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THE AUSTRALIAN NATIONAL UNIVERSITY
JOHN CURTIN SCHOOL OF MEDICAL RESEARCH
DEPARTMENT OF PHYSIOLOGY
ANNUAL REPORT - 1965

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STAFF

Professor:

Sir John C. Eccles, M.B., B.S., M.A., D.Phil., Hon.Sc.D.
(Cantab.), Hon.D.Sc.(Tas.), Hon.LLD (Melb.), F.R.A.C.P.,
F.R.S.N.Z., F.A.A., F.R.S.

Professorial Fellow:

D.R. Curtis, M.B., B.S., Ph.D.

Electronics Engineer:

J.S. Coombs, M.Sc.

Senior Fellow:

J.I. Hubbard, B.med.Sci., M.A., B.M., B.Ch., Ph.D.

Fellows:

J.C. Watkins, M.Sc., (till 31.7.65); Rosamond M. Eccles, M.Sc.,
Ph.D.; R.I. Close, M.Sc., Ph.D. from September.

Senior Research Fellow:

J. Fex, F.K., M.D., Docent.

Research Fellows:

R.I. Close, M.Sc., Ph.D. (till September)
Y. Løyning, Cand. Med. (to October)
K. Sasaki, M.D., Ph.D.
T.J. Biscoe, B.Sc., M.B., Ch.B. (from April)
G.A.R. Johnston, M.Sc., Ph.D. (from September)
R. Ryall, B.Sc., Ph.D. (from December)

Visiting Fellows:

G. Pilar, M.D. (to February)
P. Matthews, M.A., D.M. (from February-November)
P. Strata, M.D. (from September)
D.M. Lewis, B.A., MB.BChir., Ph.D. (from September)

Honorary Fellows:

D. Quastel, M.D., Ph.D. (to June)
Prof. K.T. Brown, Ph.D. (to September)

Research Assistants:

K.S. Cheah, B.Sc. (till April)
Nancy E. Stone, M.Sc., Ph.D. (from February)
Helen L. Lloyd, M.Sc. (from June)

Head Technician:

L.M. Davies, Dip.Mech. & Elect.Eng., A.M.I.I.T.A., M.Q.E.I.

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STUDENTS AND TEACHING ACTIVITIES

Six students are proceeding to the degree of Doctor of Philosophy:-

- Dr. M. Devanandan (commenced 25th February, 1963)
- Dr. R. Llinas (commenced 7th October, 1963)
- Dr. R. Harvey (commenced 6th April, 1965)
- Dr. D. Armstrong (commenced 1st June, 1965)
- Dr. D. Stenhouse (commenced 17th February, 1965)
- Dr. M. Landau (commenced 21st October, 1965)

The following students successfully completed the requirements for the degree of Doctor of Philosophy:-

- Dr. M. Crawford - "The pharmacological behaviour of cortical neurones"
- Dr. P.W. Gage - "Transmitter release from mammalian motor nerve terminals"
- Dr. Y. Løynning - "Effects of hypoxia and barbiturates on synaptic transmission".

The following were awarded the degree of Doctor of Philosophy:-

- Dr. T. Oshima - "The role of cations in the responses of cat spinal motoneurones";
- Mr. R.W. Ryall - "Mammalian synaptic transmitters and the pharmacology of central cholinceptive receptors".

Throughout the year there have been weekly departmental seminars. In February many members of the Department attended the Australian Physiological Society meeting at Sydney University, contributing five papers. Members of the department organized a very successful symposium, attended by neurophysiologists from all over Australia in honour of the great English physiologist Lord Adrian during his visit to Canberra in October.

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RESEARCH PROGRAMME

Much of the work reported for 1964 was completed and written up in 1965; some appears in the appended list of published papers, but many are still in press. Brief outlines of current research are given below.

The cerebellum

The systematic study of the function and mode of action of the various synaptic mechanisms in the cerebellar cortex has been continued with special reference to the action of the mossy fibre input, which undoubtedly must provide the information that is co-ordinated and synthesized in the cerebellum. Impulses in mossy fibres excite granule cells to discharge impulses along their axons, the parallel fibres, and usually it has been simpler to study the action of mossy fibres by exciting parallel fibres directly, so eliminating the complications inherent in these earlier stages of transmission. Thus by direct surface stimulation of a cerebellar folium a narrow band of parallel fibres has been excited giving a beam of parallel fibre impulses that travels for as far as 3 mm along the folium and in turn excites the basket and stellate cells en route. A systematic study has been made of the transverse distribution of the inhibition that these cells exert on Purkinje cells. In this way one of the principal operating characteristics of the cerebellar cortex has been defined (Eccles, Sasaki and Strata).

In addition a great simplification of cerebellar responses has been secured by the development of a most difficult operative procedure by Dr. Llinas. All nervous connections of the cerebellum with the rest of the nervous system are severed by dividing the three cerebellar peduncles on each side, but care is taken to preserve the blood supply intact. By the time of the experimental investigation some 6 to 23 days later there has been degeneration of all the afferent fibres to the cerebellum, that is the climbing and the mossy fibres. As a consequence stimulation in the depth

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of the cerebellum excites only Purkinje cell axons, ideal conditions being thus provided for investigation of the physiological events produced by antidromic propagation in these axons. Ideal conditions are also provided for the investigation of the physiological events produced by stimulation of parallel fibres because complications arising from inadvertent stimulation of mossy and climbing fibres are eliminated (Eccles, Llinas and Sasaki).

The only other input into the cerebellum, the climbing fibre, has been studied more remotely by investigation concentrated on the inferior olivary nucleus, which is the cell station for the climbing fibres. The cells in the dorsal and medial accessory olives are excited by a wide variety of afferent inputs from the hind limb. Afferent impulses from cutaneous and joint afferents are particularly effective, as also are the impulses from the secondary endings of muscle spindles (Group II). However it was also found that on brief repetitive stimulation the primary endings of muscle spindles (Group Ia) are also effective. There has been a systematic study of the spinal pathway in the ventral column (Armstrong, Eccles, Harvey, Llinas, Matthews).

The principal olivary nucleus receives its afferent input from the contralateral cerebral cortex and in turn projects to the contralateral cerebellar hemisphere. There has been a systematic physiological investigation of this pathway together with a detailed anatomical correlation (Armstrong and Harvey).

The spinal cord

During the year there was a continuation of the investigation of the presynaptic inhibition that is evoked in the spinal cord by physiological stimuli applied to muscle receptors (R.M. Eccles, Devanandan and Stenhouse). This year the investigation was designed to study the effectiveness of the γ -loop in accentuating presynaptic inhibitory effects of the Group Ia pathway in decerebrate animals. Very small (5-10 gm) stretches were applied to the anterior tibial muscles in cats with inter-collicular

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decerebrations, and the effect of this stretch was observed on the gastrocnemius and posterior biceps-semitendinosus monosynaptic reflexes recorded in the cut S_1 ventral root. The L_7 ventral root was intact. The L_7 ventral root was then cut and the experiment repeated. It was found that very brief stretches of less than 5 msec duration were more effective in depressing the monosynaptic reflex when the L_7 ventral root was intact. Evidence was obtained strongly suggesting the presence of an active γ -loop during pre-synaptic inhibition. In an allied investigation muscle contraction was used as a means of activation of the Golgi tendon organs. The effectiveness of contraction of flexor and extensor muscles of the knee and ankle in evoking presynaptic inhibition was demonstrated by observing the dorsal root potentials, the increase in the excitability of the central ends of primary afferent fibres and the depression of the monosynaptic reflex in the presence of strychnine hydrochloride.

Another line of research was the investigation of long latency effects on the monosynaptic reflexes of thigh and leg muscles when conditioned by other hind limb nerves, which are presumed to be mediated through mid-brain and hind-brain structures. The monosynaptic reflex of a flexor or extensor muscle of the knee or ankle was recorded in cats lightly anaesthetised with chloralose. The reflex was then conditioned with stimuli applied to other muscle nerves or skin nerves at various strengths. A delayed facilitation of the reflex was seen when the conditioning stimuli were applied to skin nerves or when the conditioning stimuli were greater than five times threshold for muscle nerves. This delayed facilitation could be depressed by excess anaesthetic and was abolished by cord section. It was present only when there were signs of uninjured pathways up and down the spinal cord, as demonstrated by the presence of a spino-bulbo-spinal reflex. A preliminary attempt was also made to localise the regions of the brain through which this delayed facilitation could be mediated (Devanandan, Lewis and Stenhouse).

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Reflexes from muscle afferents

A decerebrate cat usually displays a contraction of its extensor muscles when these are stretched - the classical stretch reflex. This is produced by activity in the afferents from the muscle spindle primary endings which monosynaptically excite the motoneurons. The primary endings in the soleus muscle were selectively activated by a longitudinal vibration applied to its tendon and the resultant stretch reflex in the muscle studied for different frequencies and amplitudes of the vibration (Matthews).

The auditory system

A technique has been developed for recording intracochlear events in the cat. Using this technique it has been shown that inhibition of auditory afferent activity is probably presynaptic (Fex).

Neuropharmacology

Studies have continued on the chemical sensitivity of nerve cells in the cerebral cortex and cerebellum, and a search for afferent pathways to these neurones for which acetylcholine could be the synaptic transmitter has so far been unsuccessful (Crawford, Curtis). An earlier investigation of the lack of action of strychnine upon the inhibition of cortical neurones has been confirmed, and a study commenced of the relationship between synaptic inhibition and the depression of spinal neurones by nor-adrenaline (Biscoe, Curtis). The gift of some oxalyl derivatives of amino acids from Indian research workers has led to an investigation of toxic factors responsible for lathyrism, human disease associated with the ingestion of certain peas (Curtis, Watkins). With the co-operation of the Electron Microscope Unit optimum conditions are being studied for the separation of nerve endings from brain homogenates, and methods are being refined for the isolation of possible transmitter substances from these endings (Johnston, Lloyd and Stone).

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Biophysical studies

Transmitter release. This year studies on the pharmacological (Hubbard) and electrophysiological properties of motor nerve terminals (Gage, Hubbard) were completed, as were studies on the effects of alcohol (Gage), cardiac glycosides (Gage) and hypoxia (Hubbard, Loyning) on the release mechanism. Interest has now turned to examination of the details of the transmitter release process using a number of approaches. The newest of these, which has already proven very fruitful, is the application of enzyme kinetics to the effects of ions on transmitter release (Gage, Hubbard, Quastel, Landau). The other approaches include the effect of temperature (Hubbard, Landau), the construction and testing of mathematical models (Gage, Hubbard, Landau) and electron microscopy of nerve terminals in a variety of conditions (Hubbard).

Muscle contraction. Studies on muscle concerned aspects of excitation-contraction coupling and the neural influence which controls the speed of shortening of striated muscles (Close).

OTHER ACTIVITIES

Professor Sir John Eccles had the honorary degree of LL.D. conferred on him by the University of Melbourne. He was elected a member of the World Academy of Art and Science, and to Honorary Membership of the New York Academy of Science. He was overseas on four occasions and attended the 23rd International Physiological Congress in Tokyo, the 8th International Congress of Neurology in Vienna, and the World Academy of Art and Science in Rome. He was part organizer of a conference on Neural Mechanisms of the cerebellum in Tokyo. He gave the Eddington Memorial Lecture at Cambridge. He also gave lectures to the Science Congress in New Zealand, to the Society of Biological Psychiatry in New York, to the first Nobel Symposium in Stockholm and to a Symposium of the New York Academy of Sciences. He contributed to

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a Ciba Symposium on Touch, Heat and Pain; and gave a course of lectures (3) for the Scuola Normale Superiore, Pisa. He lectured at the following universities and Medical Institutes; University of Goteborg, Sweden; University of Santa Tomas, Manila; University of Hokkaido, Japan (2); Oxford University; National Hospital for Nervous Diseases, London; Stritch Medical College, Loyola University, Chicago; National Institutes of Health, Bethesda (2); Harvard University; Yale University; Johns Hopkins University; University of Pennsylvania; University of Pisa; the Sorbonne; University of Milano. In October he gave the Boyer Lectures for the Australian Broadcasting Commission.

Dr. D.R. Curtis was elected as Fellow of the Australian Academy of Science. He was invited to present a paper at a Symposium on Neuronal Membranes and Bio-electric potentials held in Boston. He was also able to visit laboratories at Harvard, London, Mill Hill, Oxford, Cambridge and Heidelberg to discuss work in progress and to lecture. In June Dr. Curtis was advised of an award of US \$38,705 from the National Institute of Neurological Diseases and Blindness, Washington. This sum was provided to equip and staff another electrophysiological recording laboratory.

Dr. Hubbard was elected to membership of the Physiological Society. In Tokyo he attended and spoke at the IBRO cerebellar conference, the International Physiological Congress and the Comparative Neurology conference. He also lectured in Physiology departments in Tokyo, Kyoto and Osaka, and visited the Physiology department at Chulalongkorn University at Bangkok.

Dr. Rosamond Eccles also attended the IBRO conference and the International Conference in Tokyo, and visited many physiological departments in all parts of Japan, before going to Oxford for the remainder of her study leave.

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Mr. Coombs attended the 6th International Medical Electronics and Biological Engineering conference and the International Physiological Congress (both at Tokyo).

Dr. J.C. Watkins, who resigned in July to join the staff of the A.R.C. Institute of Animal Physiology, Babraham, gave a series of seminars upon Biological Membranes.

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