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FRANCIS GERALD WILLIAM KNOWLES

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BY E. J. W. BARRINGTON, F.R.S.

Sir Francis G. W. Knowles, sixth Baronet, was born in Canada on 9 March 1915, the son of Sir Francis Howe Seymour Knowles, prehistorian and pioneer of physical anthropology, and Kathleen Constance Avering, daughter of William Lennon. He was educated at Radley and at Oriel College, Oxford, graduating B.A. in 1936 in the Honours School of Zoology, M.A. and D.Phil. in 1939, and D.Sc. in 1963.

His adoption of a scientific career conformed to a pattern that had been maintained in the main line of his family for some 200 years, those with Francis as their first name having become scientists and those with Charles admirals. There was a family link with Sir Francis Knollys, who was related by marriage to Queen Elizabeth I, but Knowles himself was directly descended from Charles, fourth Earl of Banbury. The first Baronet, Admiral Sir Charles Knowles, was Governor of Jamaica. The second, Admiral Sir Henry Knowles, fought under Nelson at the battle of Cape St Vincent. An early connection with the Royal Society was provided by John Knowles (1781–1841), biographer of Henry Fuseli, and one of the original members of the Athenaeum, who was elected into the Fellowship in 1821 for his scientific work, which included researches into the cause of dry-rot in sailing ships. The third Baronet, Sir Francis Charles Knowles (1802–92), was elected F.R.S. in 1830. He was a mathematician who later gained the Telford prize 'for an intricate mathematical problem'.

NAPLES

Francis Knowles, after graduation, was awarded the Oxford University Naples Scholarship, which enabled him to carry out research at the Stazione Zoologica for a period during 1937–38. This research was in a field which would now be called 'comparative endocrinology', although it had not then been so designated. It was well appreciated that hormonal regulation occurred in animals other than mammals, but investigations into it had developed as part of the general field of zoology. The results were fragmentary, and too little was known of the principles of mammalian endocrinology for it to be possible to incorporate studies of the
lower vertebrates, not to mention the invertebrates, into any unified interpre-
tation. However, the phenomenon of colour change in animals, brought about by
pigment movements in chromatophores, had attracted much attention from
zoologists, and Parker, at Harvard, and Hogben, in the United Kingdom, had
demonstrated the importance of chromactivating hormones in regulating the
movements, especially in fish and amphibians. J. Z. Young, who was Knowles’s
tutor at Oxford, had recently extended this work to lampreys. He had shown
that there was a hormonal basis for the diurnal colour change of lampreys and
their larvae, and had further demonstrated that the pineal organ in these animals
was light-sensitive and part of the chain of communication between the environ-
ment and the chromatophores.

Knowles began his work at Naples by following this lead (‘bringing John
Young up to date’, he explained at the time, with an apologetic twinkle in his
eye). Starting with Young’s experimental proof of a photoreceptive function of
the pineal in lampreys, he aimed at discovering whether any photomechanical
changes occurred as a response to changes in illumination. He found no change
in the distribution of the guanin-like pigment of the pineal organ of the larva,
but there were nuclear movements in its retinal cells. These were difficult to
account for, but he felt that they at least provided further proof that the organ
was sensitive to changes of illumination. Four decades later, we are still sadly
short of adequate information relating to pineal structure and function in any of
the lower vertebrates. Knowles was pioneering in a field which was too little
developed to yield more than sparse results and fragile interpretations.

However, he also explored other aspects of cyclostome endocrinology; in
particular, the effects of pituitary gonadotropins on young lamprey larvae, and
upon the sexual maturation of the adults. Lampreys attain sexual maturity in
three stages. There is first a modification of the fins, then the final maturation of
the gonads, and lastly a swelling of the labia of the cloacal region, the last taking
place just before spawning. Knowles found that injection of mammalian pituitary
preparations evoked the cloacal response in larvae and in immature adults, and
that testosterone and oestrone also did so in the adult but not in the larvae. The
results were not easy to interpret; the very rapid response of larvae to even
small doses of pituitary extracts suggested a direct action of the extracts, and the
absence of any changes in the gonads of the injected larvae could be held to
support this view. But, as with all such work at that time, the uncertain nature of
the injected pituitary material (he was using alcohol precipitates of NaOH or
pyridine extracts of acetone-desiccated glands) yielded results more suited for
speculation than for firm conclusions. But, he wrote, ‘the interest of these
experiments . . . lies not only in the proof that they provide of an endocrinal
control of the secondary sexual characters in lampreys but also in a comparison
with the endocrinal control of the sexual apparatus of higher forms. They provide
the earliest instance in the phylogenetic series of the association of the pituitary
gland of vertebrates with responses of the cloacal region. It is interesting to note
that the response of this region at this early stage already includes vasodilatation,
swelling, and epithelial changes, which are in some respects similar to those
found in mammals.' And so, in those far-off years, zoologists were feeling their way towards a comparative endocrinology. Certainly the work was yielding results, but Knowles soon came to feel that it was not prospering as he had hoped. Apart from difficulties of interpretation, it was not easy either to collect the larvae or to keep them alive in the laboratory. Electric fishing was not then available, so, like other students of lamprey larvae, he had to dredge his collections (200 animals a month) from the muddy banks of rivers, in this case the Sarno. On one disastrous day he found a whole batch of newly arrived animals dead in the aquarium (sea water had been run into it by mistake) and he was disconsolate. It so happened, however, that Lewis Kleinholz had arrived at Naples as a Sheldon Travelling Fellow from Harvard, fresh from his demonstration of hormonal control of the adaptive movements of the distal retinal pigment of the crustacean compound eye. He suggested to Knowles some interesting problems in crustacean endocrinology, more particularly in relation to the regulation of colour change, a field almost untouched, but with rich potentialities that had been revealed by the 1928 publications of the independent work of Koller, in Germany, and of Perkins, a pupil of Parker, at Harvard. Knowles turned to these problems enthusiastically, and accepted gratefully the opportunity to collaborate with Kleinholz, who recalls that 'with the characteristic physical extravagance of the young we spent many long days and nights in the laboratory'.

The collaboration, with the results and the close friendship that ensued, were decisive influences for Knowles, and he never forgot this. Many years later, Kleinholz received from him a book, inscribed 'To Lew:—a small tribute on the occasion of the twenty-second anniversary of our meeting and first collaboration at Naples. At the same time an acknowledgement of the debt I owe him for suggesting to me that I should start work on Crustacean Endocrinology—This small gift is the result.' It was a copy of Carlisle and Knowles’s Endocrine control in crustacea, a book that was one of the first substantial expositions of comparative invertebrate endocrinology.

Marlborough and Avebury

Soon after his interest in crustaceans had thus been aroused, Knowles took a step that might have arrested it, for in 1938 he joined the staff of Marlborough College as Senior Biology Master. He remained at the school for 20 years, leaving behind him the memory of a well liked and extremely good teacher. It was no easy assignment, for he followed A. G. Lowndes, who had managed to instil enough enthusiasm into his pupils to bring at least seven of them into the Fellowship of this Society; a result, according to one of those pupils, of sheer brutality, a cantankerous nature and a real flair for making biology exciting. Knowles’s lively qualities as a teacher can be judged from books that he wrote during this period: The living organism and Man and other living things. These are O-level texts which marked a considerable departure from tradition in their exciting presentation, which included an abundance of photo-micrographs and an emphasis upon research.
That emphasis was no doctrinaire lip-service, for he managed to continue and
develop his work on crustaceans, and attended an international colloquium on
arthropod endocrinology held in Paris in 1947. This meeting, sponsored by the
C.N.R.S., was a small affair, with two representatives each from England,
Denmark, Switzerland and the United States, and eight from France, but it was
a sign of greater things to come. Much of his research at this period was done
during school holidays, when he paid regular visits to Plymouth, Naples and
other marine centres. The award of a grant from the Browne Research Fund of
the Royal Society enabled him to spend a sabbatical term at Bermuda, while with
a grant from the Nuffield Foundation he was able to extend his work into the
new and promising field of crustacean ultrastructure.

For the ultrastructure work he made use of the consultant service that was
then being operated at Aeon Laboratories, which permitted anyone to bring
along specimens and to have them prepared and examined in a high resolution
electron microscope. Knowles struck what appealed to the physicists in the
laboratory as a pleasingly picturesque note, when he arrived with a pail, ice and
Mediterranean prawns, which he dismembered and passed on to them for
processing. But this phase soon passed. He resolved to learn the preparative
techniques himself, and was soon arriving with prepared sections of a very high
quality. ('I like technique to be perfect' he would often say in later years.)
From these the staff were able to generate large numbers of excellent electron
micrographs.

The collaboration with Aeon Laboratories extended over some two or three
years, until he acquired, as will be seen later, his own facilities at Birmingham.
He is remembered by one who worked with him at the Laboratories as a 'tall,
erect, bespectacled figure, nearly always with a cheerful smile and infectious
good humour. This did not prevent him from driving us hard to obtain the
maximum results in the time available, and to show irritation if things were not
done in a way which suited his high standards. It was always a pleasure to work
with him—as so often it is with someone who is clearly doing good work and
knows what he wants.' The laboratory staff marvelled at the freedom that he
enjoyed at Marlborough College, and at his cleverness in discovering that he
could only work with animals that demanded frequent visits to Naples for their
collection. But his research was, of course, a great inspiration to his pupils. Some
of it was carried out during term time, and often there were one or two Upper
Sixth scholarship boys helping him. The result was a stimulus and excitement
which few if any schools could have matched at that time. And there were
benefits on the side, as was apparent to an American endocrinologist who,
during a short visit, was kept busy for half an hour trying to explain to the boys
why his countrymen were willing to put up with Senator Joseph McCarthy.

It was during this period that Knowles purchased Avebury Manor from Mr
Alexander Keiller, F.S.A., who had used this Elizabethan residence as a base
during his archaeological work on the Avebury Stone Circle, but had now sent
most of its contents to auction. Knowles intended to develop it solely for his
family, but when he took possession of it on 20 April 1955 he found the fabric in
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such need of repair that he decided to accept financial aid for its renovation, and, as a necessary condition, to open the house and grounds to the public. He was soon climbing over the roof, creeping behind panelling, crawling up chimneys, and subjecting the whole of the manor to a close biological scrutiny to ensure, as he later put it, that no fungus was left in peace, no woodworm untroubled and no beetle undisturbed.

The first tourists entered in May 1956, and thereafter, with some 30 rooms, 50 acres of grounds, 8 gardens and 1 mile of topiary at his disposal, it provided ample and continuing scope for the exercise of his acute business sense, while still remaining a friendly home where he and Lady Knowles were generous and memorable hosts. But Avebury meant much more to him even than this. It became an absorbing love, and the restoration of its structure, the beautifying of its grounds and the seeking out of suitable furnishings (for which he had an unerring eye) provided for him a fulfilment that complemented the satisfactions of his scientific research.

Crustacean neurosecretion

When Knowles first turned to the study of the chromactivating hormones of crustaceans, attention had been concentrated upon the eye-stalk and its contained sinus gland, but it had become clear that this could not be the only source of these hormones. He himself, following up a suggestion of Kleinholz, had shown in 1939 that the thoracic nervous system of prawns still contained a chromactivating factor three or four weeks after the sinus gland had been removed, and workers in the United States had shown this to be true also of the tritocerebral commissure and connectives of the shrimp. From these and a wide range of other studies, both morphological and experimental, it had become clear that the invertebrate nervous system, and especially that of crustaceans and insects, must be the source of hormones, which were probably secreted by certain nerve cells that had been shown to have the cytological characteristics of gland cells. So far, however, there had been no histological study of these regions, nor any attempt to define precisely the sources of the hormones. Indeed, crustacean endocrine organization was proving very difficult to interpret, because it did not conform to the classical pattern established for vertebrate endocrine glands.

The event which revolutionized the interpretation of vertebrate systems, and invertebrate ones as well, was the demonstration by Bargmann and his associates that the hormones of the neural lobe of the mammalian pituitary were conveyed from the hypothalamus along neurosecretory fibres as material that could be visualized by light microscopy. This fundamentally important advance provided a link, long sought, between vertebrate endocrinological organization and the concept of neurosecretion that had been so patiently developed by Ernst and Berta Scharrer, and it provided the key to the understanding of invertebrate systems, which were now seen to be predominantly neurosecretory ones. Knowles's contribution was to use this advance as a basis for the correlation of structure with endocrine activity in the tritocerebral region of the crustacean.
nervous system. Enami, working independently in Japan, was doing the same for the sinus gland and related nervous structures in the eye-stalk, as were several groups in the United States.

Knowles, by using methylene blue preparations of dissected material and by reconstructing serial sections, revealed the importance of the post-commissure nerves, the very existence of which had been overlooked by some previous workers. These nerves he found to be filled with fuchsinophil droplets, and to bear at their endings enlargements of the epineurium which were partly fused with a blood sinus, and which, like the sinus gland of the eye-stalk, were the points at which the neurosecretions were released into the circulation. Knowles and Carlisle, to emphasize the importance of these release centres in neurosecretory systems, vertebrate as well as invertebrate, designated them 'neurohaemal organs'. The term found favour and has been incorporated into the literature.

In 1951 Bargmann had suggested to the Scharrers that the new concept of neurosecretion should be firmly established at an international gathering, and it was as a result of this initiative that the First International Symposium on Neurosecretion was held at Naples in May 1953. Knowles contributed a report of his work, a full account being published a little later in the same year (Proc. R. Soc. Lond. B 141, 248). It provided an elegant and convincing demonstration of crustacean neuroendocrine organization, based upon an unassailable correlation of anatomical and physiological evidence. He also took the opportunity at Naples to suggest again that the concept of the neurohaemal organ might be included in the formal definition of neurosecretion.

Crustacean chromatophores contain several pigments, which react differently to environmental stimuli, and thus make possible the subtle adaptive responses of these animals. Knowles's injection experiments, carefully correlated with his light microscopy, showed that extracts of the tritocerebral region differed from extracts of the sinus glands in their actions upon these pigments. He was always very interested in technical equipment and gadgets, and not least in photography, and so he was able to present beautiful colour photographs (see, for example, Endeavour 14, 95) to show that sinus gland extracts produced almost transparent prawns, whereas extracts of the postcommissural nerves darkened them. All of this contributed to the evidence, accumulating in various laboratories, that a number of hormones were probably concerned in colour adaptation in crustaceans, and attempts to separate these factors were already in train.

Knowles, in collaboration with Carlisle and M. Dupont-Raabe, applied the techniques of paper chromatography and paper electrophoresis to this end. Pigment-activating materials were identified at various points along the paper strips, suggesting the presence of different and, in some instances, antagonistic hormones. But it was recognized, at this early stage, that these results gave no proof of the actual existence of these hormones. Among the possible complications was the likelihood that precursors and non-hormonal extractives, not normally released into the blood stream, might be included in the materials injected. Nevertheless, the general principle of multiple hormones remains sound
and has been supported by later work. The small size of these animals has impeded the chemical characterization of the factors concerned, but Knowles and his collaborators were able, as a result of studies on enzymatic inactivation of their fractions, to suggest that these factors seemed likely to be polypeptides, indicating another possible line of resemblance between invertebrate and vertebrate endocrine systems.

COLD SPRING HARBOR AND BIRMINGHAM

In Knowles’s career 1958 was a crucial year. Some years previously, in 1954, there had been held in Liverpool University an International Symposium on Comparative Endocrinology, largely through the inspiration and energy of Ian Chester Jones (now Professor of Zoology at Sheffield University). Some 60 persons had attended, and with such good effect that the symposium became the first of a continuing series. The second was held at Cold Spring Harbor in May 1958, with some 150 members. Knowles had been invited to present a review of the control of pigmentary effectors, thanks to Professor Howard Bern, of Berkeley, who recalls that he was the only member of the organizing committee who knew who this schoolmaster at Marlborough College was, and what exactly he was doing.

Knowles used the opportunity to report on his recent crustacean work, referring in particular to the separation studies and to his ultrastructural investigations. These, while still at an early stage, were already showing that the secretions were present in what has now become the familiar form of electron-dense droplets bounded by membranes. To re-read in Nature an account of the symposium proceedings is to be reminded that in 1958 the use of electron microscopy, and the projection of colour slides, were still matters for admiring comment. Knowles was one of the speakers singled out for commendation in these respects.

He was toying at that time with the possibility of arranging a lecture tour in the United States on the subject of the stately homes of England, inspired, no doubt, by his experience at Avebury. His highly professional performance at the symposium suggested that this might have been a very successful venture had it ever materialized. He spoke without notes, illustrating his argument with a long sequence of beautiful slides that were presented with machine-gun precision. Each change of slide was summoned by a hammer-like blow of his pointer, delivered with a vigour that would have served for Wotan’s invocation of Loge. Howard Bern was the projectionist, and he had been personally instructed in the art by Knowles. He recalls that he performed faultlessly and earned the plaudits of the lecturer.

Also present at the symposium was Professor Sir Solly (now Lord) Zuckerman, who was at that time vigorously developing the Department of Anatomy at Birmingham University. Greatly impressed by the quality of Knowles’s research, which he had already encountered at the Naples Symposium of 1953, and feeling that he could offer him better facilities than were available at
Marlborough, he invited him to join his Department as Lecturer with special responsibility for the development of an electron microscope unit. Knowles’s ignorance of human anatomy made the proposal an unconventional one, but the Faculty Board accepted Zuckerman’s argument that endocrinology was indivisible, whether the material studied was invertebrate, vertebrate or human. So Knowles moved to Birmingham in 1958, to take up what he saw from the first was to be an exciting assignment.

He rapidly established himself at Birmingham as a highly dynamic biologist and a very versatile technician, who was willing to spend without stint the time needed to demonstrate, in his exquisitely neat laboratories, what were then the new techniques of electron microscopy. At first he commuted from Avebury Manor in his aged Rolls Royce, which served also for frequent forays into Birmingham in meticulous search for the best types of drawing board, record books, plastic bins and other paraphernalia needed for the new unit. ‘He did not hide behind either his title or his standing as a scientist’, recalls one of his Birmingham colleagues, ‘but actively involved himself and others in every facet of organization leading up to the research work itself.’

Residence in Birmingham, however, was essential, if only because he liked to rise early, and to have time for pondering, and for planning the day’s work. Early in 1960, therefore, he acquired the lease of ‘The Mythe’, a house at Edgbaston which was early Victorian in date, but somewhat late Georgian in style. With it went a great deal of land and trees, a lawn, splendid rhododendrons and a tangle of derelict orchard. He established himself in a suite of rooms on the first floor, decorated in the style which he always favoured, whether here, or at Avebury, or, later, in his Mayfair flat—a tasteful re-creation of an earlier elegance. The rest of the property he leased to other tenants who included two of his departmental colleagues. So, in an area which retained at that time an attraction which has now been overridden by executive style housing, there was established, within some 20 minutes’ walk of the Medical School, a small but congenial academic community. Its members were as diverse in their domestic tastes as in their biological pursuits and educational background, but they were unified by the warmth and enthusiasm of one whom they happily accepted as the ‘Master of the Household’.

It was appreciated that he was a zoologist by training, and it was thought significant that he began at Birmingham by enlivening his room with a seawater aquarium, wherein anemones and prawns were suspected to be making the point that they were the animals that really interested him. He did, indeed, continue for a time his crustacean studies, and reported on the ultrastructure of the pericardial organs of Squilla (where he found more than one kind of secretory inclusion), but he was to work loyally up the animal scale, via dogfish and eels, until at last his attention was absorbed by the hypothalamus of the monkey.

His main interest was research, but he became deeply involved in the reorganization of the preclinical curriculum, his chief contribution being the establishment of an interdisciplinary course entitled ‘The living cell’. At first this course ran in parallel with the traditional histology course, but later the two were
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knitted together under his guidance. The scheme has by now been changed in many ways, but elements of it can still be detected. Also at this time, in 1960–61, he contributed to the construction of a separate and integrated preclinical course for dental students, while in 1962 he collaborated with P. Eckstein in the organization of a N.A.T.O. Advanced Study Institute on Techniques in Endocrine Research, the proceedings of which were later published as a valuable compendium.

His research developed rapidly after the installation of the departmental electron microscope, and his enthusiasm became infectious. He would take over half of the large museum to spread out his electron micrographs, and it was impossible not to become involved. ‘One simply stopped to look, and that was that...’ In these and other ways his activities had a considerable and lasting influence upon the Department. ‘We lost more than just a man when he left for London.’ His promotion matched his influence. He was Lecturer from 1958 to 1963 and Reader from 1963 until, in 1967, he was appointed Professor of Comparative Endocrinology. However, he left in that year for the University of London, to become Professor of Anatomy at King’s College.

FROM FISH TO MONKEYS

Knowles’s first major publication in fish endocrinology dealt with the pituitary of elasmobranchs, and was an important contribution to continuing developments in the concept of neurosecretion. This term had been restricted at first to a situation in which secretions were released direct from nerve endings into the blood stream at neurohaemal organs, without any involvement of synaptic connections, but he recognized that this restricted definition, which he had originally advocated, was now creating difficulties. In particular, there were reports of neurosecretory fibres making direct contact with endocrine cells, examples being found in the pars intermedia of the pituitary of elasmobranchs, amphibians and mammals, and in the pars distalis of teleost fish. It had thus become important to compare these presumptive secretomotor junctions with conventional neurohumoral synapses. Promising material for such comparisons was available in the neuro-intermediate lobe of elasmobranch fish, where is found a particularly high degree of penetration of endocrine tissue by neurosecretory fibres.

Knowles selected for this study the dogfish Scyliorhinus. The pituitary histology of this and related forms had already been thoroughly studied by light microscopy, and it was known that at least two kinds of nerve fibres entered the pars intermedia, one being typically neurosecretory (with inclusions stained by the standard Gomori stains), while the other did not react to these stains. Moreover, there had been good experimental analysis of the regulation of elasmobranch colour change by the melanophore-stimulating hormones (MSH) secreted by the pars intermedia.

His thorough electron-microscopic study of the neurointermediate lobe enabled him to confirm the presence of two distinct types of nerve fibres, and to
suggest differences in their functions. The conventional Gomori-positive type innervated the synthetic pole of the endocrine (MSH-secreting) cells of the pars intermedia; this type he presumed to be peptidergic. The Gomori-negative type innervated the release pole of the cells; this type he presumed to be aminergic. He designated them respectively the type A (peptidergic) and type B (aminergic) fibres, a terminology which has been accepted into the literature.

His thoughts in relation to this work were combined with those of Howard Bern in a joint communication (1966) which emphasized the need to extend the concept of neurosecretion to include other aspects of regulation beside the production of blood-borne hormones. The concept of the neurohaemal organ as an essential element of neurosecretory systems had proved useful, but his new findings were showing that it was too limited. Account had also to be taken of amine-secreting fibres, and of neurosecretomotor junctions that resembled synapses, but which released hormones by diffusion. Neurosecretory organization was proving to be unexpectedly diversified in form, function and biochemistry. Knowles and Bern suggested that one unifying feature could be discerned in the participation of all neurosecretory neurones in some form, whether direct or indirect, of endocrine control, or in the inclusion of these fibres to form all or part of an endocrine organ. They recognized that this formal demarcation still left problems to be resolved. Indeed, the statement was a compromise between two somewhat divergent viewpoints, and events have not justified Knowles’s preference for excluding non-endocrine effectors from the concept of neurosecretory regulation. But the statement was intended to simplify the issues 'for the time being', and in this the two authors were successful. Both were Canadians, and this, as Knowles pointed out to Bern, was good reason for them not quarrelling!

Knowles's study of Scyliorhinus, which was closely followed by his election into the Fellowship, led to a fertile period of collaboration at Birmingham with Lutz Vollrath, now Professor of Anatomy at Mainz. In a thorough study of the pituitary of the eel, they found type A and type B fibres in the pars intermedia, the type A ones being further subdivisible into type A₁ and type A₂ by the size of their granules. In contrast to the situation in the pars intermedia of the dogfish, these fibres did not make direct secretomotor junctions with the intrinsic endocrine cells, but their terminals were nevertheless only separated from those cells by very narrow intravascular channels into which both types of fibres discharged. The relationship was clearly very suggestive of neuroendocrine control of pars intermedia activity, and was fully in line with the expanding concept of neurosecretion.

Knowles and Vollrath also studied the pars distalis of the eel's pituitary. They applied light and electron microscopy to the analysis of the cell types, correlating their findings with aspects of the life cycle and with the evidence of other workers. They then paid special attention to a remarkable feature of the organization of the teleost pituitary: the lack of a typical median eminence and hypophysial portal system, with the pars distalis being regulated by nerve fibres that directly invade it. They concluded that these were mostly type B fibres,
which probably arose largely from the nucleus lateralis tuberis, a finding that was in line with previous evidence from the light microscopy of other investigators. As in the pars intermedia, there were no direct contacts between the fibres and the intrinsic endocrine cells of the eel’s pars distalis, but separation by spaces of some 2000–4000 Å again indicated some functional regulatory relation.

These pituitary studies revealed a feature which was to engage much of Knowles’s future attention. This was the existence in the eel of direct synaptic contacts between type A fibres and certain pituicytes which surrounded extensions of the infundibular recess and which resembled ependymal cells. Type A₂ synapses were common in fish that had been maintained on an illuminated white ground, while type A₁ synapses were only found in animals that had been recently transferred from fresh water to sea water. Knowles and Vollrath put forward the novel suggestion that the neurosecretory fibres promoted synthesis of a secretory product in the pituicytes, which was then released into the cerebrospinal fluid and transferred in this to the preoptic nucleus. They thought that this system might provide a feedback from the pituitary to the hypothalamus, the stimulus for the release of MSH effecting also release of the pituicyte secretion. But they recognized that this was largely speculative, and, in particular, that the concept of transitory synapses was an unconventional one.

The possibility that certain pituicytes (now called tanycytes) might be involved in some form of pituitary feedback system was further studied by Knowles, in collaboration with T. C. Anand Kumar, during a study of the rhesus monkey. They reported in this animal a specialized area of ependymal cells situated anterolaterally in the tuber cinereum. Long processes from these cells, packed with electron-dense granules, extended to the region of the pars tuberalis, and terminated at the junction of the pars tuberalis and median eminence, either in the walls of blood vessels or in direct contact with cells. They found evidence from injection experiments that oestrogen or oestrogen metabolites might be selectively absorbed by these tanycytes. There was thus some support for the earlier postulate of a feedback mechanism derived from the eel studies, but involving in the monkey the possibility of tanycytes taking up material from the cerebrospinal fluid, and transferring it to the region of the median eminence. It is still too early to appraise these views of Knowles regarding an ependymal–hypothalamic relation, but they certainly raised challenging questions that have helped to open up a field of great potentiality. They were still occupying his attention when he died.

**London and the End**

His removal to King’s College, London, and to a Mayfair flat from which he commuted at weekends to Avebury, led to an expansion of his pattern of research. Relatively few workers had so far benefited from close contact with him, but he now began to build up a research group, recognizing, perhaps with something less than total joy, that this was what the times demanded. Funds from the Medical Research Council and the Wellcome Foundation made possible the
purchase of an electron microscope which was housed in laboratories at Regent's Park, made available by the Council of the Zoological Society. Support from N.A.T.O. and the Science Research Council made it possible for him to enlarge his research team, and he developed collaboration with workers in the University of Lund, and, supported again by the Wellcome Foundation, with others in the Departments of Anatomy at Bonn and at Regensburg, at the Max Planck Institut, Göttingen, and at the Station de Recherche de Physiologie Animale, Jouy-en-Josas, France.

During these last years his skill in administration came to the fore. He was Dean at King's College, and in 1973 he was persuaded to become Chairman of the Biological Sciences Committee of the Science Research Council and a member of its Science Board. Such work is not everyone’s choice, and it may not have been his first love, but it was, he said, a thing that he ought to do, and he would do it. He is gratefully remembered by the Council officers for the support that he gave them, and for his handling of disappointed eminences with tact and, if need be, with a direct firmness that might not have been expected of him by casual acquaintances.

As for comparative endocrinology, his last major administrative contribution to it was the organization of the Sixth International Symposium on Neurosecretion, which was held in London in September 1973. The task was particularly welcome to him, for this gathering celebrated the twentieth anniversary of the first symposium at Naples, where his crustacean studies had attracted so much interest. The occasion was not without its problems, but the great success of the symposium was rightly applauded as a tribute to his ‘multilateral diplomacy’.

He knew that he was hypertensive, and his closest friends realized that he must be at some risk, but they were none the less shocked and saddened by the premature end of his career. He died suddenly in London, on 13 July 1974, at the age of 59, when he was already seriously considering retiring at 62 in order to devote his time to research and to the continued development of Avebury Manor. He did not live to see the appearance of the symposium volume (Neurosecretion—The final endocrine pathway) which he and Lutz Vollrath had been editing, but his elegant and perceptive introductory review (‘Twenty years of neurosecretion’) provides a fitting memorial of his own pathway through an absorbing field of comparative endocrinology.

Members of the Third International Symposium on Neurosecretion, held at Bristol in 1961, still remember the delightful hospitality of Sir Francis and Lady Knowles. ‘After feasting on salmon and champagne, the dawdlers among us were ushered out with the explanation that the first group of guided tour visitors was about to arrive.’ Tourists, indeed, were a continuing hazard for guests at Avebury, whether they were having tea in the Library, against a background of admiring comments, or taking pre-lunch drinks on the terrace by the lily pond while visitors speculated audibly as to the whereabouts of the bar. The touch of sharp contrast thereby provided appealed to the love of display that was such a marked element in Knowles’s character.
Indeed, he enjoyed all contrast and variation, both biological and social, and this enjoyment is vividly expressed in the recollection of a Birmingham colleague. He recalls seeing Knowles in the Department one Saturday morning, clad in a conventional dark suit and white shirt, and then being startled a few hours later, to see him sweep from the front door of ‘The Mythe’ to his Rolls, wearing tight trousers, an open-necked shirt, and a long cloak, with a gold cross at his throat. ‘A very spectacular exit for the weekend, somewhat reminiscent of a scene from La Dolce Vita.’

This element of display was less attractive to some than Knowles may have realized, but his friends (and they were many) were never among their number, for they recognized and appreciated the gaiety and the sense of humour that went with it. And, of course, they knew that it overlay a biologist of elegant and pioneering achievement. His early death (the more tragic in that his university career did not begin until 1958) has been mourned in many parts of the world by comparative endocrinologists who had learned to rely upon him for keen critical analysis of current concepts and an uninhibitedly provocative presentation of new ones. No less impressive was his concern with the development of links between researchers in different countries. He did not always give the impression of being susceptible to sweet reason. In fact, however, he was a humble man, and a sensitive one, always ready to listen, and not least when he could give encouragement to young research workers, and help to guide them, without ever forcing himself upon them, into paths which might lead them to new scientific concepts.

‘He had a profound influence on my way of thinking and on my career’, writes one of his colleagues, while to another, ‘life would have been a lot poorer had I never met him’. One of his American friends, who shared with him the excitement of the flowering of crustacean endocrinology, remembers his dynamism and never-failing youthfulness, and how, in a two-day visit to England, filled with enthusiastic and electrifying movement from place to place, ‘we flew, even though we were earthbound in an automobile. . . . As much as anyone whom I have known, Sir Francis demonstrated that one could be both a distinguished scholar and a warm vibrant person.’

Sir Francis Knowles left no Personal Record, but I have been greatly helped by the advice of some of his friends and colleagues, to whose recollections I have added some of my own memories of the development of comparative endocrinology. I am especially grateful to Lady Knowles for most kindly inviting me to meet her at Avebury Manor during the preparation of this memoir.

The photograph is by G. Argent.

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