Harry Raymond Ing, 31 July - 23 September 1974

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RAYMOND ING was a pioneer in establishing the subject of pharmacological chemistry, or as he preferred to call it chemical pharmacology, in Great Britain. Harry Raymond Ing was born at Alford, Lincolnshire, on 31 July 1899. His father and mother were both of Herefordshire stock. His father was orphaned at an early age and became a solicitor's clerk, which he remained all his life. Raymond remembers him as an easy-going friendly person without ambition. His mother, in spite of much ill health, was an intensely active and ambitious person who dominated her husband and three sons and in spite of her husband’s limited situation always encouraged her children to think that they could make their mark in the world. Ing married in 1941 Catherine Mills Francis, an English scholar who subsequently became a university lecturer in English at Oxford. He and his wife had in common a profound interest in the meaning of words and structure of language.

Ing’s education and career were closely bound up with Oxford. At 12 years old he won a scholarship to Oxford High School, a small grammar school which had as its main objective the training of boys for admission to Oxford University. The main subjects taught were Latin, English grammar and mathematics; Ing was especially grateful for the thorough training he received in Latin. He also owed a great deal to his science master who first aroused his interest in natural science and taught him to enjoy experimental work. During the last year at school a Fellow of New College, A. F. Walden, took three of the boys and gave them, at no charge, regular tutorials in physical chemistry. Walden later became Ing’s tutor at New College. Ing had tremendous admiration for Walden, recalling how he went away from his tutorials so excited about chemistry that frequently he did not get to bed until long after midnight.

In 1916 Ing won an exhibition at New College where he came into residence in January 1917. After an interruption due to the war (he worked in the postal censorship department), he rejoined New College, working for the final honours school in chemistry. He obtained a First in part II in 1921, then began to work
with W. H. Perkin, jun. for the D.Phil. At the same time he was charged with the teaching of chemistry at Wadham College, Oxford. The combination of teaching chemistry to undergraduates and doing research work suited Ing and he could have happily continued in this way, but had to stop after completing his thesis since no fellowship of an Oxford College became available to him. So in 1926 Ing went to work with Robert Robinson at Manchester and afterwards as a chemist to the Manchester Committee on Cancer. He was dissatisfied with this work and in 1929 he obtained a post at University College London as Lecturer in Pharmacological Chemistry. In 1937 he was made the first Reader in the subject.

Ing thus became the first chemist to hold a senior appointment in a university department of pharmacology in Great Britain. This was a notable new turn in pharmacology for which, according to Ing, credit must be given to the Rockefeller Foundation, which not only funded the first pharmacology department in Great Britain at University College London but also provided a special endowment for the employment of a chemist in the department.

Ing was left a free hand in his new employment and had to decide for himself what line to take. He rejected the idea that the post merely provided an opportunity of doing research in organic chemistry. For a while he turned his hand to alkaloid chemistry but in the end decided that as a chemical pharmacologist his central problem was to investigate the structure-action relations of drugs.

Ing was happy at University College London and considered his years there to have been 'a flowering period, full of intellectual excitement and warm friendships'. He established links with many departments and was a founder of the Natural Sciences Club, a dining club in which members of different scientific departments met and discussed their work. Among his friends there were chemists such as Donnan, physiologists and anatomists such as Lovatt Evans, A. V. Hill and Elliott Smith and, in the Medical School, Thomas Lewis and Wilfred Trotter. His particular friends in the Arts Faculty were J. E. Neale whose book on Queen Elizabeth I he greatly admired and R. W. Chambers whose acute mind, caustic tongue and profound learning fascinated him.

When J. H. Gaddum succeeded E. B. Verney in the chair of pharmacology he persuaded the Rockefeller Foundation to offer Ing a fellowship. He spent the year 1938–39 in Max Bergmann’s laboratory in the Rockefeller Institute in New York and found Bergmann to be not only an outstanding organic chemist but a very sympathetic person with whom it was easy to talk about 'the shadow which lay over the whole world in 1939 as a result of Hitler’s fanatical ambitions'.

When he returned from New York in 1939 the war had started and Ing moved to Oxford where he joined a chemical research group. He was later asked by Professor J. H. Burn to join the Department of Pharmacology. Ing was sorry to give up his post in London but the attraction of Oxford proved irresistible to him which is not perhaps surprising since he so clearly belonged
to Oxford. A New Zealand colleague said that Raymond Ing came closer to his conception of an Oxford don than anyone else he had met, and to illustrate his sense of humour he related how Ing asked him a day or two after his arrival what he had done over the weekend. When he mentioned that he had gone on a bike ride which had included the Marston Ferry Road Ing promptly told him that his tutor used to refer to this as the Fast-and-Merry Road. He then asked Ing if this was the celebrated Dr Spooner and was surprised to be told that it was.

During the Oxford period Ing, besides pursuing his research work on acetylcholine, made two general contributions which had great impact: a lecture course on chemical pharmacology and the Press Editorship of the *British Journal of Pharmacology*.

The course in chemical pharmacology for students in chemistry was started in 1945 at the Department of Pharmacology, Oxford. This was an optional supplement to the honours chemistry course which consisted of a series of thirty-two lectures and a practical class under the supervision of the pharmacology department. It was the first course of its kind in this country. Ing himself gave all the lectures which were noted for their accuracy. R. B. Barlow’s book: *Introduction to chemical pharmacology* was an outcome of these lectures. In 1946 the *British Journal of Pharmacology and Chemotherapy* was founded and Ing became its first Press Editor. He spent seven years editing the new journal and worked extremely hard at it.

**Pharmacology and chemistry**

In unpublished notes which Ing left behind he explains his belief that ‘Pharmacology, although it employs mainly physiological methods of investigation, is essentially a biochemical subject, since the action of drugs can only be ultimately explained in chemical terms. However, pharmacologists in this country have been mainly physiologists in disguise; in some sort poor relations of practitioners of a more fundamental subject. Only A. J. Clark, in my lifetime, saw clearly that pharmacology could become a subject in its own right, separate from physiology and essentially chemical in its approach to drug action. Pharmaceutical industry has for many years realized the importance of the chemist in the discovery of new remedies for disease, but university departments of pharmacology, simply because their function was the teaching of medical students, have been slow to realize the importance of having senior chemists on their staff.

‘It is true that university departments cannot afford a team of chemists or a group of technicians engaged in screening new compounds, as has been the practice of pharmaceutical industry. At the same time, I feel that every university department of pharmacology ought to employ a senior chemist who is willing to devote his special knowledge to the fundamental problems of drug action.’
Dr A. M. Richards, a G.P. who looked after Raymond Ing during his later years, provides the following recollections:

'I knew Raymond Ing as a patient only. He was short and lightly built with a receding forehead. He wore glasses with lenses limited to the lower halves, and it was his custom to look at you over the top of them. His speech was slow, carefully articulated and a little hesitant, but it failed to conceal the acuteness of the mind that lay behind. He never drove a car, a circumstance that may explain his excellence as a walker well into old age. Many of his summer holidays in later years were spent walking at La Grave in the Dauphiné Alps. After his retirement, while his wife was still busily engaged in teaching English, he was a familiar sight walking down the Banbury Road to the shops with a rucksack on his back.

'In July, when his wife was immersed in the correction of examination papers, Raymond was delighted to lend her a hand in correcting the papers on the "Uses of English", helped no doubt by his own knowledge of English literature, which was considerable.'

**Pharmacological work**

*Curariform action of onium salts*

Ing joined the Pharmacology Department of University College London in 1926 as Lecturer in Pharmacological Chemistry under Professor E. B. Verney. He had no previous training in pharmacology or physiology and 'had no idea what the chemist had to contribute to pharmacology'. This he had to find out by himself, and he was grateful to his chief for allowing him to find his way about the subject.

He turned first to structural chemistry of alkaloids, particularly two alkaloids, cytisine and anagyrine; but in the long run he had neither the resources nor the inclination to continue working in the highly competitive field of alkaloid chemistry. He decided to tackle the subject of structure–action relationships of drugs and thought that he should confine himself in the first instance to the simplest structures. He began an investigation of the curariform action of onium salts publishing two papers on this subject (with Winifred Wright) in *Proceedings of the Royal Society B* and a review in *Physiological reviews*.

Crum Brown and Fraser had shown as early as 1869 that quaternary ammonium salts, such as tetramethylammonium chloride and the metho salts of various alkaloids, had the property in common of producing a curare-like neuromuscular block in striped muscle. Boehm concluded in 1910 that the curariform property of quaternary ammonium salts was largely independent of the nature of the radicles attached to nitrogen. Ing and Wright worked on the isolated nerve-sartorius preparation of frog immersed in Ringer's solution, stimulated through the motor nerve by condenser discharges. Their
work supported Boehm's generalization, with the notable exception of compounds containing ethyl groups such as triethylmethyl and tetracetyl ammonium, which in the frog produced a neuromuscular block which was different in kind from that produced by tetramethylammonium.

They investigated the contracture-producing effect of quaternary ammonium salts in frog muscle and the effect of substituting the central nitrogen atom in the charged group by phosphorus, arsenic or sulphur.

The order of contracture activity was

$$\text{Me}_4\text{N} > \text{Me}_5\text{S} > \text{Me}_4\text{P} > \text{Me}_4\text{As}$$

In the course of this research Ing's views seemed to undergo a gradual change, away from a strictly physico-chemical orientation towards a more pharmacological and biological outlook. In earlier papers the authors try to associate curariform activity with some physico-chemical characteristic such as molecular size or ionization; for example, proposing that curariform action may be associated with ionic character and not with chemical structure. In the 1936 review, however, Ing adopts a viewpoint based on the neurohumoral theory arguing as follows: 'Since the active alkaloid of curare is a quaternary ammonium salt, it is reasonable to expect that the curariform action of onium salts in general will depend on an antagonism to the chemical transmitter liberated at the nerve endings. Acetylcholine is itself an onium cation and this fact may account for the peculiar effectiveness of foreign onium cations in blocking the action of the chemical transmitter'.

**Atropine substitutes**

Ing's work on atropine substitutes arose from the wartime need to develop a synthetic mydriatic which might be used in place of atropine if supplies of the latter became inadequate. It seemed too difficult to produce synthetic atropine while its semisynthetic substitute, homatropine, depended on the same sources of supply as atropine itself. It was decided, therefore, to develop a fully synthetic atropine substitute which could be readily manufactured. Ing started this work at the beginning of the war at the Dyson Perrins Laboratory, Oxford, where he joined a group which Sir Robert Robinson was directing for the Ministry of Supply. He then transferred to the Department of Pharmacology on being appointed Reader in Pharmacological Chemistry under Professor J. H. Burn. Ing's title was later changed to Reader in Chemical Pharmacology at his own suggestion. In the pharmacology department he was able to work in close collaboration with pharmacologists who tested his compounds and with whom he could daily discuss problems of chemical constitution and pharmacological action in which both sides were interested.

By moving to Burn's department Ing joined what was at the time undoubtedly the most active pharmacology group in the country. Two eminent refugee scientists, Edith Bülbíng and Hermann Blaschko, had found a permanent home there and Burn himself seemed determined to make his Oxford department the principal training ground for the then sadly neglected subject of
pharmacology. He encouraged promising postgraduates to work there, among them Geoffrey Dawes, R. P. Stephenson and a host of others, instructing them in the methods he knew and trying to instil into them his own high standards of technique. At the same time Edith Bulbring and others in the department kept on developing new methods many of which have since become standard pharmacological practice. The background thinking of the department was based on biological standardization on which Burn had written an important book. Their outlook was quantitative, based on dose–response curves but it was not perhaps fully realized at the beginning that whilst the dose–response curve approach is entirely appropriate for biological standardization it may be less appropriate and even meet serious difficulties when the aim is a comparison of activity of different synthetic substances. The work by Ing and his colleagues on atropine substitutes was an early illustration of the difficulties encountered.

The work on atropine was based on the neurohumoral theory of Loewi and Dale which by then was generally accepted. It took into account Dale’s distinction of two different sites, muscarinic and nicotinic, at which acetylcholine exerts a transmitter function, atropine being the typical acetylcholine antagonist at muscarinic sites. Although the word receptor does not occur in their atropine paper, Ing was certainly aware of the current idea that acetylcholine and atropine compete for muscarinic receptors and it is therefore not surprising that he should have turned to the acetylcholine molecule itself in search of a structurally related antagonist. All the atropine substitutes which he synthesized were structurally closely related to acetylcholine. Lachesine (from the Fate Lachesis, Atropos’s sister), his final choice as a synthetic mydriatic, was a benzilic ester of an ethyl-substituted choline.

The work by Ing, Dawes and Wajda on atropine substitutes is of interest as an exercise in bioassay and biological measurement as well as in structure–activity relations. Using a simple quantitative method of measuring pupil diameter in mice, they found it impossible to express the activity of their synthetic mydriatics relative to atropine by a single activity ratio, since both the dose–response relations and duration of action varied with different compounds. Only approximate activity ratios could be stated and it is a merit of their paper to have drawn attention to this fundamental difficulty which applies in some degree to all structure–activity work. Their conclusions with regard to structural requirements for atropine-like activity were (1) confirmation of Jowett and Pyman’s view that the esterifying acid must contain both an aromatic nucleus and an alcoholic hydroxyl group for high activity; (2) in their series the ethyl dimethylammonium derivative had strongest atropine-like activity; (3) that quaternary compounds are intrinsically more active than tertiary compounds, although the latter may in some cases appear to be more active due to better absorption. Their main conclusion, which has remained undisputed, was that atropine-like activity, like curare-like activity, resides in the cation, not the free base. Their finding that substances which are structurally closely related to acetylcholine may be powerful antagonists of acetylcholine.
is of general pharmacological interest in providing support for the view of structurally specific receptor sites with which agonists and antagonists interact.

**Neuromuscular block by decamethonium**

The discovery that decamethonium, a straight-chain bisquaternary polymethylene derivative of chain length 10, had powerful neuromuscular-blocking activity was made simultaneously by Barlow and Ing at Oxford and by Paton and Zaimis working independently at the National Institute for Medical Research, Mill Hill. For a time decamethonium became an important clinical drug, eventually superseded by suxamethonium, but Ing took no part in the subsequent theoretical studies or practical applications of decamethonium with which W. D. M. Paton and Eleanor Zaimis were particularly concerned.

Ing’s work in this field arose from King’s studies on the structure of tubocurarine and his conclusion that it contained two quaternary ammonium groups. (This has since been disputed, and present evidence indicates that tubocurarine contains only a single quaternary group.) It occurred to Ing that the powerful curare-like activity of tubocurarine, much stronger than the simple quaternaries he had previously studied, might be due to the presence of two quaternary groups at some optimal distance apart in the same molecule and he consequently began to study various bisquaternary series of different chain length which might provide a two-point receptor attachment. With his colleague Barlow he investigated simple polymethylene bisquaternaries. He realized that in contrast to the relatively rigid tubocurarine molecule they would be flexible molecules whose intercationic distances in solution varied according to probabilities which could perhaps be calculated from thermodynamic considerations. (His colleague E. W. Gill later made such calculations.) Since inter-receptor distances in the tissue were also unlikely to be rigidly fixed, a sharp endpoint of curare-like activity in any one homologous series could hardly be expected to occur.

When simple straight-chain bisquaternaries were tested at Oxford for neuromuscular-blocking activity, the most consistent results were obtained (by N. K. Dutta) with the rabbit head-drop method. In this test the polymethylene bistrimethylammonium compound with $n = 10$ was three times as active as tubocurarine, whereas the corresponding compounds with $n = 9$ and $n = 11$ were considerably less active. Ing concluded that these results had vindicated the theory of double attachment to receptors. He interpreted the high activity of bisquaternaries by the low probability of their simultaneous dissociation from both receptors and the high probability of reassociation after detachment from one receptor provided that the drug molecule remained attached at the other end.

**Chemical pharmacology of acetylcholine**

Ing had a special interest in acetylcholine (Ach). He knew of its key rôle in neurohumoral transmission and as a chemical pharmacologist tried to discover
which features of the Ach molecule were responsible for its 'autopharmaco-
logical' activity. Much of the work of Ing and his associates during the Oxford
period was concerned with this problem. He investigated both muscarinic and
nicotinic effects of acetylcholine but his most productive work (with Pamela
Holton) concerned interactions with muscarinic receptors responsible for the
parasympathomimetic effects of Ach.

Ing concluded that two features of the Ach molecule were responsible for
its muscarinic activity, (1) the nature and size of the 'cationic head' of the
molecule, (2) the nature and length of the side-chain attached to it. He con­
sidered that:

(1) In any series having muscarinic activity the member containing $\text{--NMe}_3^+$
as its cationic head was invariably the most active. This is shown for Ach itself
by the following results extracted from Holton and Ing's (1949) paper:

<table>
<thead>
<tr>
<th>Equipotent molar ratios of Ach analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>cat's blood pressure fall</td>
</tr>
<tr>
<td>$\text{--NMe}_3$ (Ach)</td>
</tr>
<tr>
<td>$\text{--NMe}_2\text{Et}$</td>
</tr>
<tr>
<td>$\text{--NMeEt}_2$</td>
</tr>
<tr>
<td>$\text{--NEt}_3$</td>
</tr>
</tbody>
</table>

Successive replacement of methyl by ethyl produced a progressive fall in
muscarinic activity in all the tests. Replacement of one methyl by ethyl had
a relatively small effect but replacement of two or three methyl groups by
ethyl caused a profound decline suggesting that two of the methyl groups
played an essential part in the structural specificity of the Ach molecule. Ing
considered that replacement of one methyl group by ethyl would reduce the
probability of the correct orientation for attachment but did not make it im­
possible, as the replacement of two methyl groups by ethyl would do. He thought
that the form of attachment which he envisaged—by means of short range
atomic forces—implied a high degree of fit between the drug molecule and
the site of action.

(2) If muscarinic drugs of the general type $\text{R--NMe}_3$ are considered, the
most active member of any group of homologues is usually the one containing
a 5-atom chain (excluding hydrogen atoms) in the group $\text{R}$. Thus, acetyl-
choline is more active than either formyl- or propionylcholine. The same
applies to other series of substances with muscarinic activities. Ing's '5-atom
rule' had a purely empirical basis (it is usually, though not invariably, obeyed)
but it involved the interesting new notion that spatial factors played an im­
portant part in determining the intensity of muscarinic effects.
General views on chemical pharmacology

Views on drug receptors

The Faraday Society held a general discussion on 'Modes of drug action' in September 1943 at which drug receptors were discussed. It was the first public discussion of drug receptors since the death of A. J. Clark who originated the modern phase of receptor theory. It is interesting to compare Ing's views on drug receptors, as expressed at that meeting, with the views of Sir Henry Dale who opened the discussion. Dale was sceptical of the value of the receptor concept expressing his viewpoint as follows: 'It is a mere statement of fact to say that the action of adrenaline picks out certain effector cells and leaves others unaffected; it is a simple deduction that the affected cells have a special affinity of some kind for adrenaline; but I doubt whether the attribution to such cells of "adrenaline receptors" does more than re-state this deduction in another form.' Ing's views were much more positive as the following quotation from his address show:

'The receptor theory provides an intellectual link, otherwise missing, between the diverse concepts of structure and action; ideally the relation to be thought is one between structure of the drug and receptor molecules. The first general principle . . . that similarity of chemical structure in drugs may be expected to involve combination with the same receptors.' [Receptor theory] 'is the only satisfactory means of accounting for the antagonism of structurally similar drugs.'

But he remains cautious, saying:

'The receptor theory only pushes the problem of drug action a stage further back, since it provides no explanation of the physiological efficacy of the drug-receptor combination.' [Receptor theory] 'is less useful for the consideration of the quantitative aspects of the subject because "ease of combination with receptors" is too vague a concept.'

Ing retained a positive, though cautious, attitude towards the drug receptor idea through his working life. It could be argued, retrospectively, that he remained excessively cautious towards Gaddum's quantitative receptor theory which has proved to be of great heuristic value in the development of new drugs.

Relationship between chemical structure and pharmacological action

Structure–action relations were Ing's main concern, towards which his experimental work and theoretical writings were primarily directed. He refers to A. J. Clark's 'almost despairing' statement that 'scarcely any general rules are discernible and every drug–cell system appears to be a law unto itself' but thinks that this state of affairs may be due to our reliance on mere empirical measurements. While the pursuit of empirical structure–action relations was inevitable at present, the empirical approach was needed simply because of our ignorance of the underlying mechanism. He believed that an understanding of structure–action relations required the discovery of the structural features
which determine the mechanism of action of drugs and that the fundamental presupposition of the chemist, that there must be a rational interpretation of structure–action relations, will be justified when we can interpret drug action in terms of a chemical interaction between the drug and particular molecular species in living tissues.

He wants pharmacologists to go beyond the stage of crude phenomenological description. He writes: 'It is clear to me that the chemist is helpless unless the pharmacologist is prepared to pursue his analysis of drug action by every means at his disposal. It is necessary to push the pharmacological analysis to the point at which the physiological, or better the biochemical, mechanism with which the drug is interfering can be identified. Structure–action relations, therefore, require the discovery of the structural features which determine the mechanism of action.'

As an illustration of the difficulty which the chemist encounters when studying structure–action relations he quotes the classical work on sympathomimetic amines by Barger and Dale who included in the same sympathomimetic group adrenaline and α-phenylethylamine which is one hundredth as active. The chemist finds this difficult to understand if it is assumed that the two substances act in the same way, because high potency suggests a corresponding high degree of specificity in the drug–cell interaction whereas low activity suggests that the structural features required to elicit the response are not highly specific. Why, he asks, if they act in the same way, should a purely basic compound like α-phenylethylamine produce the same kind of physiological response as the amphoteric compound, adrenaline? Ing concludes that the two compounds probably act differently, the one directly, the other, as suggested by Burn and Rand, indirectly by liberating noradrenaline from local stores.

**Homologous series**

Ing was fascinated by homologous series and frequently lectured and wrote on the subject, the last in a 32 page article on the Pharmacology of homologous series, published in *Fortschritte der Arzneimittelforschung* in 1964. He thought that a study of homologous series might lead not only to the discovery of highly active drugs but that it would reveal mechanisms of drug action which could not be revealed by a study of drugs differing more fundamentally in structure.

He distinguished five main types of pharmacological change in homologous series:

1. Activity increases regularly as a series is ascended up to one member beyond which higher members are almost, or entirely, inactive.
2. Activity increases irregularly as the series is ascended, reaches a maximum value for one or two members and then decreases again irregularly.
3. Activity increases as the series is ascended and then remains more or less constant.
4. An alternation of activity, e.g. between members with an odd and even number of C-atoms in the paraffin chain.
5. A change in the nature of the pharmacological activity as a series is ascended, e.g. higher members may antagonize the effects of lower members. Ing offers a comprehensive theory only for group 1 which includes the aliphatic anaesthetics, certain disinfectants and other depressant drugs. He explains their effects in terms of Ferguson’s theory of chemical potential which can account for the geometrical increase in activity as the number of methylene groups increases arithmetically and for the cut-off point. He emphasizes that the theory does not throw any light upon the mechanism of action of the drugs except that their effects depend on the attainment of a critical concentration of the drug in some unspecified ‘biophase’. In discussing groups 2–5 Ing does not reach firm conclusions as to mechanism except that they probably involve specific receptor interactions. For example, Gill’s finding that the optimal ionic distance for ganglion-blocking activity in the metonium series is 6–7.8 Å suggests a bifunctional receptor. But on the whole Ing reaches the ‘disappointing’ conclusion that ‘there is no hope of predicting the potency of any given number of a group of closely related chemical compounds until we know the nature of the hypothetical receptor with which members of the group form drug-receptor complexes’.

I should like to thank Mrs Catherine Ing for information about her husband and for allowing me access to his handwritten notes from which I have quoted.

The photograph reproduced is by Ramsey & Muspratt, Oxford.

**CHEMISTRY**

**BY F. L. ROSE, F.R.S.**

It will always be abundantly obvious to those who knew him well that Ing regarded chemistry, latterly at any rate, as the handmaid to his understanding of pharmacological processes, made clear when he changed his title at Oxford from Reader in Pharmacological Chemistry to that of Chemical Pharmacology. But it did not mean that he practised or tolerated indifferent chemistry; far from it, and he could hold his own with the best in argument and discussion, which was always enjoyable and stimulating to those taking part.

Ing’s practice of chemistry can be divided under three headings. The first was that engaged in with W. A. Perkin, jun. at Oxford, and which formed the basis of his doctorate, followed by a few years at Manchester as a Ramsay Memorial Fellow at the time when Robert Robinson held the chair of organic chemistry (1922–28). The second period was spent at University College London, where Robinson next moved (1928–30), and during which time it is possible to discern Ing’s growing interest in the relationship between chemical structure and biological activity. The third phase, in which this interest matured, and was passed on to his many students, was the much longer period (1945–66) spent in the Department of Pharmacology at Oxford.

The work with Perkin was in the classical mode in which so many organic chemists of Ing’s generation learned their skills, when sheer experimental
ingenuity had to be applied often over a period of years, to solve some structural problem, which today, using modern techniques in spectroscopy and the like, could probably be settled in an afternoon. It was concerned with the configuration of \( \alpha,\alpha' \)-dibromobasic acids obtained by direct halogenation of, for example, succinic, glutonic or adipic acids, or their esters and acid chlorides, and which invariably gave mixtures of stereo isomers. These then had to be separated by tedious routines of fractional crystallization and/or distillation. Assignment of configuration was usually based on the ingenious device of condensing the dibromo esters (methyl or ethyl) with, for example, ethyl sodiomalonate, to give a pair of products, one of which, since it was capable of resolution into \( d \)- and \( l \)-modifications, could only be derived (in the case of adipic acid) from the \( dl \)- or racemic acid of the configuration:

\[
\begin{align*}
\text{HO}_2\text{C} & \quad \text{HO}_2\text{C} \\
\text{HO}_2\text{C} & \quad \text{HO}_2\text{C}
\end{align*}
\]

The logistics of the arguments involved were complicated by the existence in some instances of different physical forms of the same esters, and the consequent possibility that the experimental evidence might be misinterpreted as due to intramolecular change, caused by the alkalinity of the reaction mixtures. This was always checked by separate careful control experiments. Not unexpectedly, reactions occurred in addition to those primarily intended, as exemplified by the condensation of \( \alpha,\alpha' \)-dibromoglutaric esters with sodiomalonic ester when two types of ring formation took place, to give cyclopropanes or cyclobutanes, respectively, as illustrated by the structures:

\[
\begin{align*}
\text{CH}^+\text{CO}_2\text{Et} & \quad \text{CH}^+\text{CO}_2\text{Et} \\
\text{CH}^+\text{CO}_2\text{Et} & \quad \text{CH}^+\text{CO}_2\text{Et}
\end{align*}
\]

Insistence on working up the most unlikely reaction residues was rewarded by the isolation of a bicyclic structure shown to be

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{C(CO}_2\text{Et})\text{CO} \\
\text{C(CO}_2\text{Et})\text{CHCO}_2\text{Et} & \quad \text{C(CO}_2\text{Et})\text{CHCO}_2\text{Et}
\end{align*}
\]

whose unequivocal constitution was of particular importance in relation to the nature of a ketobicycle pentane tricarboxylic ester discovered by Perkin and Thorpe at the turn of the century, and which had been the subject of much study by Thorpe and Ingold. On such foundations were the early bases of
structural organic chemistry founded. Similar types of condensation were made using cyanoacetic, benzolacetic and acetoacetic esters in place of malonic ester, but the subsequent reactions and interactions of the many complex structures so produced have to be studied in the original publications (J. Chem. Soc. 1924, 1925 and 1926) to appreciate fully the ingenuity and the experimental skills deployed.

The brief Manchester days were characterized by a study with Robinson of the effects of free and bound ionic charges (i.e. dialkyl- and trialkylammonium) on substitution into aromatic systems when the latter author was developing his classical views on these topics, and at a time when theory was perhaps tending to out-run experimental evidence. The particular point at issue arose from the interposition of a methylene group between the charge and the aromatic group, and the conclusions of Holmes and Ingold (1925) that benzylamine salts nitrated mainly in op-positions. Also, that benzylamine derivatives, containing a tervalent nitrogen atom in which formation of a salt is precluded, nitrated mainly in the m-position. The latter proposition had been supported by only a minimum of direct experimental evidence, which purported to show that diacetylbzylamine, for example, did indeed substitute in this manner.

Ing and Robinson, using a method of degradation rather than isolation of the initially formed products, were able to demonstrate that the diacetyl compound largely nitrated in the p-position, to some extent in the o-position, and possibly to a very small extent in the meta. Para and o-substitution was also shown to occur on nitration of phthalbenzylimide. Benzylpiperidine was next investigated, which gave a 50% yield of the m-isomer, with some p-nitro derivative. In a discussion on the mechanisms need to explain the results to date, Ing and Robinson favoured the view suggested to them by Lapworth that the cationic charge attracted the covalency electrons away from the o-carbon atom, and propagated a redistribution of charges in the rest of the aromatic system which favoured m-substitution by op-inhibition, illustrating this new concept (maybe for the first time) by the familiar historical picture:

\[
\text{\begin{tikzpicture}
    \draw[fill=gray!20] (0,0) circle (0.5);
    \draw[thick,->] (0.5,0) -- (0,0);
    \draw[thick,->] (0,0) -- (-0.5,0);
    \draw[thick,->] (0,0) -- (0,0.5);
\end{tikzpicture}}
\]

The Manchester period cannot be allowed to pass without mentioning two experimental devices that Ing developed with R. H. F. Manske, and which have been of great value to generations of succeeding chemists, namely, the use of dry potassium carbonate and phthalimide to promote alkylation with alkyl halides; and the subsequent removal of the phthaloyl residue as the hydrazide, with hydrazine in ethanol. Ing also served at this time as chemist to the Manchester Committee on Cancer, and collaborated with the pathologist C. C. Twort on experiments undertaken with special reference to mule-spinners' cancer of the scrotum, but, using additionally, samples of oil other than those employed in the cotton-spinning industry. Their findings are still relevant to present-day technology, especially as demonstrated in the more
recent occurrence of scrotal tumours due to the use of cutting-oils in metal fabrication. They were able to demonstrate the development of skin tumour in mice from application of the petroleum fractions used in cotton spinning, and that the passage of these oils through the machinery did not render them more carcinogenic. The higher boiling fractions of the oil were much more carcinogenic than the lower boiling fractions (tumour incidence in a ratio of 31 to 1). They further showed that shale oil was much more dangerous than petroleum oils obtained from wells, and that treatment with concentrated sulphuric acid rendered them all practically harmless. Their paper, published in 1928 (50 pages in German, *Z. Krebsforsch.*), concluded from this finding that unsaturated and aromatic hydrocarbons were possibly implicated in the development of malignancy. How true they were.

Next came the years spent at University College London, when Ing’s interest in biologically active molecules was heightened. There appeared a small series of papers on alkaloids, alone, and in collaboration with R. P. Patel and C. G. Raison (later to join the war-time I.C.I. antimalarial team). The more numerous papers related to lupine alkaloids. They described a method of isolating cytisine and anagyrine, present in the seeds of *Anagyris foetida*. Studies on the exhaustive methylation of the latter, followed by catalytic reduction at each stage, proved its close structural relationship to the former, which, in conjunction with kindred work by G. R. Clemo and his group, suggested the formulae appended, severally, for anagyrine, lupanine and sparteine:

![Chemical Structures](http://rsbm.royalsocietypublishing.org/)

Cytisine itself, because of its tropine bridged-ring system was converted to a small series of esters prepared from its N-2-hydroxyethyl derivatives, which had pronounced local anaesthetic activity (rabbit cornea and intradermal in man!). They were said to be less toxic than cocaine, and a clinical trial was envisaged.
Perhaps the most significant work to emerge from Ing's early years in Oxford was that carried out for the Ministry of Supply under the war-time circumstances described above. For this purpose Ing became a member of the Ministry staff. It involved a characteristic initial analysis of the pharmacological type of action in relation to structure of the synthetic mydriatics, and the selection of the benzilic, tropic and actrolactinic esters of choline for early synthesis and test (with A. H. Ford-Moore). This led on to a systematic study of benzilic esters of the general formula \( \text{Ph}_2\text{C(OH)COO}[\text{CH}_2]_n \overset{+}{\text{NR}}^1\text{R}^2\text{R}^3\text{X}^- \) where \( \text{R}^1, \text{R}^2 \) and \( \text{R}^3 \) were alkyl groups, \( \text{X}^- \) was \( \text{Cl}^- \) or \( \text{Br}^- \), and \( n = 2 \) or 3. Later, benzilic esters analogous to eucatropine were also investigated. Some fifty new compounds were carefully and skilfully prepared and characterized, and their comparative potency is summarized in the chemical paper (\textit{J. Chem. Soc.}, 1947).

After the war, Ing continued his interest in structure-activity relationships in the choline group, being now able to define the structural criteria for maximum activity with much greater precision than hitherto, and in the light of studies made elsewhere in the world. Two dimensional factors appeared to be important; (1) the size of the 'cationic head' of the molecule and (2) the length of chain attached to it (the '5-atom' rule). He also returned to the synthesis of new esters of tropine (with R. Foster and P. J. Goodford), for example, substituting a 9-hydroxy-fluorene-9-carboxylic acid residue for that of benzilic acid of the earlier work, and introducing an \( \alpha \)-methyl group into the tropine or \( \psi \)-tropine moieties (later corrected and shown to be \( \alpha \)-benzyl-lactates).

Finally, Ing's contribution (with R. B. Barlow) to the wartime national antimalarial campaign deserves mention. It was not published until 1950, although conceived in 1944 in association with the I.C.I. research. It was known that the synthetic agent mepacrine antagonized riboflavin with respect to the growth of certain micro-organisms, and it was assumed that this effect might in some way relate to antiprotozoal activity. The suggestion was to introduce a 'basic side-chain' into the 9-position of a 6,7-dichloroisoalloxazine, such as occurred in the analogous 5-position in the acridine ring of the drug. As so often happens, the first compound of a series of twelve had pronounced antimalarial activity in chicks, and also antibacterial action against \textit{Lactobacillus casei} antagonized by riboflavin, but despite further structural modifications, it obstinately remained the best in the series yet not quite good enough for further development.

1925 Studies in the configuration of \(\alpha\beta\)-dibromodibasic acids. (With W. H. Perkin, jun.) IV. The \(\alpha\beta\)-dibromoglutaric acids. \(J.\) \(\text{Chem. Soc.}\) \textbf{127}, 2387.

1926 (With R. Robinson) The orienting influence of free and bound ionic charges on attached simple and conjugated unsaturated systems. I. The nitration of some derivatives of benzylamine. \(J.\) \(\text{chem. Soc.}\) \textbf{1655}.

1928 (With C. C. Twort) Mule-spinners’ cancer and mineral oils. \(Lancet,\) \textbf{752}.

1931 Cytisine. I. \(J.\) \(\text{chem. Soc.}\) \textbf{2195}.

1932 Creatine and creatinine. I. Acyl derivatives of Creatinine. \(J.\) \(\text{chem. Soc.}\) \textbf{2047}.

1933 The alkaloids of \(\text{Anagris fœtida}\) and their relation to the lupin alkaloids. \(J.\) \(\text{chem. Soc.}\) \textbf{504}.

1934 (With M. C. Bourne & L. Young) Synthesis of 1-\(\alpha\)-naphthylmercapturic acid. \(\text{Biochem. J.}\) \textbf{28}, 809.

1935 The alkaloids of \(\text{Anagris fœtida}\). II. \(J.\) \(\text{chem. Soc.}\) \textbf{1053}.

1936 (With R. P. Patel) Synthesis of local anaesthetics from cytisine. \(J.\) \(\text{chem. Soc.}\) \textbf{1774}.

1937 (With R. P. Patel) Local anaesthetics derived from the alkaloid cytisine. \(J.\) \(\text{Pharmacol.}\) \textbf{59}, 401.

1938 (With C. F. Code) The isolation of histamine from the white cell layer of centrifuged rabbit blood. \(J.\) \(\text{Physiol.}\) \textbf{90}, 501.

1939 (With C. G. Raison) The alkaloids of \(\text{Mitragyne speciosa}\). I. Mitragynine. \(J.\) \(\text{chem. Soc.}\) \textbf{986}.


1947 (With A. H. Ford-Moore) Synthetic mydriatics. \(J.\) \(\text{chem. Soc.}\) \textbf{55}.


1957 (With R. Foster) α-Methytropic acid—a correction. *J. chem. Soc.* **925**.


(With E. W. Gill) Furan and tetrahydrofuran compounds analogous to ganglionic blocking agents of the 3-oxapentane-1:5-bistrialkylammonium series. *J. chem. Soc.* **4728**.


