

JULIA SHEPPARD\*

**Sir Ernst Boris Chain and the  
International Centre for Microbiological Chemistry  
at the Istituto Superiore di Sanità<sup>1</sup>**

'Dear Professor Marotta, I am greatly looking forward to October when I expect to begin my work in your Institute. It is my aim to build up with your help a strong and important European biochemical centre which would be in a position to compete with any single research unit in the world'.<sup>2</sup>

So wrote Ernst Chain to Marotta in April 1948 prior to coming here to establish the International Centre for Microbiological Chemistry. He was later to write in more detail about his first contact with the Istituto Superiore di Sanità, explaining that his first contact had come through the British Council in 1947 when he was asked to give a series of lectures on penicillin in different Italian towns. At that time Marotta had told him that the Italian government had accepted a fund from UNRRA (United National Relief and Rehabilitation Agency) to build a small penicillin plant — and that the Istituto had been given the task of erecting the plant. Chain's reaction to this was to tell Marotta that it was 'utterly uneconomical to put up the technically antiquated UNRRA plant, and in view of the high efficiency of penicillin production by private industry there was no case for the State to interfere with industry'.<sup>3</sup> He suggested however that the funds could be used to build a

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<sup>1</sup> Paper given at the Istituto Superiore di Sanità meeting in honour of 25th anniversary of death of Domenico Marotta, 9 July 1999. My thanks to Giovanni Paolini for his helpful comments, to Helen Hawkins for translating documents and to Lisa Wilkinson for information on the production of penicillin. The Chain papers cited are held by the Contemporary Medical Archives Centre at the Wellcome Library for the History and Understanding of Medicine, Wellcome Trust, 183 Euston Road, London NW1 2BE.

<sup>2</sup> Letter Chain to Marotta, 27 April 1948. CMAC/PP/EBC/C4.

<sup>3</sup> 'My activities at the Istituto Superiore di Sanità: a brief survey'. Typescript by Chain, undated. CMAC/PP/EBC/D8. See also C13 and C23.

La ricerca che segnò una svolta fondamentale nella medicina

## È morto il premio Nobel Ernst Chain (Con Fleming scoprì la penicillina)



Ernst Chain, premio Nobel per la medicina (1945).

LONDRA. — Il prof. Ernst Chain, 75enne, che nel 1945 ottenne il premio Nobel insieme a Fleming e a Florey per aver scoperto, con Alexander Fleming, la penicillina, è morto ieri (14) in Israele, la località in cui risiedeva dall'evacuazione di Londra nel 1940.

Nell'articolo scritto dal «New York Times» di Franco e Viviani a Rio di Janeiro, si ricorda il prof. Chain, il premio Nobel di Israele, negli anni del 20 e 30. Chain, come gli altri scienziati, si dedicò alla ricerca, e in seguito fu uno dei pochi a essere

in Israele nel 1946, di fatto, e nel 1952 fu stato nominato ministro per le scienze e per le tecnologie. Chain, che fu anche uno dei protagonisti della scoperta della penicillina, è stato uno dei pochi a essere in Israele nel 1946, di fatto, e nel 1952 fu stato nominato ministro per le scienze e per le tecnologie.

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che, utilizzando questo gas per il trattamento di fattori «aprotropici», non a dire quel tipo di prototipismo che è stato stabilito nel laboratorio del 1943 dal dottor Hans Christian Fleming. Chain, invece, lavorò con il Fleming in un laboratorio della penicillina (dove lavorò per un periodo di tempo) e fu uno dei pochi a essere in Israele nel 1946, di fatto, e nel 1952 fu stato nominato ministro per le scienze e per le tecnologie.

La scoperta definitiva, avvenuta una guerra nella guerra mondiale, riguarda il fatto che il Dr. Chain, insieme a Fleming e Florey, scoprì la penicillina. Chain, invece, lavorò con il Fleming in un laboratorio della penicillina (dove lavorò per un periodo di tempo) e fu uno dei pochi a essere in Israele nel 1946, di fatto, e nel 1952 fu stato nominato ministro per le scienze e per le tecnologie.

A partire dal 1945 la penicillina divenne il «re» di Israele, e il Dr. Chain, che fu uno dei protagonisti della scoperta della penicillina, è stato uno dei pochi a essere in Israele nel 1946, di fatto, e nel 1952 fu stato nominato ministro per le scienze e per le tecnologie.

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Emilio Di Stefano

research centre for chemical microbiology, with a fermentation pilot plant for research in the field of chemical microbiology for the study of substances of biochemical or biological interest and of microbial origin. Facilities like these were lacking in Europe and the failure of the British to capitalise on their penicillin research and manufacture it, galled Chain. He was convinced that heavy economic losses had been incurred in Britain by the 'virtual complete loss of the field of antibiotics and a large section of the field of growth factors to America'.

Chain, arrived in Rome, aged 39, with a tremendous reputation as the Nobel prize-winner for medicine, a prize shared with Florey and Fleming in 1945 for their role in the discovery of penicillin. He had a clear agenda of his own and it evidently fitted into Marotta's view that biochemistry had an increasingly important role to play in modern scientific development and that boundaries between disciplines should be removed. Chain's research required knowledge of biochemistry, microbiology, organic chemistry, engineering and electronics. He was also keen to see boundaries between industry and the academic environment broken down. Marotta wanted the newly appointed Head of the Dept of Pharmacology, Daniel Bovet, to work closely with a new Department of Biochemistry and Chain knew Bovet and admired his work. After hectic months of negotiation over his contract and the design and equipment of his laboratories, Chain arrived in the autumn of 1948 to take up his post as head of the Laboratory of Biological Chemistry. Somehow, in the course of that summer, Chain also found time to woo and marry Anne Beloff, a fellow biochemist. She was to become closely involved with her husband's research in Rome and became a Professor of Biochemistry herself. It was a happy partnership. Chain made sure that he could still return to the University of Oxford if Rome did not work out, and he initially had a one year leave of absence from Oxford. However, after two years he felt confident enough to resign his UK post and he was to stay in Italy until 1964, from 1961 also taking up a post at Imperial College London as Professor of Biochemistry.

When writing about these early schemes many years later during the period of the Marotta scandal, Chain stressed that he had had to be enticed by Marotta to come to Italy, and had come *in spite of* advice from his UK colleagues about how he should 'distrust all promises made by that country, as in general people [there] were thoroughly unreliable and had the habit of breaking contracts when it suited them, without hesitation or any qualms of conscience'<sup>4</sup> In truth I am sure that Chain was enamoured of the idea of coming to Rome from the beginning and, despite concerns about the state of the Italian economy at the time, he was keen to come to Italy recognising that Marotta and the Institute offered him the chance to achieve his ambitions in a way that was not on offer in the UK. He had no prob-

<sup>4</sup> Draft note by Chain on 'sequence of events which led to my scientific activities in Italy at the Istituto,' page 10, CMAC/PP/EBC/C23. See also A10.



Fig. 2. Chain and staff in fermentation plant at Istituto (from *The Life of Ernst Chain*).

lem about working in a totally new environment with new people: he was a true European with the energy and vision to see what could be achieved with the funding and opportunities offered by the Institute and Marotta.

The background to Chain's arrival in Rome illustrates his forceful personality. Once convinced of an issue he fought with vigour to achieve his aims. A Jew, whose family were of Russian/German origins, Chain was of a volatile and determined nature, indeed he called himself a 'temperamental Continental'.<sup>3</sup> He had left Berlin for England in 1933, and quickly gained a place for himself, working initially at Cambridge, then Oxford in the William Dunn School of Pathology. It was his work there with Howard Florey on anti-bacterial substances produced by micro-organisms and penicillin which led to the Nobel Prize. An excellent linguist (Russian, German, English and French) he picked up Italian so quickly that he was lecturing fluently in Italian within a few months — his written Italian is somewhat eccentric. He also had a strong artistic side to him: at one stage he considered becoming a professional musician. Chain was an outspoken and extremely confident man who I suspect could turn from being charming to unpleasant rather quickly. He did not suffer fools or bureaucracy: once in fighting mode he would do

<sup>3</sup> Ronald Clarke, *The Life of Ernst Chain*, (London, 1985).

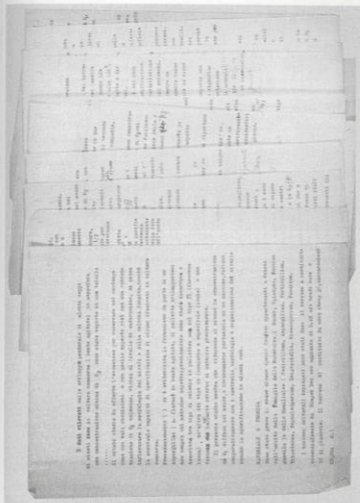


Fig. 3. Typewritten paper by Chait, possibly for a Conference, including description of experiments with fermentation process [1962]. CMAC/PP/IBC-G77

battle fiercely. He said of himself in his later years that he always seems to be involved in disputes, and this is true he quarrelled with the Medical Research Council, Imperial College London and, in the case of the Marotta scandal, made known his views forcibly to everyone. It was typical of his character that he should become so incensed about the Marotta affair and enter the fray.

What then did Chain achieve at the Institute during his 15 years there? His two main interests were microbial biochemistry and mammalian intermediary metabolism. Research in the Department of Biochemistry with Francesco Pocchiari and others, centred around the problems of studies of metabolic pathways and factors influencing the rate of intermediate carbohydrate metabolism in higher animals and micro-organisms. These included study of the mode of action of insulin. His research in this field led to the proposal of a new theory of insulin action and important work on ergot alkaloids.

The chemical microbiological research associated with the pilot plant was also productive. Not only was the large scale plant which he designed and set up effective, operating on a semi-industrial scale, but he successfully developed the techniques of fermentation (the chemical change on which the production of antibiotics then entirely depended), using a new aeration system.

Chain was a consultant for several companies including the pharmaceutical companies Beechams and Astra, and the food technology section of Rank Hovis McDougall. From the mid 1950s he developed his links with the Beecham Group for the production of tartaric acid and penicillin and he initiated work which culminated in further important advances in chemotherapy. Most importantly he was involved in the development of the first generation of semi-synthetic penicillins. It was his suggestion to Beechams that they modify the penicillin molecule, rather than search for entirely new substances, which led to the isolation by the Beecham Group of 6-amino-penicillicanic acid and the production of a series of clinically valuable new penicillins. Within months Rome and Beechams had turned this into a great commercial enterprise. The links of the Institute, (an institute of the Italian government) and Beechams (a private British company), although openly known or, were later to be questioned in the run up to the Marotta affair.

Certainly Chain and Marotta achieved their aim and Chain helped create a centre of biochemistry of world renown, with integrated multi-disciplinary teams. Its facilities were the envy of many of the researchers who came from all over the world to visit, train and work there. As Chain himself wrote in 1949: 'The Institute ... is exceptionally well equipped, in fact, almost too luxuriously: I cannot get used to this type of laboratory'.<sup>4</sup> Affiliation of the Centre for Chemical Microbiology with the World Health Organisation was made in 1951 with the establishment of the fermentation pilot plant. This brought trainees and visitors from all over the world

<sup>4</sup> Letter Chain to Prof McKenzie 1 May 1949, CMAC/PP/EBC/C14.



Fig. 4. Chain and wife with Marotta at Istituto (from *The Life of Ernest Chain*).

who were working in the field of antibiotics production by submerged fermentation. Many were celebrated scientists in their own right, underlining the status and fame of the Institute. They included Fellows of the Royal Society such as Rudolph Peters, Charles Dobbs, and Hans Krebs. Close collaboration between Anglo-Italian scientists helped developments in the industrial and academic spheres in both countries. And many of Chain's colleagues went on to do further work, contributing to the post-war growth of biotechnologically based chemotherapeutic and food industries.

The Chain papers in the archives at the Wellcome Institute for the History of Medicine contain a large amount covering his period in Rome. The whole collection consists of 69 boxes of papers which were given by his widow, via the National Cataloguing Unit for the Archives of Contemporary Scientists.<sup>7</sup> There is a full catalogue and I have described the whole collection elsewhere.<sup>8</sup>

Section C (4 boxes) covers his career in Rome with administrative correspondence, research projects and the Marotta case. But scattered throughout the collection there is much other correspondence and papers of relevance to this period. The initial correspondence with Marotta and others about the terms of his con-

<sup>7</sup> NCUACS is at the University of Bath, Claverton Down, Bath BA2 7AY.

<sup>8</sup> *Medical History* (1983), 27, pp. 434-435.

tract, arrangements for his stay, with suggestions and requests for equipment for the laboratories and their design, illustrate his immensely detailed planning.<sup>9</sup> These include 1948/49 drawings of fermenters made in Milan.<sup>10</sup> Then there were numerous requests from people to visit and work in the laboratories. There are also staff files 1939-63, with many carbon copies of letters sent out by Chain to research students and sponsored fellows, with references, discussions on the employment of foreigners, payments etc. Copies of orders placed with Italian and other suppliers and manufacturers are also to be found here. There are 12 files covering various research projects 1958-62, with grant applications, reports on some of the research being done and miscellaneous notes by Chain.<sup>11</sup> Chain described his work in the Istituto on more than one occasion and there is also what appears to be the commentary of a film script 'Manoscritto del sull'Istituto'.<sup>12</sup>

The Lecture and Conference files are useful in that they show the number and range of scientists attracted to the Istituto. The files often include Italian translations of the papers that were given in English. In 1951 there was a major symposium to mark the inauguration of the fermentation pilot plant, and the file includes notes on invitations and Chain's introductory address 'Aims and Functions of the International Research Centre of Chemical Microbiology'.<sup>13</sup> Conferences include one in 1956 to commemorate the centenary of the death of Amedeo Avogadro, with correspondence from Linus Pauling and Sir Cyril Hinshelwood. In 1958 Sir Charles Dobb's gave a talk at the Institute and the first International Symposium in Fermentation was held at the Istituto in 1960. Other papers relating to the Institute and Italy are found amongst biographical information, and in files about the many Italian societies and associations of which Chain became a member or fellow.

The general correspondence section includes letters from his many Italian colleagues and staff of the Institute including Antonio Ciccarone, Italo Domenicucci, Pietro Mascherpa, Francesco Pocchiari, and Emilio Trabucchi. Also to be found here are 4 files of correspondence with and about Domenico Marotta, dating between 1954 and 1967.<sup>14</sup> Two of these files contain correspondence about arrangements for Marotta's visit to the UK in 1955. Chain and Marotta gave an account of the work of the Institute at a meeting at the Royal Society during that visit. There is correspondence with the British Ambassador in Rome about a lunch to celebrate the award of the C.B.E. (Commander of the British Empire) to Marotta in 1958, and a further file of letters from the Marotta family to Chain 1964-70, with press cuttings about the Marotta trial.

<sup>9</sup> See Chain's correspondence with the Istituto, January to April 1948, CMAC/PP/EBC/G4.

<sup>10</sup> CMAC/PP/EBC/C30.

<sup>11</sup> CMAC/PP/EBC/C77.

<sup>12</sup> undated manuscript, CMAC/PP/EBC/C12.

<sup>13</sup> CMAC/PP/EBC/C93.

<sup>14</sup> CMAC/PP/EBC/K146-149.



ISTITUTO SUPERIORE DI SANITÀ

THE AMERICAN CHEMICAL SOCIETY  
Fermentation Subdivision

SOCIETÀ CHIMICA ITALIANA  
Roma

1<sup>st</sup> International Fermentation Symposium  
Primo Symposium Internazionale sulle Fermentazioni



*Roma 9 - 14 Maggio 1960*

Fig. 5. Cover for Symposium meeting at Istituto 1960, C/MAC/PP/EBC/C101.

Chain referred to this trial as 'a monstrous affair'.<sup>15</sup> He became personally involved when he himself was accused of 'oltraggio' (contempt of the judiciary) by the public prosecutor. In an unpublished letter to *The Times* in August 1965 Chain wrote that it was a 'dismal, sordid and often grotesque spectacle of the free-for-all fight between the judiciary and the administrative and legislative authorities which dominates the present day Italian scene and which has led to a state of indescribable chaos, and in some cases to the complete paralysis of the Italian State legislation'.<sup>16</sup>

The 9 files of papers on the case in the archive include correspondence (and draft letters by Chain), with friends, colleagues and layers, press cuttings and legal depositions. Chain was prepared to give evidence and go to court to defend his own position, and one almost gets the impression that he would have relished the fight. In a letter to Professor Dentice di Accadia he writes: 'I am not at all certain whether the Italian authorities will take positive actions with regard to starting the law suit, and, to be frank, I really do not care whether they do or don't — the whole thing is just too ridiculous for words. If it comes to a public hearing I should certainly enjoy making mincemeat of Ricciardi [the public prosecutor]'.<sup>17</sup> Back in May 1965, an article in *L'Espresso*<sup>18</sup> alleged irregularities in the financing and patenting of Chain's research and led to correspondence with solicitors and draft statements for the withdrawal of the statement. In May 1965, following official charges, Chain had some correspondence with Domenicucci who urged him to write to the President of the Tribunal. At that time Chain refused, in a carefully worded letter,<sup>19</sup> when he said that whilst he supported Domenicucci he has to be careful not to do anything which might cause more harm to the various participants. Subsequently, in June, Chain in fact sent a telegram to the Prosecuting Counsel and others, protesting at the libellous allegations made against him personally, which led to further accusations against Chain. All this is well documented in the files.<sup>20</sup>

Chain's threat to take legal action himself developed into a farce when the public prosecutor's office passed the papers to a lower court at Velletri which did nothing but claimed that it did not have Chain's address to service the papers to him. Charges against Chain were eventually dropped under an amnesty in May 1966.

It is clear that Chain felt very strongly about what happened to Marotta, not only because of his personal regard and friendship with him, but because he felt it damaged Italy and the scientific community and contacts he had worked so hard to

<sup>15</sup> 'A monstrous affair for Italian Science' *New Scientist*, 29 July 1965, p. 254, CMAC/PP/EBC/C22.

<sup>16</sup> Chain's unpublished letter to *The Times*, August 1965, CMAC/PP/EBC/C24.

<sup>17</sup> Chain to Prof Dentice di Accadia, 30 December 1965, CMAC/PP/EBC/C26.

<sup>18</sup> CMAC/PP/EBC/C15.

<sup>19</sup> Chain to Domenicucci, 21 May 1965, CMAC/PP/EBC/C18.

<sup>20</sup> CMAC/PP/EBC/C.19 Telegram June 1965 and letters of support from Professors G. Giulianini, G. Serlupi, and G. Szemzenti to newspapers, 6 November 1965, C.25.

*Copia*

Roma, 6 novembre 1965

Al Direttore de "IL TEMPO"  
"IL MESSAGGERO"  
"IL CORRIERE DELLA SERA"  
"LA STAMPA"

Egregio Signor Direttore,

La stampa italiana ha riportato all'onore delle cronache il Prof. S.M.Chain Premio Nobel 1945, contro il quale è in corso una istruttoria per aver egli replicato con un telegramma giudicato offensivo ad alcune affermazioni del Pubblico Ministero del "processo della Sanità" che l'aveva dipinto come un "scoc d'affari".

Per una valutazione più equilibrata delle vertè, sembra opportuno e noi, che col Prof.Chain abbiamo collaborato per oltre un decennio, ricordare che la scoperta della penicillina non solo ha dato alla medicina un farmaco che ha salvato innumerevoli vite (il cui valore anche puramente economico è incalcolabile), ma ha dato l'avvio allo sviluppo di una colossale industria nuova: quella degli antibiotici; ha prodotto in tutto il mondo un nuovo monte d'affari di miliardi di dollari e, in Italia in particolare, ha contribuito non poco al "miracolo economico".

Da tutto questo il Prof.Chain, a differenza di alcuni scopritori di successivi antibiotici, non ha tratto alcun profitto personale, non avendo egli protetto la penicillina con alcun brevetto.

Si auguriamo che la completa e serena valutazione di questi elementi di fatto permetta di riconfermare a Chain le riconoscenze dovutagli da tutta l'umanità.

Prof. G. Gianini  
Prof. G. Serlupi  
Prof. G. Sernoni

Prof. G. Sernoni  
ROMA, Via Tuscolana n.12  
Telefono 4247190

Fig. 6. Copy of letter of support for Chain, sent to newspapers, 6 November 1965. CMAC/PP/EBC/C25.

# ITALIAN SCIENTISTS IN DISARRAY

From Our Own Correspondent—ROME

In the depression that follows a sudden shock, a number of leading scientists are convinced that research of real value is seriously threatened, if not doomed, in Italy. Whether or not their ears are justified, their lament sounds through the field of some of Italy's most respected institutions.

abandoning research... The point is that administrative reform is one of the urgent necessities about which much has been said for years and nothing done; and it would take a courageous man now to think of stretching the law to further the cause of research.

A second point, possibly of greater importance in its final effect, is the fragile character of imposing institutions. The Institute of Health had an international

Fig. 7. Newspaper report, *The Times*, 1 May 1964, CMAC/PP/EBC/A233.

build up during his time in Rome. Chain made as much noise about the whole business as he could, writing to colleagues internationally and to the press. He drafted a letter to *The Times* which they used in a leading article on 24 August 1965 headed 'The Extent of Corruption in Italy'.<sup>21</sup> Certainly Italy did not get a 'good press'.<sup>22</sup> Chain was critical of academic colleagues who did not speak out, but his harshest words were for those indulging in political squabbling without concern for the consequences: 'It will take many years before Italy recovers from the blows inflicted on it, not by foreign forces, but by irresponsible groups of its own people, who put their own petty jealousies and ambitions before the national interest, and unfortunately the love of 'scandals' of the Italian press and large sections of the population have favoured their activities. It is a very sad state of affairs and I am far from optimistic as far as the political future of the country is concerned'.<sup>23</sup>

From Chain's first contact with Marotta in 1947 friendship and respect were

<sup>21</sup> Leading article in *The Times*, 24 August 1965, CMAC/PP/EBC/G24.

<sup>22</sup> See for example article 'Italian Scientists in Disarray' *The Times*, 1 May 1964, CMAC/PP/EBC/A233.

<sup>23</sup> Letter, Chain to Prof Giacomello, 22 Feb 1966, CMAC/PP/EBC/C.26.

always there. Chain later wrote of their first meeting that he 'gained an excellent personal impression of Professor Marotta, who struck me from the beginning as an exceptionally able, dynamic, energetic and broad minded administrator, and ... a man in whose words one could trust. I also had very favourable reports on Professor Marotta's personality from Dr and Mrs Bovet whom I had known for almost 15 years and in whose judgement I trusted'. Chain went on to praise Marotta for his 'unequalled talent to organise symposia and congresses in a way which was not only interesting from the professional point of view, but at the same time appealing as a tourist attraction'. He went on to say: 'Professor Marotta undoubtedly made clever and conscious use of the unparalleled treasures of art and historical monuments which Italy possesses to attract scientists to his country, but these attempts to link Italy again to the mainstream of international scientific research would have failed, could he not have demonstrated to his scientific visitors that there was a hard core of scientific achievements worth becoming acquainted with'.<sup>24</sup>

It seems very appropriate therefore that I can end with a note of thanks to the organisers and to Professor Marotta, (since this meeting is held in his honour), that I too have been able to come to this Institute and will be able to enjoy some of Italy's treasures.

<sup>24</sup> Deleted passage in draft paper by Chain on Marotta, CMA/PP/EEC/C24.