Ernst Chain and Paul Garrod

The lives of two men with international reputations in the field of antimicrobial chemotherapy came to an end, within a month of each other, in 1979. Ernst Boris Chain died on 12 August, aged 73, and Lawrence Paul Garrod on 11 September at the age of 83. They could scarcely have been more different; their interests in chemotherapy and their happy marriages were almost all they had in common, apart from a love of music: Chain was an amateur pianist of distinction; Garrod played the violin.

Chain was born of Jewish parents in Berlin and emigrated to England from Hitler's Germany after graduating in chemistry and physiology at the Fredrich-Wilhelm University. He obtained a Ph.D. in 1935 for work in Sir Frederick Gowland Hopkins' Department at Cambridge and was then offered a position in the Sir William Dunn School of Pathology by Howard Walter Florey (later Lord Florey) who had just been elected to the Chair of Pathology in Oxford. Paul Garrod was born into a Congregationalist family, educated at Sidcot—a Quaker school—Kings' College Cambridge, and St. Bartholomew's Hospital. In later life he became a Roman Catholic. He qualified in medicine in 1920, and studied clinical medicine for the following five years; but then, like Paul Fildes before him, he decided to become a bacteriologist and devote himself to laboratory medicine.

In Oxford, Florey suggested to Chain that he should study the mode of action of lysozyme. This led to many discussions between them on other naturally occurring antibacterial substances and to a decision to make these substances the subject of a systematic investigation. They were motivated more by scientific curiosity than by the hope of finding substances of clinical value. But a consequence of the decision was the purification of Fleming's penicillin by a small group in Oxford and the discovery of what then seemed to be its almost miraculous power to save patients from systemic infections that were expected to be fatal. Chain's great achievement, for which he shared a Nobel Prize in Medicine with Fleming and Florey, lay in the part he played in the initiation of the project and his enthusiasm for it once it had got under way.

Years later, when he was Scientific Director of the International Research Centre for Chemical Microbiology in Rome, Chain advised the Beecham Group to look for new forms of penicillin rather than for entirely new antibiotics. This advice was taken and led Beecham to the isolation of 6-aminopenicillanic acid and the production of new penicillins.

Garrod's contributions to chemotherapy were of a different kind. His training in clinical medicine kept his thoughts close to the patient. His high reputation came partly from the quality of his advice on the use of chemotherapeutic substances and the integrity of his judgements on their value and limitations. But his opinions had a solid basis, provided by meticulous experimental work in the laboratory. His early studies on antiseptics and disinfection were followed by assessments of the therapeutic properties of the sulphonamides. Later, after the advent of penicillin, he devoted special attention to the treatment of subacute bacterial endocarditis and published many valuable papers on antibiotics with Pamela Waterworth. His authoritative and critical views found expression in Antibiotic and Chemotherapy, written first in collaboration with Mary Barber and later with Harold Lambert and Francis O'Grady, which provided the clinician with information needed for the rational use of the many antibiotics becoming available; and his advice on questions relating to antibiotics and antibiotic resistance was often sought by the World Health Organization.

No one who knew Ernst Chain and Paul Garrod will ever forget either of them—the one colourful, bubbling with eloquent enthusiasms for his own views and equally critical of policies with which he disagreed, the other with more reserve, but with warmth behind a sometimes forbidding manner and
with a clarity and honesty of expression that
demanded respect. Both men knew a time
when the effective use of chemotherapy in
systemic bacterial infections was no more
than a forlorn hope. But within two decades
the outlook had entirely changed. Within this
time Chain played a major role in one of the
most dramatic discoveries in the history of
medicine; and Garrod had begun a series of
studies to help his clinical colleagues make
wise use of penicillin and its successors.

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Bacteriocins—are they broad-spectrum anti-
biotics?

Bacteriocins, bacterial proteinaceous prod-
ucts, are ubiquitous in nature being pro-
duced by a variety of Gram-negative and
Gram-positive bacteria (Konisky, 1978). The
bacteriocins have been considered as antibi-
otics with a narrow bacterial-host range of
activity, which depends on their accessibility
to suitable surface receptors on the sensitive
bacteria (Fredericq, 1946). Indeed, the bac-
teriocins recognize subtle differences in the
receptors of sensitive bacteria such that they
serve as a valuable tool for epidemiologi-
cal studies, differentiating between bac-
terial types within a given species (Farmer,
1972; Jones et al., 1974; Farkas-Himsley, &
Pagel, 1977). The absence of receptors on the
bacterial surface results in bacteriocin resis-
tance (Maeda & Nomura, 1966). Conversely,
bacteria exist with suitable receptors for bac-
teriocin absorption, while nevertheless
remaining refractile to its action (tolerant
strains); these strains contain a highly specific
immunity protein which neutralizes the bac-
teriocin (Sidakaro & Nomura, 1975). There-
fore, the accessibility of the outer-membrane
receptors can not be the only determinant for
the successful activity of a bacteriocin.

The definition for bacteriocins as being
narrow-host range antibiotics needs to be
reconsidered as more information becomes
available about their mode of action. Indeed,
the specificity of bacteriocin-receptor inter-
action in Gram-negative bacteria disappears,
upon removal of the cell wall outer-
membrane. Thus, in bacterial L-forms,
derived from Proteus mirabilis (Smarda &
Taubeneck, 1968) or Escherichia coli
(Schumann & Taubeneck, 1969), the inter-
action with the bacteriocin was not abol-
ished, but rather the sensitivity was en-
hanced. It was also shown by Bhattacharyya
et al., (1970), that upon removal of the outer-
membrane of a resistant strain, bacteriocins
interacted with the inner-membrane and thus
inhibited cell metabolism. These results indi-
cated that the outer-membrane receptors
were not prerequisite for bacteriocin killing,
and that the bacteriocin can interact with
suitable receptors on the inner-membrane
provided they are accessible (Smarda, 1977;
Smarda & Schumann, 1977). Recently,
Watson & Sherratt (1979) substantiated the
effective and reproducible interaction of
bacteriocins with inner-membrane vesicles,
while confirming the specificity of interaction
conferred by the receptors of the inner-
membrane vesicles. Furthermore, the direct
interaction of the bacteriocin with its target
(upon removal of the immunity protein from
the bacteriocin) appears to lack any specifici-
ity. This was shown for colicin E₃, which
degraded cell-free DNA preparations from
bacteria and both single-stranded and
double-stranded viral DNA, as well as
eukaryotic DNA (Schaller and Nomura,
1976). Thus, under these conditions the
bacteriocin assumes broad-spectrum activity.

From the foregoing, it may not be surpris-
ing that even eukaryotic cells, which do not
possess a cell wall are found to be targets for
bacteriocin action. Thus, the polypeptide
antibiotic neocarzinostatin, produced by
Streptomyces carzinostaticus, was shown to
inhibit both bacteria and various mouse
ascites tumor cells (Kunimoto, Hori &
Umezawa, 1972). According to Konisky
(1978) neocarzinostatin is to be regarded as a
bacteriocin. Following this observation we
tested the bacteriocin vibriocin, (Farkas-
Himsley & Seyfried, 1962), against mammal-
ian cells (Farkas-Himsley, 1974). The mode
of action of vibriocin had been extensively
studied (Jayawardene & Farkas-Himsley,
1969, 1970; Krol & Farkas-Himsley, 1971a,
1971b, 1972). It was found to resemble
the mode of action of neocarzinostatin
(Kunimoto, Hori, & Umezawa, 1972), and
colicin E₃ (Nomura, 1963; Ringrose, 1973),
in that vibriocin inhibited DNA synthesis
and promoted its degradation causing leakage
of nucleotides from the cells (Jayawardene &
Farkas-Himsley, 1970; Krol & Farkas-
Himsley, 1970). However, the mode of action
of vibriocin also resembled that of colicin E₃,
causining changes in the membrane permea-
bility which thus enhanced K⁺ efflux
(Jayawardene & Farkas-Himsley, 1970) and