination preparations of penicillin or Streptomycin, which by then had also come onto the market, then these combinations were made in Delft. For example, when broad-spectrum antibiotics such as Chloramphenicol came into demand, NG&SF supplied it under their trade name Globenicol. The first oral penicillin that could be given as a capsule or syrup, named Acipen-V, followed this. This obviated the need for injection. Ultimately, semi-synthetic penicillins such as Delprosyn and Amfipen were developed in Delft.[52]

At the same time, the NG&SF Sales organisation was continually improved. A team of carefully selected and specially trained medical representatives kept doctors informed of NG&SF's new products. They in turn were supported by detailed written material and advertisements that were regularly sent to all doctors in NG&SF distribution areas. As a result, a large assortment of medicines, produced under strict NG&SF quality control, were sold with great success by a team of specialised workers and agents in many different countries.

In the course of only a few years, the export organisation also underwent significant changes. The first Packing Station was constructed in Egypt and in Portugal a complete penicillin and

[51] *De Fabrieksbode* 24 April 1970.
[52] *De Fabrieksbode* 24 April 1970.

streptomycin factory was built.[53] This factory came under the technical leadership of J.P. van der Berg, one of NG&SF's first, post-war, *bedrijfs assistenten* who had originally been employed for the scale-up of penicillin production.[54]

NG&SF 1950

As Jellema's correspondence and Scheurkogel's *Fabrieksbode* article clearly illustrate, the first penicillin sales and distribution reflect a determined commercial activity, not only within the Netherlands but also in the wider international market. All this diversification was based on increased production. This, in turn, was based on keeping abreast of the most modern methods being applied elsewhere. In 1949, the new Queen Juliana, with her husband Prince Bernhard, visited the Gistfabriek. The celebration was of the foundation of NG&SF 80 years earlier. This visit was followed, in 1950, with the gift of the predicate *Koninklijke* (Royal)[55] A gift that was also a fitting celebration for the successful development of Dutch penicillin at Delft.

Only four years earlier, on 27 February 1946, Deputy Director F.G. Waller had reported to the Company President, W.H. van Leeuwen, and his brother, Deputy Director H.F. Waller, his thoughts on the pharmaceutical industry. 'Penicillin', he said, raised the question of whether or not 'we want to move further into the pharmaceutical and chemical industry'. If they limited themselves to the production of penicillin and the delivery of bulk penicillin to the pharmaceutical wholesalers, in his opinion, this would lead to very few practical problems or objections. They would deal with the same *Rijksbureaus* and *Vakgroepen* (Trade Associations), and they could allocate resources such as equipment and raw materials themselves. If they decided to market penicillin themselves there would certainly be resistance. Added to that, the

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[53] *De Fabrieksbode* 24 April 1970.
[54] Personal Communication, April 2005; this thesis, Chapter 7, p.214.
[55] Website dsm.com 28/02/05

setting up of a wholesale trade with medical representatives and a distribution system should not be underestimated. He had considered the possibility of collaboration but was adamant that, should such collaboration take place with, for example Organon, then NG&SF should share, not just in the production profits but also in the sales profits.[56] At the end of the war, and at a time of national economic crisis, there is no doubting Waller's determined business skill.

As has been shown, in the end, NG&SF valued their knowledge and expertise higher than the pharmaceutical experience of Organon. They preferred to develop penicillin themselves. By 1950, they had taken the step from being a well-established yeast fermentation factory to being a major producer of the world's bulk penicillin. Penicillin had become the cornerstone of their production.

Yet insecurities about the step into the pharmaceutical world remained. In 1950 Scheurkogel described the repeat of a projected joint venture with Organon. Organon was to be the export facilitator, Koninklijke NG&SF the penicillin supplier.[57] In 1957, F.G.Waller followed van Leeuwen as President Director, a position that he filled until 1965. Under his leadership KNG&SF broadened its pharmaceutical base.

On Waller's retirement the function as President was set aside and the remaining three Directors formed a Joint Management Team. Jellema was the spokesman.[58] He achieved two important steps in the Company's history. He was the first leader not to be a direct descendant of its founder, Jacques van Marken; and, in 1967 he proposed and executed the merger of the Koninklijke Nederlandsche Gist- en Spiritusfabriek with the pharmaceutical company, Brocades,

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[56] GB:CA, F.G. Waller Jnr Archive,Report Waller – W.H. van Leeuwen, H.F. Waller, 27 February 1946.
[57] *De Fabrieksbode* 24 April 1970.
[58] Website: inghist.nl 03/03/2005.

Stheeman & Pharmacia. This merged company became known as Gist-Brocades. In 1968 Jellema was appointed Chairman of Gist-Brocades.[59] The headquarters remained at Delft but, again, this merger was a clear indication that, the in development of penicillin, the fermentation experts of Delft felt a need for the experience of a pharmaceutical base. Jellema retired in 1971.

In 1998 Gist-Brocades was taken over by Dutch State Mines.[60] However, market forces take the production of DSM penicillin to India and China. In March 2005, penicillin production at Delft ceased. Almost exactly sixty years from the end of the Second World War, the vision of the NG&SF's Delft team ended.

The Delft Team

At the end of the war those in Delft were not young men. Waller, for example, was born on 29 September 1895. At the time of occupation he was 45 and, by the end of the war he was approaching his 50th year. At the end of the war Kluyver was 57, Rombouts and Querido were the youngest at 36 and 33 respectively. Stheeman was the same age as Waller, 50. Struyk, born in 1903, was 42. He had joined NG&SF from the TH in Delft in 1928. Stheeman did the same in 1930. Both remained at NG&SF until their retirement. After the war, Rombouts was the only one to leave. In 1948 he went to the Colonial Microbiological Research Institute, Port of Spain, Trinidad.[61] The Kluyver Archive shows that he returned to the Netherlands in January 1952, to take up employment at Philips Roxane in Weesp.[62]

At the end of the war, NG&SF's researchers were joined by Scheurkogel, employed to set up the first NG&SF pharmaceutical department, Afdeling Antibiotica. The research team expanded to

[59] Website: inghist.nl 03/03/2005.
[60] Website: dsm.com 28/02/2005.
[61] KA, Catalogue 1990093, Folder 2, Letters N-S, J.R. Rombouts to Kluyver, 12 March 1949.
[62] KA, Catalogue 1990046, Folder 2, Letters L-Z, J.R. Rombouts to Kluyver 26 January 1952.

include the newly formed *'bedrijfs assistenten'*, Company assistants. A group of young men in their late teens and early twenties, they had survived the ravages of occupation. They were employed for something that had never been done at the Gist before - the fermentation of penicillin. For this they were specially trained. Elzenga recalls attending Kluyver's fermentation classes. Van den Berg's study book on penicillin fermentation is contained in the Kluyver Archive. As de Horn points out, in this new process, often they had to 'think on their feet'. They became penicillin experts. Their homes in the Agnetapark, Mostert reminisced, became known as 'penicillin corner'. Like their wartime counterparts, most remained at NG&SF until retirement.

Further insight into those who developed penicillin at NG&SF is gleaned from the *Fabrieksbode* account of the celebration of Waller's 25 years service, which took place on Saturday, 22 May 1948.[63] Van Leeuwen gave the first speech in which he spoke of Waller's love of research but also his commercial acumen. He referred to the war years and how Waller had, with head held high, used humour to overcome and control the difficulties of occupation. During the war, the Delft plant had branched out, making food enhancers and vitamin C, but the crown in Waller's work was the development of penicillin.[64]

Kluyver also spoke at this celebration, not as a member of staff but as 'an old friend'. He described Waller's strength as - a Director who also managed to remain a team player. 'Like the conductor of an orchestra', he was able to bring out the best in all of his individual players. Nonetheless, when decisions were needed quickly, he was a resolute and firm leader who was not afraid to accept the consequences of his actions. He was a man who combined the abilities of Director, research leader and businessman.[65]

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[63] *De Fabrieksbode*, Wednesday 2 June 1948. Extra number, p.1.
[64] *De Fabrieksbode*, Wednesday 2 June 1948, p.2.
[65] *De Fabrieksbode*, Wednesday 2 June 1948, pp.6-10.

Kluyver spoke of his pride when he met Fleming at the Pasteur Institute in Paris in November 1946. His pride lay in the samples of NG&SF penicillin he had brought with him to give to Fleming; and the fact that he was able to say that these samples had been made in Delft without any Anglo-American help.[66]

In his reply Waller paid tribute to his staff. A staff he described as full of talent and diversity. He specifically thanked Kluyver as, 'after all', he had 'educated most of them'.[67]

However, while the achievement of NG&SF's Dutch penicillin is often referred to in Company publications, the members of the Delft team are never mentioned as individuals. There is no list of 'participants'. Pieter Lagrou, puts forward the thesis that the occupation had been experienced as a collective affliction by the whole of Dutch society. At the end of the war, there was a communal moral outrage but there was also a desire for anonymity. No one group seemed to want to take precedence over the wartime experience of another. At the same time, Dutch society became obsessed with reconstruction, wanting an end to its economic backwardness.[68]

Lagrou's hypothesis in part explains the desire of NG&SF and Kluyver at the end of the war to 'catch-up' with wartime academic research. It could explain the decision of NG&SF to continue the production of penicillin. De Horn reflects the 'engineer' mode referred to earlier, 'we were not writers, we were do-ers'[69]

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[66] *De Fabrieksbode*, Wednesday 2 June 1948. p.10.
[67] *De Fabrieksbode*, Wednesday 2 June 1948, p.10.
[68] P. Lagrou, *The Legacy*, p.292-295.
[69] Personal Communication, H.M. de Horn, November 1999.

In the difficult economic climate at the end of the war, Waller had to make the decision: To stop penicillin research or to carry on? To stop meant staying with yeast and *Jenever.* To carry on meant continuing the research and development of an exciting new drug. But to carry on also meant moving further into the pharmaceutical industry, not just in the Netherlands but also worldwide. This was an industry that had become stronger during the war years. However, as has been shown, it was also an industry eager to advise on the production of much wanted penicillin. In February 1946, Waller's decision was to carry on.[70]

Conclusion.

At the end of the war, as Houwaart points out, the reconstruction of the Dutch Health Service required an enormous amount of both intellectual and financial input. Before the war, the Dutch healthcare system had been based on the German, hierarchical, model. After the war, they looked to the example of the Anglo-American medical world. This meant consultative 'teamwork'. In order to underscore this new way of medical thinking, the Dutch government funded study trips by Dutch doctors to both Britain and the United States.

At NG&SF, the new Anglo-American methodologies were embraced through the Medical Brains Trust set up to inform Dutch doctors and medical researchers of the advantages of penicillin. Initially, Querido and Goslings played the major role but they were aided in this by Kluyver, den Dooren de Jong and Mulder. It was Mulder who organised the medically approved Clinical Trials with NG&SF penicillin at Leiden University Hospital.

When Querido went to study new medical practices in the US in 1949, Mulder joined the MBT. During his time in America Querido acted as a commercial scout for Waller, and regularly sent back samples of new methods of administering penicillin. There can also be no doubt of the value

[70] GB:CA, F.G. Waller Jnr Archive, Report Waller – W.H. van Leeuwen, H.F. Waller, 27 February 1946.

of Kluyver, his reputation and his contact list, when he joined Waller and Berends in their 1949 visit to the United States. NG&SF knew they had the ability to develop penicillin. They were eager to expand their knowledge and production techniques. In this the NG&SF advisors were invaluable.

Questions have been asked if, at the end of the war, the Dutch Government favoured Dutch penicillin over that of Britain or American. As has been shown, American penicillin was available for import. However, the precarious state of the Dutch economy and their foreign exchange position limited importing penicillin. The fact also remains that high quality Dutch penicillin was ready and available and, while initially it may have been considered expensive, as production increased the price dropped.

As the 1949 NG&SF Annual Report illustrates, the drop in profit from the Yeast Division brought with it the expansion of penicillin production. The Antibiotic Department continued to grow and exploration into possible export markets was embarked upon. At the end of the war, the decision taken at NG&SF to continue their research with penicillin was the beginning of a unique, ground breaking, experience. It was, however, an experience that ultimately changed the complexion of the company as they went from yeast fermentation to pharmaceuticals.

It should be noted that, at the end of the war, an impoverished Netherlands would have posed no apparent market threat to the giants of the British and American pharmaceutical producers. By 1950 the development of a Dutch penicillin industry had taken place. They were gifted the predicate 'Royal'. Unlike the might of the British and American joint efforts, however, this had been achieved by a small team of individuals and advisors under the leadership of NG&SF Director F.G. Waller. At the outbreak of war they were not young men. By the end of the war they had endured five years of brutal occupation. In 1945, NG&SF's reconstruction continued the

development of penicillin with a 'new' group, specifically employed for the large-scale production of penicillin. By 1950 they had achieved this, NG&SF stood as one of the world's largest producers of bulk penicillin.

Chapter 9

Conclusion.

The development of penicillin is as much a history of the Second World War as a history of medical science. That the Dutch authorities relied on German recognition of their desire for neutrality can, in retrospect, be seen to be naïve. A German administration bent on pan-European domination was never going to leave a potential entry point from the south and east of England open. Following Germany's *Blitzkrieg* tactics, within eight days the Netherlands had capitulated. The flight of Queen Wilhelmina with most of her Cabinet to London led to the establishment of a Government-in-exile but they left behind a shocked and traumatised nation. The Netherlands itself became the territory of the civilian appointed by Hitler himself, *Reichskommissar* Arthur Seyss-Inquart. He was to rule for almost exactly five years. His task was to incorporate the Dutch economy into the wartime economy of the Third *Reich* and to prepare the Dutch for incorporation into *Gross-Deutschland.* In the former he was successful, in the latter he failed.

De Jong in his fourteen volumed *Het Koninkrijk der Nederlanden in de Tweede Wereldoorlog* addresses the historiography of the Netherlands during the Second World War. But, discussion of whether the actions of the Dutch society of that time resulted in 'accommodation' or 'collaboration' is still under debate. Klemann shows how, during the war, Dutch society was turned into Speer's 'Slave State' and van der Hiejden has asked: Given the same circumstances, what would I have done? Other historians claim that wartime Dutch society came to reflect a sense of solidarity against the occupier but Blom submits that post-war Dutch society almost immediately returned to its *verzuild* compartments.

Nonetheless, resistance, if slow to begin with, did build up. The railway strike of September 1944, when almost 30,000 people went on strike in support of the Allies at Arnhem is a massive demonstration of the depth of loathing Dutch society had for its occupiers. With the

failure of Arnhem, these strikers could not go back to work. They had to *onderduik* which must have put pressure on the already meagre ration scheme. Also, Seyss-Inquart's retaliation to this strike took the form of lack of provision for the Dutch population and meant that those in the western Netherlands paid the high price of the *hongerwinter*.

It was under the duress of these circumstances that NG&SF began research with *Penicillium* strains at Delft. The majority of the team were graduates in Chemical Engineering from Delft's TH. During the war years Kluyver, Professor of Microbiology at the TH, remained their mentor and advisor. Querido, their medical advisor, was denied them because he was incarcerated in Jewish concentration camps. Yet, these adverse conditions also offered 'chance' a role in the dissemination of information on penicillin. Nonetheless, at the end of the war, there must have been other factors in the framework that catapulted this Dutch yeast producer to a world supplier of penicillin within six years.

In the development of penicillin, David Wilson challenges what he calls the acceptance of a 'standard version' of the history of penicillin. This version, he states, relates only to the development of penicillin in Britain and the United States. It seldom goes further than that.[1] The crucial questions for the development of penicillin in the Netherlands, therefore, become: Why did a small, confined team succeed when whole nations failed? Was there really no other interest in the development of penicillin within the Netherlands? How could a fermentation factory in Delft match the gigantic cooperation of the Allied effort?

Alexander Fleming's 1929 publication had been one of the few available to the Delft team in 1943. The difficulties Florey, Chain and the Oxford group faced are highlighted in Chapter Two. The main difficulty was not in growing penicillin in small quantities, but in extracting and processing it. Large-scale production was even more difficult. During the war it became clear that a multidisciplinary group including chemists, biochemists, microbiologists and

[1] D. Wilson, *Penicillin*, pp.3-4.

fermentation experts was required. In every country where penicillin was successfully produced, Britain, the United States of America and Canada this was the case. This can also be seen in Japan's near success.

Another criterion in the successful development of penicillin was the interest and involvement of central government. In Britain, America, Canada and Japan this was present. Ironically Japan's role in the wartime development of penicillin failed at the point of defeat when overcome by another centralised wartime project of the Allies, the atomic bomb.

In Germany, the influence of a centralised research does not appear. It has been suggested that Germany sat back on its laurels, continued the use of the Sulphonamides with the expectation that a chemical method for the development of penicillin would soon come to the fore. However, the *Reich* offered no centre to coordinate any joint venture in the development of penicillin, chemical or otherwise. Germany was ruled by the dictatorship of Hitler and the Nazi Party. Small groups held on to what power they had and this was also true in the development of penicillin. Yet to say there was no interest in the production of penicillin in wartime Germany, flies in the face of informed German publications.

In France, too, the influence of centralised research and academic communication does not appear. However, France was an occupied country. It is difficult to see how academics in an occupied country could mount an operation on the scale of the War Production Board or the Therapeutic Research Council. In fact, France's experience holds true for the occupied Netherlands but in the Netherlands other mechanisms were in place that supplanted central government.

What is curious is why there was such a delay in interest between the publication of Florey, Chain, Abraham, *et al.*, and the European-wide request for *Penicillium notatum* which flourished 1943/1944. It is obvious that the first two publications of the Oxford Team brought

to the fore the viability of large-scale production of penicillin to the wider European audience. That this interest remained in spite of war conditions is plainly seen from the archive of the CBS in Baarn and, in particular, the correspondence between Westerdijk and Penau. There is no doubt that the publications of Florey, Chain and Abraham re-opened the search for further information surrounding the research, development and production of penicillin. Furthermore, from the CBS archive it can be seen that within the Netherlands the interest in penicillin research was no different than elsewhere in Europe. Consequently, in the wider context, the dissemination of scientific information on penicillin development in wartime offers a matter for reflection. Initial research with penicillin in both Axis and occupied countries came as a spin off from papers published in Britain in 1940 and 1941 but the floodgates did not open until reports of the success of penicillin in the North Africa campaign in 1943.

Chapter Three highlights the consequences for Dutch Health Care under occupation. In doing so it illustrates the increasing grip on doctors and pharmacists by the Occupier. It shows the way in which these professional bodies sought to protect themselves and the Dutch population from continuing shortages. At the end of the war improvisation in the medicinal field was common.

Chapter Three further illustrates the tendency to myth forming in the story of the development of Dutch penicillin. As the Allies liberated the Netherlands they would certainly have brought penicillin with their military medical services. Even though this was primarily for use by their own troops, it has been shown that some found its way into the Dutch civilian sector. There are, therefore, conflicting claims for the first use of penicillin in the Netherlands. Considering the conditions applying at the time this is hardly surprising. However, how much the awareness of Allied penicillin stimulated Dutch doctors in the use penicillin remains unclear. At the end of the war, as has been shown, Waller had to invent the Medical Brains Trust and *Digesta Antibiotica* to inform Dutch doctors on the use of penicillin.

Chapter Three also addresses and dispels the myth that penicillin and its qualities were unknown in the Netherlands during the war years. Albeit under the constraints of occupation, contact between European academics did take place. Data on penicillin and penicillin-like substances was available from a variety of French, German, British, American and Swiss sources. There were also reports on penicillin in Dutch publications and a national newspaper, the NRC. While the amount of information in both academic and commercial publications may have been small, for both Kluyver and the NG&SF Research Department it would have been sufficient for them to begin to think about duplicating the development of penicillin.

However, in attempting to develop penicillin or a penicillin-like substance Kluyver and NG&SF were not alone. This is clearly seen in archival evidence from the CBS, which cites several sources of interest in penicillin in the Netherlands during the war years. In particular the CBS archive provides a detailed correspondence with the Dutch pharmaceutical company Brocades, Stheeman & Pharmacia over their product Expansine. Expansine was produced by fermentation using a *Penicillium* strain and had an antibacterial action. The development team had been made up not only from BS&P's own research department but also Dutch University colleagues and Government institutions. The CBS archive shows that in July 1944 it was the clear intention of BS&P to publish their findings in the *Nederlandsch Tijdschrift voor Geneeskunde*.[2] However in 1944, because of toxicity problems, BS&P had to take the decision not to continue with Expansine. In fact, Expansine was the only BS&P excursion into the production of penicillin. Nonetheless, shortly after the war ended the Research Department of BS&P produced two small articles on what had been achieved but which, owing to wartime conditions, had remained unpublished. It had, however, been openly reported upon in the NRC newspaper.

Another myth in the development of penicillin in the Netherlands is the role of Professor A.J. Kluyver. Two authors, Bosman-Jelgersma and Spykens Smit, have asserted that Kluyver led

[2] CBS Archive 1944, Correspondence File, No. 73.

the NG&SF penicillin team. This is not so. The team leader was undisputedly F.G. Waller. However, that Kluyver was a vast influence on the NG&SF team is not under dispute. Kluyver enjoyed a worldwide reputation and corresponded frequently with other leading microbiologists. He was an expert in fermentation techniques. David Wilson writes: 'It is the biggest single failing of the myth about penicillin that it ignores the technological breakthrough of deep fermentation, a breakthrough that was every bit as vital to the successful development of penicillin as any of the more dramatic laboratory work'.[3] In 1933 Kluyver had published on submerged culture. He, therefore, had the required technical ability to guide and advise on in-depth fermentation. So too did his pupils.

As stated earlier, most of the research staff at NG&SF consisted of his former students. As NG&SF advisor he had weekly, Monday, meetings with them. Apart from personal ties, the Kluyver Archive offers evidence of exchanges of academic information with NG&SF staff, but none on penicillin. It is his correspondence with another former pupil, J.C. Hoogerheide, which indicates that in October 1941 Kluyver was aware of research with penicillin and penicillin-like agents taking place in the United States, not only by Hoogerheide but also Coghill and Waksman. Kluyver would have known the possibilities contained in Hoogerheide's 'H1' product.[4] America's entry into the war in December 1941 put a stop to the Kluyver-Hoogerheide correspondence. It would not resume until October 1945. These few letters, however, illustrate Kluyver's active and informed interest in anti-bacterial properties. There can be no doubt he would have discussed this with his post-graduate researchers, Waller, Struyk and Stheeman, at NG&SF.

As has been shown, knowledge of penicillin also came to the Netherlands with the advance of the Allies. Also, Struyk's report of 29 July 1944 illustrates that the anti-bacterial product Bacinol was developed at Delft during the years 1944-1945. Bacinol was an antibacterial

[3] D.Wilson, 'Penicillin', p.207.
[4] KA, Catalogue 1990083 Folder 3, Leters H-Z 1941, Hoogerheide to Kluyver 24 March 1941.

substance identical to penicillin. In order to achieve this the Delft team had to be, and were, able and committed research scientists. While NG&SF did not openly publicise or publish information on their achievement, its successor, Gist-Brocades, has recorded the event in Company publications such as 'Van Fleming tot Flemoxim Solutab' and *De Fabrieksbode.* Yet, within these publications an 'authorised' version of the development of penicillin at NG&SF between the years 1940-1945 seems to have been created. Within this 'authorised' version there are two main areas of uncertainty. Firstly, how did the information on penicillin that prompted NG&SF research reach Delft? Secondly, what was the source of the American penicillin used to compare with Delft penicillin?

In the first case it may be simply that the information was received at different times, through different routes by different persons. Apart from Kluyver's correspondence with Hoogerheide, Chapter Four highlights the claim that information on penicillin came through listening to 'illegal' radio broadcasts and the propaganda leaflet the *Vliegende Hollander.* While radio possibilities remain, it has been shown that the *Vloegende Hollander* could not have been a source that brought news of the wartime use of penicillin to Delft. It has been shown that another propaganda source, *De Wervelwind,* did contain publications on penicillin in December 1943 and February 1944. There is the possibility, however, that the *Wervelwind* of December 1943 was not put into curculation. What is not in doubt, is that when information on penicillin did present itself, each and all of the Delft team were capable of understanding the possibilities this meant for penicillin research at NG&SF. In fact, Waller alludes to this when he states that the experiences gained in making vitamin C for the Ministry of Health took them out of their 'known microbiological area of yeast fermentation' but 'stood us in good stead with penicillin'.[5]

[5] *De Fabrieksbode,* 15 October 1960, p.269.

At the same time, Waller points to the initial lack of scientific information when he says that in 1943 'only one publication was available', that of Fleming.[6] However, the Kluyver Archive has shown that from 1943 a trickle of information on penicillin became available in the Netherlands. Albeit limited, this information came through a wide variety of sources and questions the efficacy of the 'secrecy' embargo by Britain and the US. Publications found in the Kluyver Archive include German, French and Swiss academic publications, the Dutch newspaper NRC and the German Foreign Trade News, the NfA. Notwithstanding the difficulties of occupation therefore, research with antibacterial substances was disseminating through academic research workers in Europe, in particular from 1943. This information would also have been available to Waller's team. In fact, Struyk's research reports underscore his knowledge of contemporary publications and his ability to interpret such up-to-date information.

In the second case, the reason for the lack of a source for the American penicillin used by Struyk to compare NG&SF's Bacinol, may be clandestine. As has been shown, given the conditions necessary for the storage of penicillin at the time, it is unlikely that American penicillin came into the Netherlands with the food drop at Ypenburg in April-May 1945. A more likely source, as suggested by Hofmyer and Sijtsema, would be the military doctors accompanying the 21st Army Group. However, the climate of 'secrecy' at NG&SF would have ensured that the true source of the penicillin 'made by Chas. Pfizer & Co. and supplied by Upjohn of Kalamazoo, Michigan',[7] was never revealed.

There is, however, no doubt of the success of Delft's research during the war years. Maria Geene, a patient in Delft's Bethel hospital was the first patient to receive NG&SF penicillin in

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[6] *De Fabrieksbode*, 15 October 1960, p.269.
[7] GB:R&D, NG&SF Report 244-246, July 1945; B. Elema, *Opkomst*, p.37; M.Burns, Codename Bacinol, p.68, M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process, p.197.

November 1945. Her recovery was startling. However, it was a success that brought with it consideration of the possible further development of Dutch penicillin.

At the end of the war the Dutch government was faced with the reconstruction of its plundered country. The economics of the day further drove home the difficulties Dutch politicians faced. This rationalisation of services brought with it the need for a professional, financial approach. There was also an overwhelming desire to 'catch-up' with what had taken place in Allied countries during the years of occupation.

In the *Gezondheidszorg* there was a shortage of everything – doctors, nurses and medicines. As early as October 1945 the Director of the State Institute for Public Health, W.A. Timmerman, reported to the Minister for Social Services on the difficulties of importing British or American penicillin. He recommended that a centre for research on penicillin and other antibiotic medicines be set up in the Netherlands. From the outset, therefore, only a few months after the end of the war, the development of penicillin and the idea of 'making it ourselves' had taken root in Dutch State institutions. In the end, whether Dutch penicillin should be made by the State, by commercial firms or by a mixture of both was open to discussion.

At the end of the war the decision making process at NG&SF stands in clear contrast to bureaucratic conclusions of the Dutch State. NG&SF did enter discussion with the Dutch pharmaceutical company, Organon, over the possibility of cooperation in penicillin research and marketing. In the end these talks fell through, mainly because Organon felt they were being relegated to the role of experienced wholesaler and NG&SF felt that their technical expertise was being undervalued. To an extent NG&SF were right to refuse Organon. In reality, Organon were only offering their experience as a sales organisation. They did not have fermentation possibilities or a fermentation staff. Indeed, Organon failed to recognise

the leading position NG&SF held in the microbiological world. As a result, NG&SF decided to develop their penicillin on their own.

Little is known of NG&SF Deputy Director F.G. Waller's bold decision in February 1946 to continue development of penicillin at Delft. On 15 May 1946, Waller took the lead role in the first industrial scale inoculation. In doing so, Waller entered a completely new branch of production. He added to a well-known fermentation concern, a newly emerging pharmaceutical branch.

In order to do so NG&SF had quickly to 'catch-up' with development of penicillin that had taken place in the Allied countries. In this task the role played by NG&SF advisors Querido and Kluyver, and their networks, proved to be crucial. For example, Querido focused on the medical field and provided Waller, a microbiological technical engineer, with pharmaceutical facts. On his first fact-finding post-war trip to London, he used his time to gather specific information for Waller and *Penicillium* strains for Kluyver and Struyk.

In contrast to the well-meaning but painfully slow official attempts to provide information on penicillin and other medical advances, the influence of Kluyver is striking. There is no doubt that Kluyver opened up his 'network' to Waller. These included the foremost names in the penicillin field, such as Fleming in London and Peterson in Iowa. This, in turn, allowed Waller to profit from the unprecedented openness of both academic institutions and industrialists taking part in the production of penicillin in Britain and the United States. An example of this openness is reflected in Kluyver's letter introducing Spiers to the penicillin world of the US. Such friendship and frankness would not be considered possible today.

At the time, however, it has to be noted that the Netherlands, a small country, was not a major pharmaceutical market. At the time NG&SF was not a pharmaceutical company. It offered no market threat to the larger American and British drug industries. At the end of the war

penicillin was in short supply. There was also a desire in the Allied countries to help those in mainland Europe recover from the years of occupation. The number of reprints on penicillin research sent directly to Kluyver from contacts in Britain and the US verifies this. For the technically minded Waller and his team such sources proved invaluable. However, not only was there a technology push, there was also a market pull.

The decision to continue or stop with the research and production of penicillin in both the United States and Britain proved difficult. The investment in expensive fermentation equipment looked bleak in the face of expected synthetic chemical production. At the time those companies that continued were seen as the 'winners' whereas those who had opted out, Merck and ICI, were deemed to have lost a very important market. With hindsight this did not turn out to be the case. Nonetheless, at the end of the war in both the United States and Britain, the decision of whether or not to invest in the new penicillin market must have taken great consideration. It also brought a return to pre-war market rivalries as each producer strove to gain as much of the market as possible. The same is true for NG&SF in Delft. The decision to continue with the development of Dutch penicillin must have been carefully considered but, for Waller, it became a logical, and deliberate, step. NG&SF did not just 'drift' into pharmaceuticals.

In the face of national economic hardship, NG&SF 1946 Company Accounts show a fairly healthy profit. Their fermenters were producing exactly what its re-emerging society needed, namely, food supplements and yeast for the food industry, alcohol and paint for the construction industry. Whether it was on the basis of humanitarian ideals, or the excitement of being included in a new market, or a bit of both takes second place to the fact that in August 1946 the Nederlandsche Gist- en Spiritusfabriek were able to introduce 'Penicillin, Our New Product'.[8] To achieve this statement, the influence of British and American reprints is not in

[8] *De Fabrieksbode*, 10 August 1946.

doubt. Nor is the advice and help of Westerdijk, Querido and Kluyver. This is not to say that the expertise of the Delft team did not stand on its own. Clearly it did.

At the end of the war there was a will to succeed at Delft. The involvement of help from other war-torn companies such as Nutricia and Reineveld and the take-over of the LAF bears witness to this. However, although the NG&SF' factory was physically unhampered by war damage there had been no re-investment in plant and machinery during their five years of occupation. Nonetheless, a new Penicillin Department was founded in January 1946. A 'new' upscaling team of young men looked on as Waller inoculated the first fermenter and started NG&SF's industrial production on 15 May 1946. The first sales of NG&SF penicillin happened in June 1946.

In order to continue, proof of the effectiveness of NG&SF's penicillin had to be established. Medical doctors had to be encouraged to prescribe it, batch testing had to be established in formal Clinical Trials, and the price to the customer had to be kept to an acceptable level. The Dutch government may have controlled the import of penicillin but in the production of penicillin NG&SF constantly reiterated their quest for a high quality product at an acceptable market price. In this the determination of NG&SF management is nothing short of astounding.

At the end of the war the Dutch Health Service was faced with the new Anglo-American technique in healthcare based on teamwork. This veered away from the Dutch pre-war hierarchical system. Before the war, the accent in medicine meant the patient deferring to the doctor; after the war, in the new medical world, the accent meant the services of a team of experts. In its effort to 'catch-up' two things happened in the Dutch medical world. Firstly, Dutch doctors went to the United States to study new methods and English became the '*lingua-franca*'. Leiden University Hospital is a good example of this. Mulder and Goslings,

as has been shown, formed the base of clinical trials with NG&SF penicillin while, as early as September 1945, Querido went to London.

NG&SF were keen to spread the knowledge they had gathered to the wider Dutch medical circle. The setting up of the Medical Brains Trust was an example of this. They wanted to overcome what was perceived to be the conservative and reserved habits of Dutch doctors. In order to do so they used their medical advisors, Querido, Goslings and Mulder.

In order to reach the widest audience possible, the Medical Brains Trust published the *Digesta Antibiotica.* This contained articles specifically pointing to the new 'wonder drug' penicillin and its usage. They were also pleased to answer any enquiries on medical and/or commercial fronts. As such the MBT presented and encouraged up-to-date reports and discussions on the development of penicillin.

However, the first article to be published in the Digesta Anibiotica by Querido and Goslings underscores the benefit to NG&SF of Allied information on penicillin. It is entitled *Penicillin therapy and control in the 21st Army Group.* Published in May 1945 by the Stationery Service of the British Army of the Rhine, this report covers a wide variety of treatments; investigations into the use of penicillin; methods of penicillin application; and, the widespread use of parenteral penicillin at the most forward surgical levels. In fact, this military use of penicillin from the Normandy landings until May 1945 offered the reader the results of what can only be considered one of the largest clinical trials ever held. It offers a complete demonstration of the nature and use of penicillin. The availability of this publication to NG&SF would have been invaluable.

The years 1947-1950 illustrate the ongoing influence on the development of Dutch penicillin by NG&SF's advisors. In Leiden, Mulder not only set up the first Clinical Trials for NG&SF penicillin, but he ensured that these continued. In addition, his reputation in the medical world

assisted NG&SF in the Dutch (Governmental) Health Service consultations. In his 1949 study trip to the United States, Querido acted as Waller's medical eyes and ears. He sent back not only academic information but also commercial samples of new applications with penicillin. Similarly, Kluyver's *blitzkrieg* trip to the US with Waller and Berends provided Waller with a network of that could not be surpassed.

While NG&SF Annual Reports reflect the expansion of the Antibiotic Department and ever increasing sales of NG&SF penicillin, they also show that this required increased financial input. By 1949 the Annual Report shows that there was a drop in profit in the Yeast Division, due to the drop in demand for immediate post-war 'essentials', such as bread. On the other hand, the demand for penicillin was high and Delft was pleased to continue with its development and production. Whether this was from a desire to 'help' the country or a desire to ensure commercial growth remains a matter of opinion.

However, at some point F.G. Waller must have realised that he was changing the face of NG&SF. In order to progress, he had to leave the simple marketing of yeast and enter the more complex pharmaceutical world. This latter was high-tech, information based and full of arcane practices in which Waller was unfamiliar. The technical improvements in penicillin yields would not have worried him, he, as we have rightly seen, had faith in his team and confidence in their ability. But NG&SF was a medium sized company in a small country. The habits and customs of the medical world were unknown to him. The fact that he considered and re-considered a partnership with the pharmaceutically wise Organon shows an insecurity in NG&SF's lack of pharmaceutical experience.

Yet, instinctively, NG&SF's decision was to 'go it alone'. By surrounding himself with expert advisors, establishing the MBT, *Digesta Antibiotica* and the Medical Scientific Services, Waller followed the path of an emerging pharmaceutical company. In establishing the Antibiotics Department and gradually adding commercially trained staff, he created what

would become a pharmaceutical division with its own production, commercial and medical departments.

In 1950, Queen Juliana awarded the predicate *Koninklijke* to NG&SF in celebration of their 80th year in production. It was also a fitting testament to the Delft team in the development of Dutch penicillin. However, while this achievement is often referred to, it is covered mostly within Company publications. While some individuals are named there is no set list of those who partook in the development of penicillin at NG&SF. At the end of the war no publication setting out NG&SF's wartime research appeared. De Horn, however, points quite simply to the fact the NG&SF wanted to carry on. From then on, the company followed its normal course for product protection, secrecy.

There is no doubt that in the development of Dutch penicillin, F.G. Waller was the leader of the Delft Team. His role was pivotal. Waller knew he was entering a new world when he began research with *Penicillium* strains in 1943/44. He knew he was entering a new world when he began the commercial development of NG&SF penicillin in 1945/46. By 1950 NG&SF was one of the world's largest producers of bulk penicillin. An achievement all the more striking where, as has been shown, so many others failed.

It could be said that the Delft researchers did not have to discover penicillin. At the end of the war, they also had access to the mass of clinical trial reports published by the Allies. Admittedly, therefore, they did not have to prove the therapeutic value of penicillin. However, while the Allies had shown that penicillin could be grown, it needed academic ability and technical expertise to manufacture it. Clearly, the Delft Team had both. NG&SF mirrored, in miniature, the success of the large-scale British and American ventures.

In order to do so, NG&SF's research had used a *Penicillium* strain that was neither of those favoured by the Allies, *notatum* and *chrysogenum*, NG&SF penicillin came from *Penicillium*

baculatum. At the end of the war, tests showed no reason to change. NG&SF's penicillin proved a worthy equal to British and American products.

In the early post-war years, at a time of great economic uncertainty, F.G. Waller invested in plant and personnel specifically for the manufacture of penicillin. A new production methodology was developed; a new department, Afdeling Antibiotica, was created; and, a new marketing network established. In doing so, Waller ensured the continued manufacture of penicillin at Delft. Ultimately, the commercial success of NG&SF's penicillin overtook its traditional yeast base.

In the development of penicillin in the Netherlands, there can be no doubt that the role of F.G. Waller at NV Nederlandsche Gist- en Spiritusfabriek is pivotal. It was, however, a desire he shared with a tight-knit group of individuals, each part of a team with a will to succeed. At the end of the war, those involved with Bacinol watched as their antibacterial substance rightly took its place in the medical world. It is all the more disconcerting, therefore, that almost exactly sixty years later, market forces have deemed the fermentation of penicillin at Delft end.

The Delft Team

Wartime research.

F.G. Waller (François Gerard): Deputy Director.
H.F. Waller (Herman): Deputy Director.
W.H. van Leeuwen (Wilhelmus Hendrik): President Director.

Microbiology.

A.P. Struyk, (Albertus Petrus, Piet).
Assistant:
L.P. Lagendijk.

Biochemistry.

A.A. Stheeman, (Ayolt Albert).
Assistants:
Dhr. Knotnerus.
G. Th. Mathu.
C.W.F. Spiers.

Biology.

J.E. Rombouts (Johannes Eliza).
Assistant:
A. Addeson (Ans).

Fermentation.

W.A. Verkennis.
Trials:
J.M. Klokgieters.

Upscaling.

Technical Services Department:
H.M. de Horn.
L.M. Rientsma.

First Clinical Application.

E. Verschuyl, (Evert).

Post-war Research.

W. Berends.

Post-war Penicillin Production.

W.A.Verkennis - Head.
J.B. van der Lek.

Post-war Production Team.

A new team specifically employed for scaling-up process.

J.M. Jongbloed – Leader.
J.P. van den Berg (Jon).
C.H. Enzenga (Rien).
E.W. ter Horst (Eppie).
Ir. Kamps.
G. Mensinga (Gerard).
G. Mostert.
A.H. Saltet.
D. van der Zijde.

Post-war Marketing.
A new department Afdeling Antibiotica.
K. Scheurkogel (Klaas) – Head.

Penicillin Commercial Department.
R.A. Jellema (Ruud Auke).

Post-war Penicillin Sales.
J.A. Marmelstein.
S. Vonk (Sam).

Packaging.
J. van Vlanderen.

Advisors.
A.J. Kluyver (Albert Jan), TH, Delft.
J. Westerdijk (Johanna), CBS Baarn.
A. Querido (Andries), University Hospital Leiden.
W.R.O. Goslings (Willem), University Hospital Leiden.
J. Mulder (Jacob), Leiden. University Hospital Leiden.

Other Influences.
J.C. Hoogerheide (Johannes Cornelius).
L.H.C. Perquin, TH, Delft.
L.E. Den Dooren de Jong, TH, Delft.

Delft Team Chronology

F.G. Waller:
When we first started looking, in 1943, only one publication was available, that of Fleming 1929. It was on that basis we started our research. (*De Fabriekbode*, 15 October 1960).

1943 - News of penicillin arrives at NG&SF:

Via
BBC Radio Broadcast / Propaganda magazine *De Wervelwind.*

NG&SF gathers information.

Publications to hand:
1929:
Fleming, A., 'On the Antibacterial Action of Cultures of a Penicillium with Special Reference to their Use in the Isolation of *B. influenze'*, *British Journal of Experimental Pathology*, 10, (1929), pp.226-236.

Publications gathered:
1940:
Waksman, S.A., 'Antagonistic Interrelationships among Microorganisms', *Chronica Botanica*, 6, (30 December 1940), pp.145-148.
1943:
Wagner-Jauregg, Th., 'Die Neueren Biochemischen Erkentnisse und Probleme der Chemotherapie', *die Naturwissenschaften,* 31, (16 July 1943), pp.335-344.
Vonkennel, J., Kimmig, J. and Lembke, A., 'Die Mycoine, eine Neue Gruppe Therapeutisch Wirksamer Substanzen aus Pilzen', *Klinische Wochenschrift*, 22, 16-17, (17 April, 1943), p.321.
Kiese, M., 'Chemotherapie mit Antibakteriellen Stoffen aus Niederen Pilzen und Bakterien', *Klinische Wochenschrift*, 22, 32-33, (7 August 1943), pp.505-511.
Penau, H. and F. Hagemann, F., 'Essais d'Éxtraction d'une Substance Bactericide d'Origine Fungique', *Comptes rendus des Séances de la Société de Biologique et ses filiales*, 137, 23-24, (December 1943), pp.724-725.

1944 - NG&SF Wartime Research.

March – June 1944 presented 29 July 1944:
Struyk Report: 412, 413, 414.
Bereiding van Bacinol – Production of Bacinol.

July 1944-March 1945:
Stheeman Report: 847/904.
Report on the research with Bacinol.

July/August 1944:
Wettstein, A., 'Penicillin', *Schweizerische Medizinische Wochenschrift*, 74, 23, (10 June 1944), pp.617-625.
Received via Querido.

F.G. Waller:
By around *Dolle Dinsdag* we had a small amount of a substance, which we hoped, and which later to our joy proved to be, penicillin.
(*De Fabriekbode*, 15 October 1960).

September 1944:
Codenamed Bacinol. A small amount of gold/brown antibacterial substance.

1945 – NG&SF Bacinol: Research and Development.

April-May 1945:
Stheeman Report 243. Research with Bacinol.

June-July 1945:
Stheeman Reports 244-246.
Cultures of *Penicillium baculatum* on diluted grain-mash.

November 1945:
Maria Geene receives the first clinical application of Bacinol at the Bethel Hospital, Delft.

1946 - NG&SF Post-war Penicillin Production.

Publications used in Penicillin Production:
Nature, 'Chemistry of Penicillin', 156, (29 December 1945), p.766
Raper, K.B., Alexander, D.F. and Coghill, R.D., 'Penicillin. II. Natural Variation and Penicillin Production in Penicillium Notatum and Allied Species', *Journal of Bacteriology*, 48, (6 December 1944), pp.639-658.

15 May 1946:
F.G. Waller, first industrial scale fermentation.

June 1946:
First flacons of NG&SF penicillin.

July 1946:
Rombouts, pyrogenicity testing.

August 1946:
Struyk Reports 419-420.
Production of Bacinol - Preliminary experiments with submerged cultures, 10-11 August 1946.

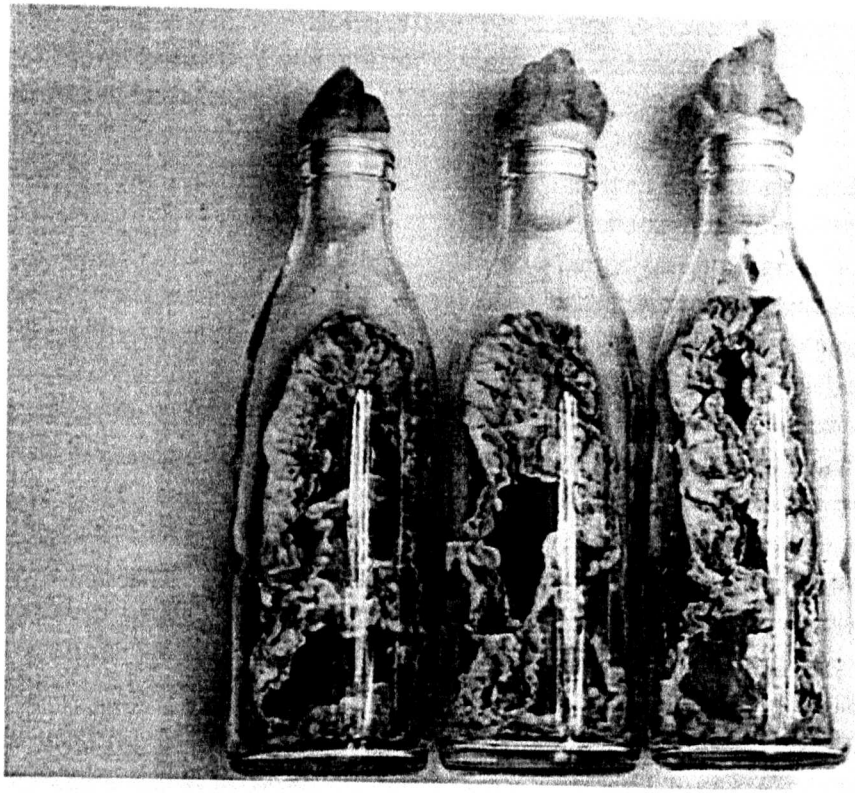
Appendix 1.
The twenty-one strains used by Struyk were:

Code	Strain	Origin
P1	*Penicillium corylophilum* Thom[a]	Thom (CBS)[b]
P2	*Penicillium notatum* Westling	Thom
P3	*Penicillium cyano-fulvum* Biourge	Brourge
P4	*Penicillium chrysogenum* Thom	L.M.[c]
P5	*Penicilium meleagrinum* Biourge	CBS
P6	*Penicillium baculatum* Westling	Thom
P7	*Penicillium corylophilum* Thom[b]	Thom (France)[b]
P8	*Penicillium chloro-phaeum* Biourge	Biourge
P9	*Penicillium brunneo-rubrum* Dierckx	Biourge
P10	*Penicillium citreo-roseum* Dierckx	Biourge
P11	*Penicillium griseo-roseum* Dierckx	Biourge
P12	*Penicillium expansum (Link)* Thom	CBS Van Luijk Neth
A13	*Aspergillus clavatus* Desm. (Abott)[c]	CBS, Wolf
A14	*Aspergillus giganteus* Wehmer	Thom
A15	*Aspergillus flavus* Link	Nattrass, Thom, Walker
P16	*Penicillium commune* Thom	Thom (CBS)[b]
P17	*Penicillium corymbiferum* Westling	CBS
P18	*Penicillium citrinum* Thom	Thom
P19	*Penicillium cyclopium* Westling	Thom
P20	*Penicillium baculatum* Westling	April CBS[b]
P21	*Penicillium notatum* Westling	CBS[b]
	Cacao fungus 1	NG&SF isolate
	Cacao fungus 2	NG&SF isolate

[a] Struyk mentions in his report that this probably should be *P.coryphilum* Dierckx.
[b] This additional information is from Struyk; it is not mentioned in the CBS catalogue.
[c] Laboratory of Microbiology, Delft (Kluyver's Lab.).

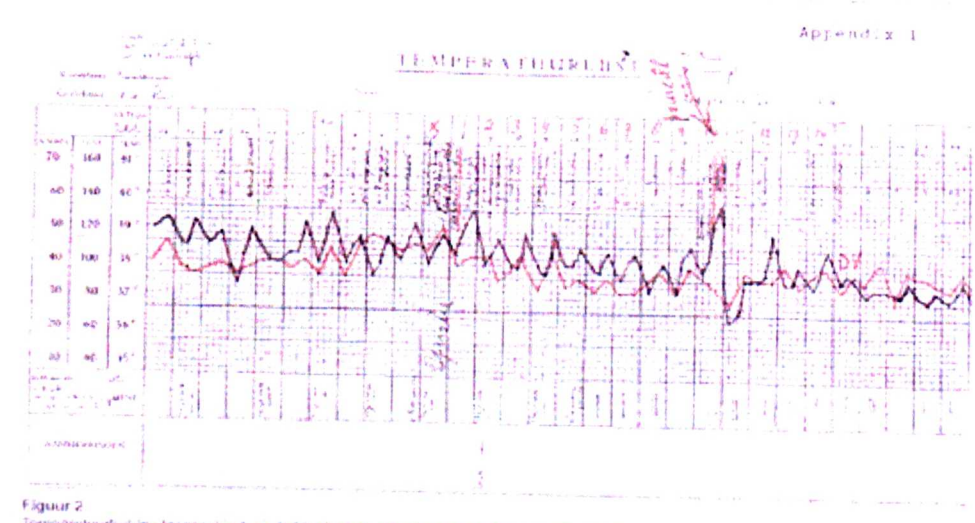
Source: GB:R&D Archive, Report 412, July 1944. M. Burns, 'Codename Bacinol', p.60.
Table adapted from: M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process', p.192.

Appendix 2.
Milk Bottles Containing Penicillin Culture

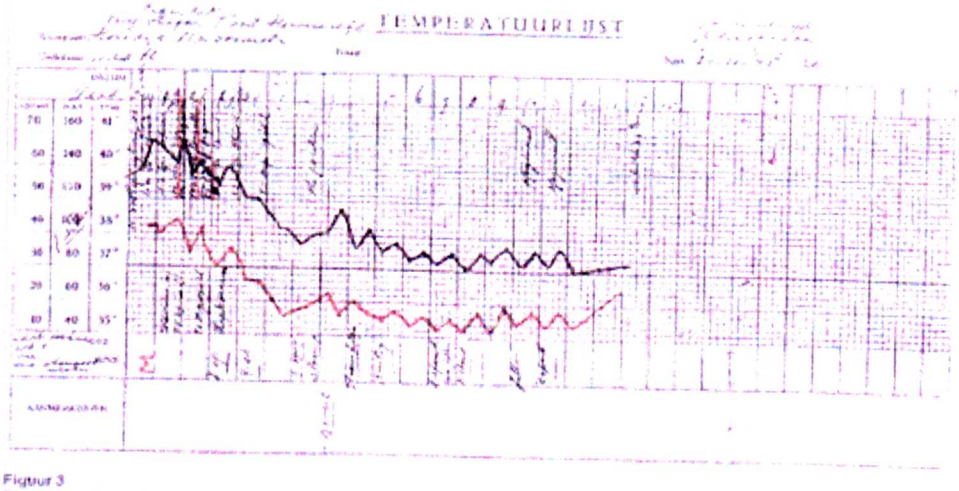


Source: '35 jaar Penicilline', Gist-Brocades NV, Company Publication, 1978; M. Burns and P.W.M. van Dijck, 'The Development of the Penicillin Production Process in Delft, The Netherlands, During World War II Under Nazi Occupation', *Advances in Applied Microbiology*, 51, (2002), p195.

Appendix 3.
Temperature Charts of the First Patients Treated with NG&SF Penicillin



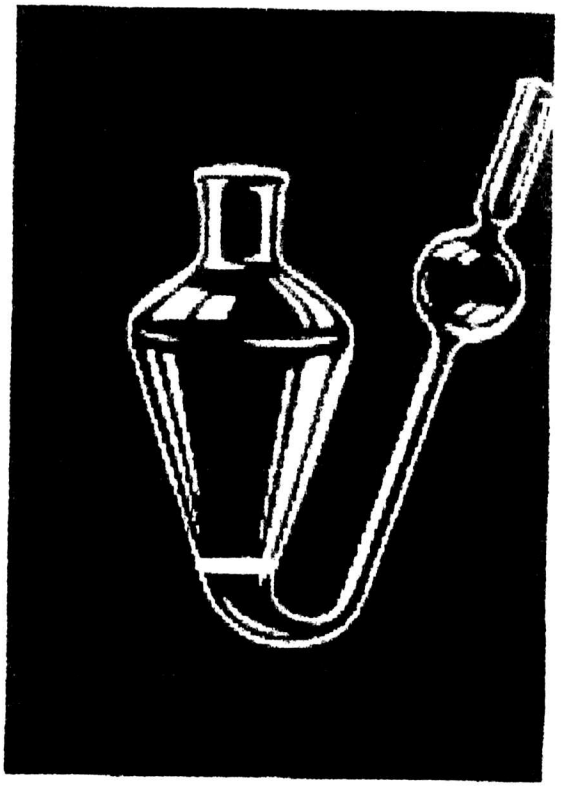
Figuur 2



Figuur 3

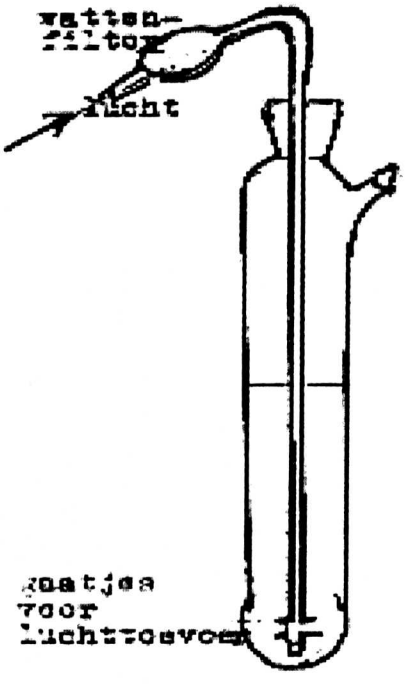
Source: H.L. Houtzager en M.A. Verschuyl, 'Delfts pionierswerk: de fabricage en klinische toepassing van penicilline', *Medisch Journaal Delft*, 4, (December 1995), p.196.

Appendix 4a.
Kluyver Submerged Culture Vessel



Adapted from cover of: Kamp, A.F., La Riviere, J.W.M. and Verhoeven, W., eds., *Albert Jan Kluyver. His Life and Work*, (Amsterdam: North-Holland Publishing Company, 1959). Source: Kluyver Archive.

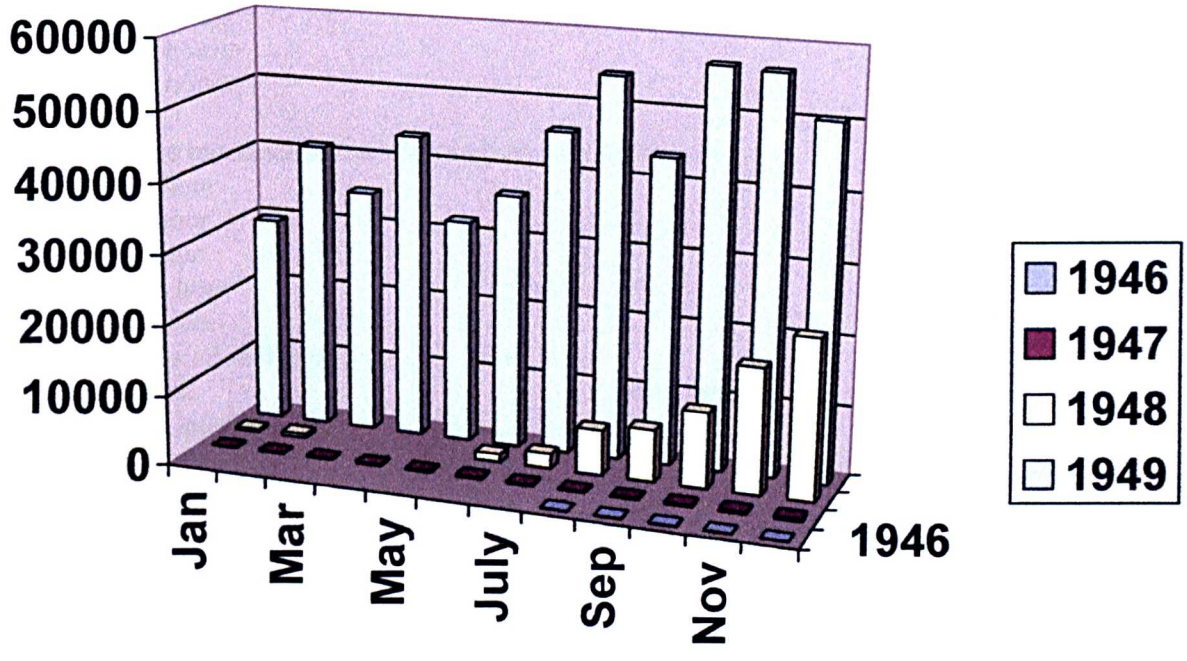
Appendix 4b.
B-Vessel used by Struyk for Submerged Culture Experiments



Source: GB:CA, NG&SF R&D Report 419, A.P. Struyk, 'Bereiding van Bacinol – Orienteerende proeven met submerged cultures',10 August 1946.

Appendix 5.
Millions of units of penicillin manufactured in the years shown by NG&SF

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
1946								82	90	110	100	80
1947	87	168	232	269	240	273	243	239	286	316	327	412
1948	315	513				1167	2261	6562	7541	10922	18069	23019
1949	29445	41019	34844	43633	31917	36297	46047	54385	43716	56809	56407	50467



Source: This table and diagram have been made up from figures contained in NG&SF Penicillin Monthly Reports 1946-1950. Source: GB:CA.
Note: Figures obtained from the Rijksbureau voor Genees- en Verbandmiddelen show that by December 1948 NG&SF was supplying all penicillin needs for the whole of the Netherlands.

Appendix 6.
Translation of Clinical Trial Form

Penicillin Report

Preparation number:
Name :
Diagnosis :
Date :
Intramuscular :
Subjective feeling after inter-muscular injection:
Pain by injection :
After injection : pain; swelling; redness
Temperature Other symptoms
Before the injections:
After ½ hour
1 hour
2 hours
3 hours
4 hours
5 hours
6 hours
Later:
Titre of the blood serum after inter-muscular injection
After ¼ hour
½ hour
1 hour
1 ½ hour
2 hours
Intravenous : 5,000 units
Temperature Other symptoms
Before the injection:
After ¼ hour
½ hour
¾ hour
1 hour
2 hours
5 hours
6 hours
Later:
Intravenous : 50,000 units
Temperature: Other symptoms
After ¼ hour
½ hour
¾ hour
1 hour
2 hours
5 hours
6 hours
Later:

Conclusions:

Signed:

Appendix 7.
Patient Trials of NG&SF Penicilline for Toxicity, Pyrogenicity and Blood Levels

Date	Batch	Patient	Diagnosis	Route	Dose i.u.	Side Effects	Pyrogen	Blood Levels*
5/7/46	n.a.	G	Stomach carcinoma	i.m.	50,000	None	No	15 - 30
n.a.	n.a.	n.a.	n.a.	i.v.	5,000	None	No	n.a.
n.a.	n.a.	n.a.	n.a.	i.v.	50,000	None	No	n.a.
All the reports above are handwritten – those below are typed onto forms								
6/7/46	12	J.O.	TB	i.m.	50,000	None	No	15 - 30
6/7/46	12.	L.H.	X-Ray	i.v.	5,000	None	No	Normal curve
6/7/46	12	A.S.	Malignant Granuloma	i.v.	50,000	None	No	Normal curve
10/7/46	13	H.M.	Rheumatism	i.m.	50,000	None	No	15
10/7/46	13	B.	Femoral Vein Thrombosis	i.v.	5,000	None	No	n.a.
10/7/46	13	C.V.	Rheumatism	i.v.	50,000	None	No	Normal curve
19/7/46	1515	R.vdH.	Heart Murmur	i.m.	50,000	Slight pain	No	15 - 30
19/7/46	1515	A.E.	TB	i.v.	50,000	None	No	Normal curve
29/7/46	1516	VdV.	Angina	i.m.	50,000	None	No	15
29/7/46	1516	S.	Steatorrhoea	i.v.	5,000	None	No	n.a.
29/7/46	1516	H.	Sarcoidosis	i.v.	50,000	None	No	Normal curve

i.m. = Intramuscularly
i.v. = Intravenously
n.a. = Not available
* Time in minutes after injection at which maximum blood levels were measured.

Appendix 8
Summary of Surgical Results of Penicillin Treatment in the Field

Injury	Total cases	Deaths	Percentage Recovery
Head Wounds	2506	157	94
Facial Wounds	3501	53	98
Chest Wounds	2329	223	90
Abdominal Wounds	5737	1498	74
Limb Amputations	2656	200	94
Spinal Injuries	509	65	87
Open Fractures	8684	157	98
Joint Injuries	2511	12	99
Burns	1038	22	98
Flesh Wounds	12976	109	99
Total	**42447**	**2496**	**94**

Adapted from: *Penicillin therapy and control in the 21st Army Group*, (British Army: Published under the direction of the Director of Medical Services, 21st Army Group, 1945), p.363.

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