BIOGRAPHICAL
MEMOIRS

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Biogr. Mems Fell. R. Soc. 1995 **41**, 397-418, published 1 November 1995

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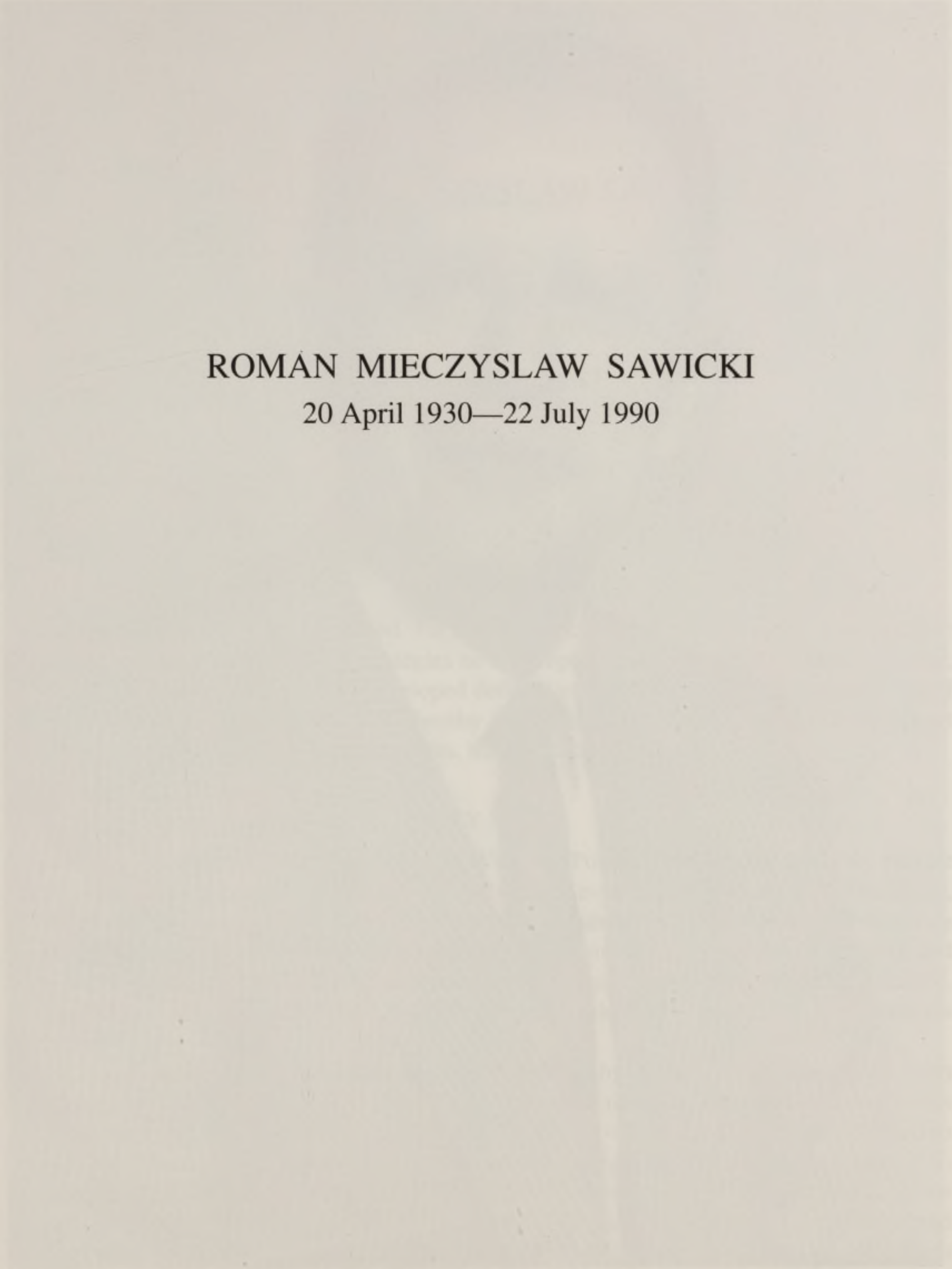

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Elected F.R.S. 1987

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ROMAN SAWICKI was renowned for his research on the origins of resistance to insecticides in insects, and for the strategies he developed to prevent such resistance. Earlier, in one of his first projects, he had developed definitive bioassays comparing the activities of the constituents of natural pyrethrum, thereby contributing significantly to the development at Rothamsted of a new class of insecticides, the synthetic pyrethroids.

EARLY YEARS

Roman Mieczyslaw Sawicki was born at Wilno in Poland. He was an intensely private person who communicated little about his early years even to his beloved wife Micheline, although there were indications of much suffering and sadness in his background. Reluctance to discuss these aspects of his life was entirely consistent with his absence of self-pity and with the dignified nobility of his character, qualities sensed after even a brief acquaintance. The riches of his personality and intellect were revealed only gradually as friendships deepened.

His father, Kazimierz Witold Sawicki, was described by Roman as a draughtsman from Eastern Poland; his mother was Helena Majer, a Russian national. She died of tuberculosis when Roman was four years old. At this time his father was in the U.S.A.; he returned to Poland but also died shortly afterwards. Roman was brought up by Lt. Gen. and Mme F.S. Skladkowski, following a request by Roman's mother to Mme Skladkowska. Mme Skladkowska, *née* Germaine le Boeuf, a French national, had a strong personality and exerted great influence on Roman's cultural life. He owed to her his mastery of the French language and his excellent knowledge of French history, literature and poetry. His environment in this period was luxurious and a chauffeur drove him to school, but he suffered from a lack of companions of his own age. Roman worshipped and deeply loved both his guardians, and was devastated when they died.

General Skladkowski was Prime Minister of Poland from 1936–39, the critical years before the German invasion in 1939, when Roman attended the Lycée Français de Varsovie, Warsaw. General Skladkowski fled to Rumania after the invasion of Poland, intending to govern from there. However, he was interned, but then escaped to rejoin the Polish Army in Palestine in 1940. Roman seems to have spent two years travelling with Mme Skladkowska until he found himself in Palestine. There he developed his interest in natural history by collecting specimens, especially of marine animals. Having attended Polish primary and secondary schools in Tel Aviv from 1940–45, he joined the Polish Cadets in 1945 and attended the Young Cadets School at Barbara, Palestine from 1945–47. In 1947 he came to the U.K., was demobilized, and from 1948–49 attended a course for Polish ex-servicemen at Haydon Park, Sherbourne in preparation for London Matriculation, which he attained in 1949.

UNIVERSITY EDUCATION

Roman's education continued at Chelsea College of Science and Technology, University of London, from 1950–56. He said later that throughout his university career he 'worked very hard', of necessity because he had not been taught science at school. Despite the war he considered he had received a good schooling, but found his English 'barely adequate' when he started studying at University level. Any deficiency he may have sensed subjectively at that time would not be apparent to readers of his technical papers only a few years later; he evolved a simple direct prose style entirely appropriate to scientific communication.

Roman was always very interested in biology. In 1953 he gained a B.Sc. General Degree in Botany, Chemistry and Zoology, remarkably without having studied these subjects for the London University Matriculation examination. The results in Zoology were so good that the college authorities requested him to study for a further degree. This he achieved with first class honours in Entomology in 1954; in that year he was also awarded London University full colours for rowing. Curiously, and despite his significant attainments, he lacked self-confidence and a sense of career direction. Fortunately his latent ability was recognized and Dr M. Sutton of Chelsea College suggested a subject: 'Asexual Reproduction of Salps', for research towards a Ph.D. This topic was consistent with Roman's long established interest in marine biology. His Ph.D. thesis in 1958 (1)* was the first publication in which his talents, including immaculate artistry and attention to technical detail, are perceived.

MOVE TO ROTHAMSTED

Roman's abilities and reputation at Chelsea came to the attention of Charles Potter, a Governor of Chelsea College and Head of the Department of Insecticides and Fungicides at Rothamsted Experimental Station. In 1956 Roman was appointed to the staff of Potter's Department, where he was based for the remainder of his scientific career.

This Department at Rothamsted had studied natural insecticides including pyrethrum under its first Head Frederick Tattersfield from the 1920s. Pyrethrum flowers from Harpenden were of such high quality that they were supplied to Kenya to help establish the pyrethrum-growing industry there. Charles Potter was Head of the Insecticides and

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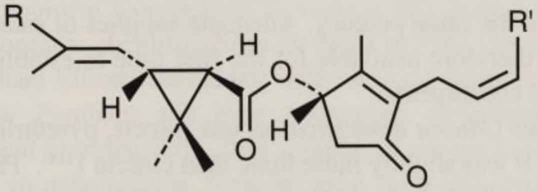
*Numbers in this form refer to the bibliography at the end of the text.

Fungicides Department from 1947 until 1972. He became personally involved with pyrethrum following an early success in using it to control the pests *Plodia interpunctella* and *Ephestia elutella* on dried fruit stored in warehouses. This application emphasized the outstanding properties of pyrethrum – great potency to insects combined with safety to mammals. In 1948, therefore, in his new Department Potter initiated a multidisciplinary project to study how the insecticidal activity of natural pyrethrum was related to the structure of its constituents. At the time some thought the decision to do so ill-judged; the synthetic insecticides (including DDT) already emerging were considered likely to be adequate to deal with all insect control problems.

When the organic chemical work on pyrethrum started in 1948, the insecticidal activity was attributed to four constituents (pyrethrins I and II and cinerins I and II; see figure 1) based essentially on investigations in Switzerland (1910–16), in the United States (1935–45), and from 1942 onwards by Stanley Harper (a colleague of Charles Potter at Rothamsted, 1935–42) and a succession of collaborators (including Crombie) in the U.K. (Crombie 1995).



	R	R′		R	R′
pyrethrin I	CH_3	$CH{=}CH_2$	pyrethrin II	$CH_3OC(O)$	$CH{=}CH_2$
cinerin I	CH_3	CH_3	cinerin II	$CH_3OC(O)$	CH_3
jasmolin I	CH_3	CH_2CH_3	jasmolin II	$CH_3OC(O)$	CH_2CH_3

FIGURE 1. Structures of natural pyrethrins.

At Rothamsted, Roman started to examine aspects of the insecticidal activity of these natural constituents, a study in which Rothamsted collaborated with workers at the Tropical Products Institute in London. Potter had visited Kenya, Tanganyika (now Tanzania) and the Belgian Congo (now Zaire), to advise the Colonial Office on the establishment of a research station for pyrethrum production in Kenya. He recognized that knowledge of the relative potencies and susceptibility to synergism (by piperonyl butoxide and related compounds) of the four known insecticidal constituents against various insect species was inadequate to guide the breeding programmes underway in Kenya.

RESEARCH ON NATURAL PYRETHRINS

Roman's first important contribution, with E.M. Thain of the Tropical Products Institute, was to show that the insecticidal activity of commercial pyrethrum against houseflies depended upon pyrethrins and cinerins with the structures shown in figure 1(5). This early investigation was made with the attention to detail and thoroughness which was to characterize all his subsequent work. His demonstration that only such esters contributed to this activity was significant for other studies in the Department into the relationship between insecticidal activity and chemical structure of the pyrethrins. Solutions containing the active constituents in the same ratios as in commercial products were shown to have activities similar to those of the corresponding extracts; therefore any non-pyrethroid material was inert. With esters of higher purity than had been available for previous tests, pyrethrin II was found more active than pyrethrin I, and the cinerins much less so. This result was to influence the direction of the parallel structure–activity project in the Department, where emphasis was then placed on synthetic pyrethroid esters with multiple centres of unsaturation in the alcohol components rather than on those with one double bond as in cinerins I and II and the synthetic compound allethrin.

With colleagues at Rothamsted and the Tropical Products Institute, Roman next conducted detailed bioassays with samples of the pyrethrins isolated from commercial pyrethrum extract by displacement chromatography, and with compounds reconstituted from naturally derived acids and alcohols (7). The esters from the two sources had identical physical and chemical properties and the same potency. Adequate supplies of esters from chromatography or reconstitution were therefore available for the first time to establish precisely the relative potencies of the natural constituents.

Using adult houseflies (*Musca domestica*) as test insects, pyrethrin II was more toxic than pyrethrin I and cinerin II was slightly more toxic than cinerin I (14). Previously both Gersdorff and Incho & Greenberg (see 8) had reached the opposite conclusions but under different experimental conditions. The relative toxicity of the four constituents varied not only with the technique of application but also with the species of insect used: against the mustard beetle (*Phaedon cochleariae*), the order of decreasing relative toxicity was pyrethrin I > cinerin I > pyrethrin II > cinerin II. This was another result that was to influence significantly the studies in the Department on the development of synthetic pyrethroids. It confirmed that synthetic esters with conjugated rather than single unsaturation in the alcohol side-chain might have superior activity. Subsequently, he made one further contribution to knowledge of pyrethrum constituents with bioassays (15) of a newly isolated ester, jasmolin II (figure 1), first identified in fresh and dried flowers by gas–liquid chromatography. When jasmolin I was found (Crombie 1995), the total of recognized active constituents of pyrethrum was brought to six.

In practice the natural pyrethrins were usually formulated with synergists such as piperonyl butoxide (PBO), which made possible lower concentrations of the expensive pyrethroids. Only one study had been made in which the separate contribution of each of the natural esters to the overall synergistic effect was measured (Incho & Greenberg, see 8). This had used a turntable spray method of application, in which the amount of poison picked up by the flies could not be known. To overcome such uncertainties, Roman refined a measured drop technique for dosing individual flies to determine activity per unit weight of insect for each constituent of the extract (8–11). For the first time determination of both absolute and relative increases in the toxicity of constituents in the presence of PBO, and changes in the order and magnitude of their relative toxicities at varying ratios of pyrethroid to synergist became possible. This more rigorous approach to quantifying synergistic effects gained rapid acceptance, and was to underpin Roman's subsequent work exploiting PBO and other synergists to aid characterization of resistance mechanisms.

INFLUENCE ON THE DEVELOPMENT OF SYNTHETIC PYRETHROIDS

Another project initiated by Charles Potter was attempting to define the structural requirements for activity by examining a range of synthetic esters. The bioassays required had been refined by 1961 to topical application of measured drops of acetone solutions to *P. cochleariae* by the entomologist Paul Needham and to *M. domestica* by Roman. Developing concepts of the structural requirements for activity had suggested that the simple ester 4-allylbenzyl chrysanthemate (ABC) would be worth evaluating (20). Although ABC was active it did not show exceptional potency against *P. cochleariae*. However, Roman detected a high level of activity against houseflies, which he confirmed as twice that of the natural pyrethrins. This finding generated considerable excitement, because earlier no comparably simple synthetic compound had even approached the activity of the natural esters against any insect. His observation of this level of potency for such a simple compound influenced the National Research Development Corporation to support this project, and so made possible the appointment of two organic chemists, Norman Janes in 1962 and David Pulman in 1971, to collaborate with Michael Elliott. This team, with bioassay support from Roman Sawicki, Paul Needham, Andrew Farnham and their colleagues, developed first the household pyrethroids resmethrin and bioresmethrin, then a range of commercial photostable synthetic pyrethroids culminating in deltamethrin, then the most powerful insecticide discovered and subsequently one of the most widely used (Elliott 1995).

TRANSITION TO WORK ON INSECTICIDE RESISTANCE

Between 1961 and 1963 Roman relinquished much of his work on pyrethroids, having been requested by Charles Potter to take over work on insecticide resistance in the Insecticides and Fungicides Department. Through this reassignment of duties, Potter laid the foundations of yet another long-term research programme of major international standing. Having revitalized work on resistance, Roman was to stay with the subject for the remainder of his career, thus assembling a multidisciplinary team with unrivalled breadth of expertise.

The challenges facing him at this time were rendered all the more daunting by the relative novelty of resistance, and the considerable scepticism regarding its respectability as a research topic. Its significance as an evolutionary phenomenon was already widely recognized by population geneticists. Mechanisms that had been postulated to confer this phenomenon included slower penetration through the insect cuticle and more rapid detoxification in the haemolymph by hydrolysis of insecticide esters. Those based on the modification of insecticide target-sites, prominent in Roman's subsequent research, had hardly been discussed. Few appeared to share Potter's view that resistance posed a tangible and potentially very serious threat to insect control with insecticides. More commonly, it was perceived as a curiosity of fundamental interest but limited practical importance. Any doubts that Roman may initially have entertained were rapidly dispelled; by the late 1960s he was a powerful advocate of the need for greater investment in resistance research, and by 1980 his name was synonymous with this cause.

Comparable research into the nature of resistance was already underway in several laboratories. The most notable of his contemporaries included A.W.A. Brown, G.P. Georghiou and F.W. Plapp in the U.S.A., M. Tsukamoto in Japan, F.J. Oppenoorth in the Netherlands, J. Keiding in Denmark, R. Milani in Italy and J.R. Busvine in the U.K. By the late 1960s, however, many would have conceded that Roman's inspired research rendered him pre-eminent in the field.

EARLY WORK ON RESISTANCE

Between 1963 and 1970 Roman's work centred on the housefly, *M. domestica,* a species that had already assumed 'laboratory white rat' status in resistance research due to its short life-cycle and high fecundity, proven propensity to develop resistance to insecticides, and relatively tractable genetics. A fly strain termed 'SKA', already established at Rothamsted by K.A. Lord, was prominent in these initial experiments. Lord had shown SKA to resist DDT and some of the earliest organophosphorous (OP) insecticides, but progress had been hampered by inexplicable variation in bioassay results, and by failure to select such resistance to workable levels. A reappraisal of techniques was, therefore, essential for investigating the nature and genetic basis of resistance to different insecticide groups.

Through his work on pyrethroids, Roman already had a sound appreciation of the merits and limitations of different bioassay and insect-rearing methods. Some of these had either been invented by Roman himself, or substantially refined to improve precision and repeatability (2, 4, 12, 13). These were now adopted for experiments on resistance. Two papers published in 1965 (16, 17) demonstrate Roman's attention to detail, and his determination to explain anomalous experimental results.

For several years, SKA flies had been selected with the OP diazinon by confining females in cylinders of filter paper impregnated with insecticide. Survivors were paired with unselected males. After 70 generations this procedure had rendered SKA flies 25-fold resistant to diazinon. Roman now adopted the novel approach of selecting both sexes in each generation by the precise method of topical application, and after only 10 generations increased diazinon resistance to 100-fold (16). An important finding was that the response of adult houseflies and their level of resistance changed with age. Roman initially associated this phenomenon with gonad development and reproductive maturity – processes largely regulated by the corpus allatum. He pursued this suspicion by comparing the response of normal and allatectomized females (17). Few would have contemplated conducting this delicate operation. Judging from his later recollections, memories of doing so left an indelible impression on Roman himself. SKA females showed no difference in sensitivity to diazinon, dieldrin or pyrethrum extract whether allatectomized or not, i.e. the increase in resistance to diazinon with age was unaffected by allatectomy and the consequent failure of ovaries to mature.

Roman's next paper (18) was the first to delve directly into the mechanisms of resistance in SKA flies, hinting at the complexity of factors present and heralding a series of publications of unprecedented significance. It was also notable as the first paper written with Andrew Farnham, to whom Roman, with characteristic generosity, assigned first authorship. The partnership with Farnham, who was appointed to Rothamsted in 1963, was a productive association that endured throughout the rest of Roman's career.

From bioassays supplemented by chemical assays for diazinon and its metabolites, Andrew and Roman concluded that there were at least two resistance mechanisms. Slower penetration through the cuticle clearly played a role, but enhanced detoxification was also strongly implicated. At this stage, however, little could be inferred of the nature and genetics of enhanced detoxification, its contribution to the overall resistance phenotype, or its likely interaction with coexisting factors such as reduced penetration. This situation was to change rapidly, after Roman's only extended period of work overseas.

DEFINITION OF MULTIPLE RESISTANCE IN HOUSEFLIES

In 1964 Roman spent three months at the University of Pavia, where he acquired techniques that profoundly influenced his future research. R. Milani, Director of the Institute of Zoology, was at that time the world's foremost authority on housefly genetics. With M. Tsukamoto and T. Hiroyoshi in Japan he was accumulating a large library of visible mutant markers and assigning them to linkage groups in *M. domestica*, thereby providing essential tools for mapping insecticide resistance genes.

In collaboration with Milani and M.G. Franco, Roman embarked on a complex series of crosses to investigate the linkage relationships of factors conferring diazinon resistance in SKA houseflies (21). Partially dominant factors were identified on autosomes 2 and 5 that individually conferred similar and rather low levels of resistance to diazinon when heterozygous, and which were partly cumulative in the double heterozygote*. The autosome 2 factor appeared equivalent to gene *a*, coding for a carboxylesterase variant already reported by F.J. Oppenoorth and F.W. Plapp in Holland and the U.S.A. repectively, and to the detoxification factor identified in the earlier paper by Farnham *et al.* (18). The nature of the autosome 5 factor remained unknown at this stage.

Roman's visit to Italy achieved almost mythological status among his colleagues at Rothamsted. He worked in the laboratory from early morning to late at night, seven days a week, taking only two day's leave during the whole three-month period. During the little spare time he allowed himself he took his pad and pencil into Pavia and produced some outstanding sketches of ancient monuments and buildings.

Recognizing the power of these new genetical techniques, Roman then embarked on an ambitious set of experiments culminating in three papers published with Farnham under the collective heading 'Genetics of resistance of the SKA strain of *Musca domestica*' (24, 25, 27). This work aimed not only to resolve OP resistance, but also to investigate factors conferring resistance to other unrelated insecticides. It is appropriate here to emphazise the technical difficulties this entailed. Although the phenomenon of mechanisms conferring *cross-resistance* to different insecticides in the same chemical group was already well-established, the possibility of genes conferring cross-resistance between different chemical groups was still subject to speculation. Disentangling true cross-resistance from *multiple resistance*, whereby resistance to different groups is conferred by distinct, coexisting and potentially linked genes was a challenge requiring extreme attention to detail, great patience, and scrupulous powers of observation and interpretation. Fortunately Roman possessed all these attributes, and in this work was to apply them to outstanding effect.

The first paper (24) considered the fact that the SKA strain, as well as resisting diazinon, was virtually immune to the unrelated organochlorine insecticide DDT. On the face of it, this fact alone was strong evidence for cross-resistance between diazinon and DDT, or at least very close linkage between OP and DDT resistance factors. The true situation proved more complex; test-crossing and bioassays identified three factors contributing to DDT resistance in SKA houseflies. A gene termed *DDT-ase* (coding for the mechanism DDT-dehydrochlorinase, degrading DDT to DDE and other metabolites) mapped to autosome 2, where it was linked to (but distinct from) gene *a* contributing to diazinon resistance. A

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*Interpretation of work on housefly genetics published at this time was complicated by the use of three distinct systems for numbering the five pairs of autosomes in *M. domestica*. In this article we adopt the numbering system that has now gained universal acceptance.

second factor on autosome 5 was identical to that implicated previously in diazinon resistance, and conferred cross-resistance to both diazinon and DDT. This was attributed to a mechanism termed DDT*md* (or *Ses* in some early publications), enhancing microsomal oxidative detoxication of DDT and some OP compounds. The third factor was largely recessive; it was unaffected by synergists known to block dehydrochlorination and oxidative detoxification pathways, and segregated independently of the other two DDT resistance factors. Roman correctly allocated this factor to autosome 3, showing that it was either identical or closely linked to a newly-characterised factor on this linkage group conferring weak resistance to diazinon (25). The factor in question (*pen*) was that responsible for delayed penetration of insecticides of various chemical groups.

The only aspect of SKA resistance still unresolved involved dieldrin, another insecticide to which this strain had not been exposed in the laboratory. Although both dieldrin and DDT are organochlorine insecticides, cross resistance between them is unlikely. Indeed, the only feature found in common between dieldrin and DDT resistance was the minor protection conferred by the *pen* gene on autosome 3 (27). The principal factor of dieldrin resistance was a gene (Dld_4 or DR_4) on autosome 4 that had no effect on the toxicity of DDT or diazinon. Unlike other mechanisms in SKA, which either delayed penetration or enhanced the detoxification of insecticides, Dld_4 has since been confirmed to involve a structural change in the insecticide target site itself.

Roman also started work on the biochemical basis of OP resistance in SKA houseflies. His initial approach was to co-apply insecticides with synergists considered to inhibit specific detoxification pathways, and hence to diagnose enzyme systems potentially capable of conferring OP resistance (25, 28). Although the use of synergists to aid the characterization of resistance was not uniquely Roman's innovation, his experiments combining these with formal genetics studies pioneered a more integrated approach to resistance research that has prevailed to the present day. As he cautioned, however, synergists are not infallible as indicators of particular mechanisms; they may themselves become subject to resistance that obscures their diagnostic potential (38). Nor did he consider them a substitute for *in vitro* studies of insecticide metabolism or pharmacokinetics. Biochemical work was not Roman's forte but it assumed a much higher profile at Rothamsted following Alan Devonshire's appointment to his team in 1970. Before this he nonetheless supervised other research into resistance mechanisms including radio-metric experiments directly implicating genes *a* and *Ses* in the hydrolysis and oxidative metabolism of diazinon respectively (34).

The occurrence and potential complexity of multiple resistance was now firmly established. However, the nature of interactions between coexisting mechanisms remained far from clear. Roman confronted this challenge in a characteristically ingenious manner. Having transferred individual resistance factors from SKA into genetically marked strains, he reconstituted stocks containing specific combinations of two or more mechanisms. Bioassays quantified the resulting interactions and their relative contributions to the parental SKA resistance phenotype (31, 35). Much of the resistance in SKA could then be explained by interactions between already isolated mechanisms. However, such interactions were, as Roman concluded, 'inherently unpredictable'. Despite two more decades of intensive work on resistance, this largely remains the case today.

SEQUENTIAL SELECTION OF RESISTANCE

Roman's next objective was to investigate whether the order in which different OP resistance mechanisms were selected in *M. domestica* bore any relationship to the history of treatment with insecticides. For this he required strains collected from sites where the sequence in which chemicals had been applied was precisely documented. Denmark proved the ideal source of such material. Since the late 1940s, Johannes Keiding and co-workers at the Danish Pest Infestation Laboratory (DPIL) in Lyngby had monitored the use of insecticides against houseflies on livestock farms. Fly samples had been collected annually and tested to record the development of resistance to insecticides of the same or different chemical groups. In the process, DPIL staff had accumulated a unique collection of strains with known treatment histories. The working relationship that Roman established with Keiding developed into a close friendship based on shared extra-curricular interests as well as a commitment to long-term research on resistance.

The history of resistance development disclosed by Keiding's work can be summarized as follows. Following the rapid failure of DDT due to resistance in the late 1940s, fly control in Denmark relied for over 20 years on older OP insecticides including parathion and diazinon, supplemented by pyrethrum sprays. From 1965, emphasis switched to the OP dimethoate following the discovery that parathion- and diazinon-resistant insects were well controlled by this insecticide. Dimethoate gave excellent results for several years but by 1972, when Roman started his collaboration with Keiding, dimethoate resistance had also become widespread. Many OP resistance mechanisms were assumed to have been selected over the years, but these had not been characterised.

The dimethoate-resistant strain $49r_2b$ was the first of Keiding's strains to be investigated at Rothamsted. It was shown to possess several resistance mechanisms (38, 40). Some of these (e.g. *pen* and *Ses*) were equivalent to ones already detected in the SKA strain. Others absent from SKA were possibly more specific to dimethoate. One notable discovery, made in collaboration with Alan Devonshire, was a gene on autosome 2 coding for a mutant form of the enzyme acetylcholinesterase (AChE), the target site of OP and carbamate insecticides. The mutant enzyme showed reduced sensitivity to inhibition by dimethoate in particular (40). This mechanism termed 'AChE-R' had previously been reported for other pests but was apparently still rare in houseflies.

Work explaining the occurrence of AChE-R in $49r_2b$ and other strains selected with dimethoate, and its absence in ones (e.g. SKA) collected earlier and selected with other AChE inhibitors was summarized in a major paper in 1981 with Keiding as co-author (53). Roman's explanation was as follows. The earliest OPs including diazinon selected primarily for metabolic resistance, since their relatively slow penetration through the insect cuticle renders them vulnerable to esterase detoxication. Being much more polar, dimethoate penetrates much faster. It and its active oxidation product omethoate consequently accumulate at higher concentrations in the haemolymph, rendering detoxification systems less effective as resistance mechanisms. Selection with dimethoate therefore led to the gradual disappearance of gene *a*, and its replacement by AChE-R. Compared to parathion and diazinon, dimethoate is a poor inhibitor of AChE; even slight insensitivity is likely to confer a considerable selective advantage to insects exposed to this chemical.

Had dimethoate been used earlier for fly control in Denmark, selection of AChE-R with its broad spectrum of cross-resistance to OPs would have considerably diminished the choice of replacements. However, the Danes' success with managing resistance to OPs was wholly fortuitous. Using biochemistry to predict the order in which mechanisms are likely to be selected is another matter. In his 1981 paper (53) Roman paraphrased this problem succinctly:

> Entomologists cannot exert, as yet knowingly, a comparable influence because of lack of understanding of the biochemical principles leading to the preferential selection of resistance mechanisms, and until they do, the risk of accelerating the selection of resistance mechanisms, through the untimely introduction of new insecticides, will always be possible.

PYRETHROID RESISTANCE IN HOUSEFLIES

The first highly active synthetic pyrethroids released for commercial use in the early 1970s were resmethrin and bioresmethrin. Photostable analogues (including fenvalerate, permethrin, cypermethrin and deltamethrin) followed during the mid- to late 1970s. Pyrethroids rapidly gained widespread use owing to their efficacy against many insect pests, including those already strongly resistant to OPs and most organochlorine insecticides. Roman was ideally placed to start work on resistance to pyrethroids as soon as they became commercially available. The phenomena of multiple and sequential resistance were as prominent in this research as they had been with the OPs.

By the mid-1970s, resistance to pyrethroids was still rare, even though natural pyrethrins, usually applied in conjunction with the synergist PBO, had been used for many years. Roman's initial experiments yielded contrasting results depending on the fly strain under investigation. One study, again involving $49r_2b$, explored whether pyrethroid resistance was facilitated by prior exposure to unrelated chemicals such as dimethoate (38). Laboratory selection with dimethoate increased resistance of this strain to synergized pyrethroids, but much less so to unsynergized compounds. Roman suggested that dimethoate resistance was somehow associated with either the ability to develop resistance rapidly to pyrethroids, or with the presence of pyrethroid resistance at low frequencies through exposure to the OP. Most remarkably, dimethoate resistance appeared possibly to have facilitated indirectly the development of resistance to synergized pyrethrins by conferring cross-resistance to the synergist rather than to pyrethrins *per se*.

Another mechanism being characterized at this time was to assume greater significance for the future of synthetic pyrethroids. Ironically, this mechanism, known as knockdown resistance or *kdr*, was initially implicated largely by default. It performed no known metabolic function and was unaffected by synergists applied to block expected detoxification pathways. *Kdr* also confers resistance to DDT, and was first located on autosome 3 in relation to DDT resistance by R. Milani at Pavia in the late 1950s. However, Rothamsted was subsequently to play the primary role in resolving its genetic and toxicological properties, and its interaction with other pyrethroid resistance factors.

Andrew Farnham first showed unequivocally that *kdr* factors in fly strains from Sweden (kdr_{NPR}), Italy (kdr_{Latina}) and the U.S.A. (*kdr*-Orlando) were almost certainly allelic, and probably identical given their similar cross-resistance characteristics (Farnham 1977). In 1978 Roman reported a second, putatively allelic variant termed *super-kdr* that conferred 10 to 50 times stronger resistance than *kdr* itself to most of these agents (49). *Super-kdr* was first identified in a Danish strain (153y3), and has probably since become the more common variant in *M. domestica* due to the very high degree of protection to pyrethroids it confers.

During the 1980s, research at Rothamsted into pyrethroid resistance followed two main directions, one exploring resistance mechanisms in more detail, and the other its significance under field conditions. Although Roman examined mechanisms other than *kdr*(59), the latter dominated his research over this period. Significant findings included the identification of new, genetically distinct factors conferring little resistance on their own but interacting strongly with *kdr* to intensify its phenotypic expression (68, 78). Further bioassays showed that strains collectively exhibiting *super-kdr* levels of resistance possessed at least two variants (*super-kdr*$_{3D}$ and *super-kdr*$_{A2}$) differing subtly in their cross-resistance characteristics (81). Collaborative work with chemists in the Department also exposed a rare weakness associated with *super-kdr* resistance; some synthetic amides related to insecticides from plants in the genus *Piper* (Piperaceae) proved up to four times as effective against houseflies with this gene than against susceptible populations (75). Unfortunately, amides with this property proved insufficiently active for commercial development. Nonetheless, this work demonstrated the principle of negative cross-resistance that now drives the rational search for resistance-defeating insecticides.

The mechanism of *kdr* resistance remained elusive, due in part to a poor understanding of the mode of action of pyrethroids and DDT. Electrophysiological studies at Birmingham University hinted towards a solution by showing abdominal nerve and metathoracic leg preparations from *kdr* strains to be less sensitive to stimulation by pyrethroids (86, 94). However, major progress attributing *kdr* resistance to modifications in the voltage-gated sodium channel on axon membranes had to await the application of molecular biology to the subject immediately after Roman's death (Williamson *et al.* 1993). His characterization and isolation of different *kdr* variants remains vital to this area of research.

The introduction of synthetic pyrethroids for housefly control in the U.K. at the start of the 1980s provided an ideal opportunity to study resistance development from a more practical perspective. With Andrew Farnham and Ian Denholm he started field work on animal farms near Rothamsted, relating the occurrence of resistance to the bionomics of fly populations, and their ease of control with pyrethroids. This work in turn directed Roman's thinking towards the subject of resistance management that dominated the final stage of his career.

The relationship between laboratory bioassay data and the field performance of insecticides is difficult to predict. Investigating this for houseflies entailed relating the intrinsic tolerance to pyrethroids of 42 fly strains to available information on insecticide use and control efficacy on farms where these strains originated (69, 71). Results enabled the definition of 'threshold' levels of resistance at which control failure was likely to occur, and demonstrated that such thresholds are highly dependent on the chemical used for monitoring purposes. At the time this represented one of few validated means of forewarning of control failure and of confirming resistance as the cause.

Field work with houseflies demanded great perseverance. Roman, however, considered that wading into dung heaps or slurry pits in search of fly breeding sites was only a minor inconvenience. Friends and family may have thought otherwise, since the smell of pig manure lingered on clothing and wafted along corridors! This work identified many factors governing the selection of resistance genes (72). In particular, sites where flies overwintered actively in heated animal houses proved of crucial importance, acting as reservoirs of resistance and sources of widespread recolonisation during the early summer. Such overwintering sites were clearly where control practices aimed at managing resistance were most urgently required.

Roman acquired an unparalleled knowledge of pyrethroid resistance in insect pests. This culminated in 1985 in a comprehensive review of its incidence, causes and management(74) – a publication still widely admired for its critical interpretation of results and accurate prognosis of future developments. His abiding concern was that pyrethroids should not be squandered and share the fate of older insecticide groups. This sentiment is encapsulated in the closing sentence of his review: 'The *raison d'etre* of insecticides is after all the effective, safe and reliable control of insect pests, and pyrethroids are particularly suited to this task'. Sadly, these words went unheeded by the pest management community at large; pyrethroid resistance continued to escalate, principally through widespread over-reliance on this class of chemistry. As Roman predicted, it now constitutes one of the most serious constraints to disease management and effective crop protection.

RESISTANCE IN PEACH-POTATO APHIDS

By the end of the 1960s, reports of pesticide resistance in arthropods were increasing at an almost exponential rate. Roman had recognized by this stage the importance of extending his research to a species of more immediate relevance to U.K. agriculture. He identified the peach-potato aphid, *Myzus persicae*, as a species in urgent need of attention. This decision gave Rothamsted a substantial lead in resolving what has since become one of the most serious resistance problems on arable and horticultural crops in temperate regions of the world.

In Europe, *M. persicae* achieves greatest importance as a vector of virus diseases in potatoes, sugar beet and glasshouse crops. By 1969, when Roman started work on this species, resistance to OPs had already been well documented in glasshouses, largely through work at the Ministry of Agriculture laboratory in Harpenden. In the field, resistance was still rare or under-recorded, and virtually nothing was known about the mechanism or its cross-resistance characteristics. In collaboration with Paul Needham, Roman first conducted topical application bioassays and preliminary biochemical tests against a glasshouse strain of *M. persicae* that had been maintained in the laboratory under heavy selection pressure with OPs(33). Resistance factors varied considerably between insecticides, being greater than 100-fold to parathion and dimethoate but only 12-fold or less to demeton-S-methyl and the carbamate pirimicarb. Resistance in this and other strains was associated with increased levels of carboxylesterase activity. One puzzling result was that this resistance sometimes dropped dramatically when OP selection pressure was withdrawn.

In collaboration with Broom's Barn Experimental Station in Suffolk, Roman initiated extensive surveys of resistance in sugar beet-growing areas of East Anglia. These surveys showed moderately resistant aphids to be widespread in East Anglia, and a more strongly resistant variant to be well established on potatoes in Scotland (43, 45, 47, and other papers by Needham and Devonshire cited in these publications). Techniques for detecting resistance in *M. persicae* were also substantially refined. The cumbersome approach of topical application was initially replaced by a much simpler and faster 'aphid-dip' test(43), which was adopted by the United Nations Food and Agricuture Organisation (FAO) as an internationally approved method applicable to several aphid species(62). For more incisive monitoring, this test was supplanted by a biochemical assay for diagnosing different levels of carboxylesterase activity in individual aphids(47).

Alan Devonshire's contributions as a biochemist ensured rapid progress with understanding the mechanism of resistance in *M. persicae*. He succeeded in implicating a single esterase (E4) in the degradation of OP and carbamate insecticides (Devonshire 1977). Its increased activity in resistant aphids was shown to be a consequence of overproduction of the E4 enzyme. These findings led Devonshire and Sawicki to postulate in 1981 that resistance in *M. persicae* reflected a series of tandem duplications of the structural gene coding for this enzyme (51). Gene duplication had not previously been proposed as a mechanism of resistance to pesticides. Subsequent work by Devonshire and his colleagues (e.g. Field *et al.* 1988) fully confirmed this farsighted hypothesis. Roman's early observation of the instability of resistance, which he subsequently quantified in much greater detail(52), also became explicable as a phenomenon whereby highly amplified E4 genes can be 'switched off' in the absence of selection pressure, causing resistant aphids to revert towards a susceptible phenotype.

Another facet of Roman's work on *M. persicae* arose from his preliminary observation that aphids appeared to avoid contact with pyrethroid-treated foliage (48). He surmised that such an effect could contribute to restricting the spread of plant viruses. However, further experiments conducted with the virologist R.W. Gibson proved disappointing. Deltamethrin did hinder infection of healthy plants with a range of viruses, but this effect appeared attributable to the toxicity of the pyrethroid rather than modification of aphid behaviour (57).

Undaunted, Roman turned his attention to chemicals with known repellent properties, and whose effect was less likely to be impaired by insecticide resistance. Two compounds recommended for this purpose were dodecanoic (lauric) acid and polygodial, a sesquiterpene dialdehyde derived from foliage of Water Pepper, *Polygonum hydropiper*. Since the second of these could not be purchased or easily synthesized, Roman and chemist colleague John Pickett collected their own supply of *P. hydropiper* from a marshy wood near Welwyn Garden City. Pickett recalls that they became completely lost in the wood, largely through Roman's exuberance on finding luxuriant stands of the plant.

In experiments undertaken with Gibson and Pickett, both compounds decreased acquisition of viruses by *M. persicae* to some extent(58), highlighting the potential for exploiting non-insecticidal, behaviour-modifying chemicals (semiochemicals) as components of crop protection strategies. Research into the development of semiochemicals has since flourished under Pickett's leadership to become, as Roman once remarked impishly, 'almost as famous as the work on insecticide resistance!'

RESEARCH ON OTHER PESTS

The next species to be included in Roman's programme, in 1985, was the tobacco or cotton whitefly *Bemisia tabaci*. To many this seemed an esoteric choice; *B. tabaci* was then only of localized importance in the tropics, and of rare occurrence in Europe. His decision, however, was based on extensive discussions, especially with pesticide manufacturers who regarded this species as a significant target for their products. Contacts with Ciba Geigy during 1984 led to a substantial contract to investigate its resistance mechanisms and to assist with development of novel control agents.

Ciba's support enabled the appointment of another entomologist and biochemist to Roman's team, and financed the construction of sophisticated apparatus for simulating field treatment of whiteflies and resistance development in the laboratory. These 'field simulator' chambers (93) were the culmination of Roman's ideal to incorporate more realism into laboratory selection experiments, thereby gaining a clearer insight into its buildup in the field. This apparatus proved extremely successful and has since been extended at Rothamsted to more complex systems including both whitefly natural enemies and insecticides as control agents. Meanwhile, as Roman anticipated, *B. tabaci* has undergone a dramatic increase in importance and geographical range. It is now the most feared pest in many tropical cropping systems, occurs throughout southern Europe, and is regularly found on protected crops in the UK. Rothamsted remains at the forefront of research into managing resistance in this species.

The last species Roman introduced to Rothamsted, in 1989, was the European Red Mite, *Panonychus ulmi*. Although a serious problem on deciduous fruit in Europe, little was known about its resistance due to difficulties with culturing strains in the laboratory. Roman's last field trip was to collect mite samples from Kent to initiate this project. By then his final illness had been diagnosed, but despite being physically weak he was clearly buoyed with enthusiam for the challenges this species presented. Sadly, Roman did not survive to see this aspect of his programme reach fruition.

INSECTIDE RESISTANCE MANAGEMENT AND WORK OVERSEAS

From the mid 1980s onwards, Roman gradually found far less time to spend at the laboratory bench. This partly reflected a burgeoning administrative workload; his research team now consisted of 10–12 employees, and his responsibilities had increased accordingly. He nonetheless maintained close contact with senior colleagues and an active involvement with research projects. Formerly a reluctant traveller, he now accepted readily speaking engagements and even involved himself in the organization of conferences including the 11th International Congress of Plant Protection in Manila in 1987, and an international symposium on 'Combating Resistance to Xenobiotics' held at Rothamsted in 1986 and published as a monograph (85). One reason for undertaking these duties was the need to publicize his group's achievements during a period of severe cutbacks in support from funding bodies. Another was his growing determination that the wealth of information accumulated on resistance should be applied more effectively to combat this problem in practice. The management of resistance cannot be tackled adequately in an isolated laboratory environment. Its success demanded commitment from scientists working alongside all other sectors of the pest management community. Roman was to devote much of the remainder of his career to promoting the cause of resistance management on a global scale.

The objective of insecticide resistance management (IRM)* is to conserve susceptibility to insecticides, through control strategies aimed either at curbing resistance to currently used compounds, or preventing the development of resistance to existing or new pesticides. In a series of critical and influential reviews (54, 80, 82, 87, 88, 90), Roman explored the utility of tactics proposed for this purpose, and comcomitantly undertook research and several overseas consultancies that gave him an unprecedented insight into factors influencing the implementation of IRM strategies. Three examples suffice to highlight his achievements in this respect.

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* This acronym was first coined in a a review paper by Sawicki and I. Denholm(82). Another option considered at the time was 'RMS'–an abbreviation of 'Resistance Management Strategies'. This, however, coincided precisely with Roman's initials and was more than his immense modesty would bear!

Roman's earliest encounter with resistance management arose from work on the potential for pyrethroid resistance in Danish and U.K. housefly populations. In 1978, registration authorities in Denmark refused to approve residual pyrethroid formulations for fly control on the grounds that such residues would lead to intense selection for pyrethroid resistance. As a result, Danish farmers continued using space-sprays of non-persistent pyrethroids to good effect. Roman submitted a confidential document to the Ministry of Agriculture and pesticide manufacturers emphasizing the severe risk of resistance if residual formulations were to be approved in the U.K. Such warnings were ignored, and pyrethroid resistance rapidly increased on animal farms as a consequence (55, 69).

Roman refused to accept this situation as a lost cause. He initiated laboratory and field experiments that confirmed the selection potential of residual formulations, and showed that regimes based on space-sprays could maintain effective control, even of populations with a proven ability to develop pyrethroid resistance (65, 84, 92). Confronted with such unambiguous results and supporting evidence from the Ministry of Agriculture's Central Science Laboratory, the U.K. registration authorities relented and withdrew approval for using photostable pyrethroids against houseflies inside farm buildings. Existing products were re-labelled to warn of the resistance risks that his team had substantiated so convincingly.

Roman's first involvement in IRM overseas followed a visit in 1975 to Egypt. Before 1976, cotton pests in the Nile Delta region had been controlled by several applications of the same insecticides. This had led rapidly to control failures through the sequential development of resistance in the leafworm *Spodoptera littoralis*. Trials in 1975 and 1976 showed that the new synthetic pyrethroids were outstandingly effective against DDT- and OP-resistant leafworms, and prompted the Egyptian authorities to ensure that the pest would not develop resistance to this group of insecticides. Roman was invited to inspect laboratories, visit field sites, and to advise on possible IRM tactics. His recommendations prevailed and, in 1978 the Egyptian Cotton Protection Committee released pyrethroids for agricultural use with strict instructions that they were to be restricted to a single application per year, used only against *S. littoralis,* and applied only to cotton. This tactic was closely adhered to and achieved its objective. Until 1989 at least there were no reports of *S. littoralis* having developed resistance to pyrethroids in the field, even though laboratory experiments confirmed its potential to do so.

Although IRM was implemented five years earlier in Egypt than in Australia, events in the latter country during the 1980s attracted more widespread publicity. The Australian Field Crops Insecticide Strategy owed its origin to a dramatic failure of pyrethroids to control the bollworm, *Helicoverpa* (*=Heliothis*) *armigera*, on cotton in Central Queensland in January 1983. Laboratory tests confirmed pyrethroid resistance, and prompted the Australian authorities to implement, within six months, a strategy to prevent the extension of resistance to the rest of Eastern Australia.

The Australian strategy depended for its success on goodwill and compliance from growers and the agrochemical industry. Through visits to Australia in 1985 (73) and 1987, Roman played a crucial role in sustaining this showpiece strategy. In Australia he lectured at most of the participating research centres, and through patient diplomacy convinced dissident growers and insecticide manufacturers of the merits of the scheme. Although a large number of entomologists visited Australia during these formative years, Roman is widely acknowledged (especially within the country) as having provided the most constructive support from overseas.

Roman made many other contributions to resistance management. Procedures for monitoring resistance received critical appraisal in several research and review articles (29, 62, 71, 83, 88). Recognizing the key role of the agrochemical industry in facilitating IRM, he maintained a close dialogue with major companies both individually and through the Insecticide Resistance Action Committee (IRAC) – their forum for addressing resistance problems and funding research projects. Roman was regarded with great affection and respect within the industry, even though some of his views conflicted with short-term commercial interests. His influence in these areas was encapsulated by the Australian entomologist Neil Forrester who, addressing the International Congress of Pesticide Chemistry in 1994, referred to Roman as the 'father of insecticide resistance management'.

Concluding remarks

Roman's scientific achievements should not obscure his many personal qualities. Although a hard taskmaster when needs dictated, his approach to management was informal and aimed at providing staff with as much freedom as possible. His unstinting support of colleagues was never more apparent than during a period of severe financial attrition in the mid 1980s; his group was one of few that escaped any reduction in staffing. Among research leaders at Rothamsted, Roman was also probably unique in continuing to share unpopular insect-rearing duties at weekends on a rota system with junior colleagues and technical assistants. Such activities reflected an instinctive generosity that endeared him closely to the team he assembled with care, and led by inspiration and example.

In his final years, Roman received numerous invitations to attend conferences, give lectures, visit academic and industrial organizations and undertake consultancies. His conscientious fulfilment of these engagements involved many hours of exhausting travelling. These activities progressively drained his resources but his sense of duty drove him on whilst he was convinced of their beneficial consequences. He was, moreover, motivated by the desire to find satisfactory scientific solutions to problems widely considered intractable. Having spent many years working often seven days a week, he was buoyed by the prospect of retirement in 1990 and a period of relaxation in which to pursue his interests in classical music, natural history, art, architecture, photography and gardening. He was also looking forward to travelling with his Belgian wife Micheline, whom he married in Brussels in 1955. Together they dreamed of finding and renovating a farmhouse in France where they could savour the simple pleasures of life. Roman cherished the prospect of catching butterflies with his two granddaughters Gabriella and Florence born in 1987 and 1989 respectively. He derived much satisfaction from the achievements of his two daughters: Viviane Ann, born in 1957, who gained the final Diploma of the Institute of Linguists in French, and Veronica Helena M.B., B.S., born in 1958. Linguistic ability within his family was fostered by Roman and Micheline who always spoke to one another in French; English was reserved for national and international scientific communication.

Roman's garden in Harpenden was immaculate, and the envy and despair of his neighbours and friends. He brought to it the precision and eye for detail used in his scientific work. Alpine plants were a speciality with specimens collected on the motoring holidays that he took occasionally with Micheline and his daughters. He gladly placed his gardening skills at the disposal of any who could benefit, and on one occasion 'persuaded against his better judgement to help at an Open Day at Rothamsted, he soon abandoned his allotted task of explaining insecticide resistance and embarked on a highly successful gardening clinic' (The *Times*, 30 July 1990).

He failed to acknowledge as especially significant his contributions to human welfare. Although modest he was extremely proud and delighted with his election to Fellowship of the Royal Society in 1987, but typically a portrait photograph was not considered a priority. His only regret was that his guardians were not there to share in his joy and that of his family. He modestly avoided most social occasions where public recognition of his achievements might be accorded, but he did receive with his colleagues at Rothamsted the UNESCO Science Prize in 1978, and in 1989 was awarded the Gold Medal of the British Crop Protection Council for his outstanding contributions to research on insecticide resistance. In contrast, when his obligations took him abroad to numerous conferences his colleagues found him a delightful, relaxed and humorous companion whose fluent French often smoothed contacts for those less erudite.

FINAL DAYS

The news in 1989 that Roman had been diagnosed as suffering from a terminal illness was a devastating shock. To all who knew him this appeared a cruel reward for years of selfless devotion to science. Even while undergoing extremely debilitating treatment, Roman outwardly retained great optimism for the future and continued to visit Rothamsted to advise colleagues whenever his condition permitted. His official retirement in April 1990 was marked in a typically modest manner; he hosted a small party where he bade farewell to colleagues and acquaintances individually. Sadly, his condition then deteriorated rapidly. He died on 22 July 1990 in Cirencester, Gloucestershire, in the company of his close family.

Roman's friends and colleagues still feel a deep sense of personal loss. Andrew McIntosh, who was especially welcomed as a companion by Roman towards the end of his life writes:

> As a colleague at Rothamsted he was, at first, rather distant; this was the abiding product of a background very different from everyone else's. Gradually, we learned that he was a linguist, an artist, a superb swimmer and a gardener of professional quality; and that he had a great warmth and unusual humour, often directed at himself. The ability to stand apart from life was one of his many strengths; it ensured that he was unaffected by success, and helped him to accept his final illness without any self-pity.

ACKNOWLEDGEMENTS

Many of Roman's family, friends and colleagues provided great assistance with the preparation of this memoir. We particularly thank Micheline Sawicki, Andrew Farnham, Norman Janes, Andrew McIntosh, John Pickett and John Stevenson for their recollections of Roman, and for their critical reading of the manuscript.

The frontispiece photograph was taken in 1989, at Rothamsted and is reproduced with permission of the IACR.

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