

PROGRESS IN BRAIN RESEARCH

VOLUME I

BRAIN MECHANISMS

*INTERNATIONAL COLLOQUIUM SPONSORED BY
THE INTERNATIONAL BRAIN RESEARCH ORGANISATION (IBRO)
ON SPECIFIC AND UNSPECIFIC MECHANISMS OF
SENSORY MOTOR INTEGRATION: PISA, 1961*

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Introductory Remarks on Behalf of IBRO and UNESCO

HERBERT H. JASPER

It is with great pleasure that I have accepted the invitation of Professor Moruzzi to speak on behalf of the International Brain Research Organization at the inaugural ceremonies of this Colloquium. In so doing, I am merely the spokesman for the many scientists from varied disciplines and special training in many countries who have formed a world community of colleagues with common interests in the brain sciences. We have been working together and communicating more frequently with each other during recent years.

The formation of the International Brain Research Organization in October 1960, less than one year ago, is only the formalization of a growing body of scientific workers determined to promote and improve the quality of basic research on the brain independent of political barriers which separate us, often by chance, into different countries. We are also determined to do what we can to improve the working relations between our various countries by our demonstration of cordial and effective collaboration in spite of political situations which would seem to place us in conflict one with another. But in keeping with the traditions of the first international scientific colloquium held in Pisa in October of 1839, 122 years ago, we will abide by the wishes of the Grand Duke of Tuscany and try to refrain from political discussions during our formal meetings — though we cannot make any promises for many informal sessions which are often the best part of such colloquia.

I take pleasure also in bringing greetings and salutations from UNESCO to this first colloquium sponsored by their very young offspring, IBRO, which is actually less than a year old. I must say that Unesco is somewhat astounded by the vigor of their young child, and perhaps fearful at times that we are trying to run before we have learned to walk, but the splendid manner in which Prof. Moruzzi and his co-workers have organized this colloquium with the generous assistance of the Valentino Baldacci Foundation — and the eminent scientists gathered here from near and far — should reassure them that we can not only walk, but we can run and even fly.

We are particularly grateful to Prof. Ugo Baldacci who has made this conference possible — even before IBRO was formally organized, and certainly before we have become sufficiently well established financially to undertake such a meeting. We are pleased to be able to pay tribute in this manner to his distinguished father, Dr. Valentino Baldacci of Pisa.

This is one of a series of colloquia started by the Laurentian symposium on *Brain*

mechanisms and consciousness held in 1953 (Blackwell, Oxford, 1954). This was followed by the Detroit symposium *Reticular formation of the brain* (Little, Brown and Co., Boston, 1958), the CIBA conference on *Neurological basis of behaviour* (Churchill, London, 1958), and the Moscow colloquium on *Electroencephalography of higher nervous activity* (*Electroenceph. clin. Neurophysiol.*, 1960, *Suppl. 13*). Several additional symposia were held along the same lines, as for example the Montevideo symposium on *Brain mechanisms of learning* (Blackwell, Oxford, 1961).

I would like to take this occasion to pay tribute to one of our members who has provided much of the initiative and inspiration for many of these symposia, including the first held in 1953 in Canada, that is Professor Henri Gastaut. He has worked in the background for many of these important meetings, and he deserves more credit than is usually given him in the publication of their proceedings.

The proceedings of this colloquium are to be published *in extenso* for the benefit of our many colleagues who are unable to be with us. The Baldacci Foundation is to publish the French edition, while IBRO will publish the English edition, in keeping with our policy to publish in the two working languages of UNESCO.

Introductory Remarks by the Honorary President

PROFESSOR FREDERIC BREMER

My dear Colleagues,

I owe to the date of my birthday the privilege and pleasure of expressing on your behalf our gratitude to all who have made this Colloquium such a pleasant reality.

We are all especially grateful to the University of Pisa for the hospitality it has offered us at the Istituto di Fisiologia, and for the interest expressed in our work by the presence at this inaugural session of Professor Faedo, Rector of the University, and Professor Puccinelli, Dean of its Medical Faculty. You will all wish me, I am sure, to ask them to accept our sincere thanks for their kind attendance.

Our thanks are due also to the International Brain Research Organization, who are the sponsors of the Colloquium, and to our colleague Herbert Jasper, the energetic Executive Secretary of this Organization, who has played a major role in the preliminary stages of the excellent arrangements made for this meeting. Equally grateful are we to our dear colleague Giuseppe Moruzzi and to Mrs. Moruzzi, who have devoted so much time and ingenuity to ensure that the Colloquium will be the success that it already promises to be.

Further, I should like to thank on your behalf, the Fondazione Valentino Baldacci, whose generous financial aid has been so valuable. The director of this Foundation, our colleague Professor Ugo Baldacci, and its secretary, Doctor F. Suma, have once more shown the meticulous solicitude and cordiality which have been, in the past, characteristic of the contributions made by the Fondazione to the success of scientific enterprises.

The Pisa meeting follows, after three years, the memorable Moscow Colloquium. The support given to us by the International Brain Research Organization is an indication that this Organization approves of the idea that the understanding of cerebral integration requires the spatial and spiritual cooperation of those who are studying this supreme problem in neurophysiology. In this era of political unrest in which we are condemned to live, our meeting here will be a vivid symbol of what can be done by friendly cooperation in a domain of science which is so intimately associated with the problems of human destiny and progress.

We shall work in the shadow of the great monuments of a glorious city. They are the comforting testimony that great things can be accomplished in the midst of struggle and warfare, though the warfare to which I allude was certainly, I must

admit, a warfare performed with the "conventional" weapons of the 12th century!

To me it is particularly moving that our session will be held in the Institute of my old friend Giuseppe Moruzzi, an Institute which has made, as you know, outstanding contributions to the themes that we shall discuss.

Our only regret is that Professors Beritashvili, Narikashvili and Smirnov and Doctor Terzian are unable to share in our meetings.

As a compensation for this, however, we shall enjoy the full attendance of Professor Richard Jung, who has happily recovered so quickly from the accident which recently, as a result of his passionate interest in Romanesque architecture, he had the misfortune to suffer.

Dedication to Professor Bremer

This volume is dedicated to a friend whose work has greatly advanced our understanding of the nervous system, whose presence can enliven the dullest meeting and whose 70th birthday gives us the excuse for expressing our feelings.

Fortunately Frédéric Bremer's age has no relation to his present activity. Forty years in the laboratory have not lessened his keen interest in new investigations and his critical appreciation of the problems they bring. Though he can look back to the string galvanometer, he has retained his mastery of experimental technique.

The use of some new technique has often led to a rapid advance in the physiology of the nervous system. Few nowadays can appreciate the difficulties of experiments on the brain before the barbiturates were available: indeed the introduction of Dial as a suitable anaesthetic in 1930 can count as a major advance in technique and the short note on it by Fulton, Liddell and Rioch deserves to rank as a turning point in the history of cerebral physiology. But the brain depressed by drugs is not the normal brain and another turning point came when Bremer introduced the "Cerveau isolé" and "Encéphale isolé" preparations in 1935-36. His preparation solved the problem of anaesthesia by providing for the division of the pathways for pain below the cerebral level leaving intact much of the regulating mechanism for cortical activity. He found, after mid-brain transection, that the pattern characteristic of sleep would be shown both in the EEG record and in oculomotor behaviour: the pattern changed from time to time to that characteristic of arousal and he found that the change could be brought by appropriate sensory stimuli. Thus his "Cerveau isolé" and "Encéphale isolé" preparations made it possible to start a new chapter in the analysis of the brain stem regulating centre. They have given a fresh impetus to research on the problems of sleep and attention and have opened up fields which are still the centre of interest.

This work on the brain stem in relation to cerebral activity has been a major contribution to the physiology of the central nervous system but it is far from being the only important contribution he has made. His early study of the cerebellum in Sherrington's laboratory and his more recent work on the auditory and visual pathways and cortical responses have established valuable results, and Bremer has always been attracted by the general problems which have been left unsolved because there is so much detail to be filled in. He has been concerned with the waves as well as the spikes, with the factors which can lead to synchronised rhythms in the cord and in the brain and with the general problem of auto-rhythmicity.

It is indeed his concern for the whole advance and his knowledge of the way it has gone which gives him a special claim to our good wishes. Research on the central

nervous system offers an immense variety of topics, from the anatomy of the cell to the psychology of the individual: very few of us can hope to follow all the developments recorded in so many fresh publications, but Bremer has never lost touch with the major issues. In any discussion he can refer to the details and make us see them as part of the whole picture: and we can enjoy his own papers for their light on our immediate problems as well as for the lucid writing which commands our interest.

Throughout his career Bremer has influenced the development of research on the central nervous system. We have profited by the methods he has introduced and the ideas he has given us. It is a pleasure to express our thanks to such a colleague and to send our congratulations on his seventieth birthday.

ADRIAN

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Postsynaptic and Presynaptic Inhibitory Actions in the Spinal Cord

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Sherrington was the first neurophysiologist to appreciate fully the key role of inhibition in the integrative action of the nervous system, particularly in the spinal cord. For him synaptic inhibitory actions ranked equally with synaptic excitatory actions. Despite his leadership both in experiment and in conceptual development, there is still today a tendency to consider the nervous system as operating very largely along excitatory pathways. The present paper is, in part, an attempt to redress this unbalance; but a more compelling motive derives from the necessity for reconsidering the whole central inhibitory story now that it has been established that there are two quite distinct synaptic inhibitory mechanisms. The recent recognition of presynaptic inhibition (Frank and Fuortes 1957; Eccles 1961a,b; Eccles, Eccles and Magni 1961; Eccles, Magni and Willis 1962; Eccles, Schmidt and Willis 1962; Eccles, Kostyuk and Schmidt 1962a,b) has led to a reinterpretation of many experimental investigations that have been made over the last few decades. A brief historical *résumé* will serve to remind us once again that inhibitory phenomena provide the most fascinating problems in basic neurophysiology.

Gasser and Graham (1933) found that dorsal root volleys produced slow positive potentials (P waves) of the cord dorsum, and that the time courses of these waves corresponded approximately to that of the inhibition of flexor reflexes when one dorsal root volley was employed to condition the flexor reflex evoked by another volley. Consequently, they asked "whether the positive potential may not be connected with the process responsible for inhibition?" In a further communication Hughes and Gasser (1934) provided additional evidence supporting this correlation, and later Gasser (1937) attributed the inhibition to a depression of interneurons in a common central pathway that was produced by the positive after-potential that followed their activation by the conditioning volley. Barron and Matthews (1938) found that dorsal root volleys also gave rise to a depolarization that spread electrotonically along the same or adjacent dorsal roots and postulated that this dorsal root potential was produced by the same potential generator that gave the P wave, and that this generator was also responsible for inhibition; but it was suggested that this inhibition was brought about by electric currents which caused blockage of conduction in the collateral branches of interneurons.

In recent years the evidence relating both the dorsal root potential and the P wave of the cord dorsum to a central inhibitory action has been lost sight of because the interneuronal theory of inhibition (Gasser 1937; Bonnet and Bremer 1939; Bremer and Bonnet 1942) could not explain inhibition of monosynaptic reflexes (Lloyd 1941, 1946; Renshaw 1941, 1942), and also because there was such convincing evidence that inhibition was due to the postsynaptic action of special inhibitory synapses (Eccles 1953, 1957, 1961a; Fatt 1954; Fessard 1959). By intracellular recording it was shown that inhibitory and excitatory synapses had opposed actions on the postsynaptic membrane; and inhibitory action seemed to be fully accounted for by the observed interaction of the postsynaptic currents and potentials produced by excitatory and inhibitory synapses, much as was originally postulated by Sherrington (1925) in his concept of algebraic summation.

This position is no longer tenable because it has been shown that a large proportion of the inhibitions exhibited in the spinal cord is due to a quite different mechanism, which has been called presynaptic inhibition. Depolarization of excitatory presynaptic fibres causes a diminution in their synaptic action (Hagiwara and Tasaki 1958; Takeuchi and Takeuchi 1962; Eccles, Kostyuk and Schmidt 1962). It has now been shown that virtually all medullated primary afferent fibres in the spinal cord are depolarized by suitable conditioning volleys, and that this depolarization reduces their excitatory effectiveness and so results in the inhibition which has been designated presynaptic inhibition. This presynaptic depolarization that is responsible for presynaptic inhibition is also manifested both in the P wave of the cord dorsum and in the dorsal root potential, which thus re-establishes the earlier hypothesis of Gasser, Matthews, Bremer and their colleagues. However, the detailed mode of operation of presynaptic inhibition is very different from the earlier suggestions. It is now postulated that special interneurons form depolarizing synapses close to the synaptic terminals of the primary afferent fibres; the presynaptic depolarization so produced results in a diminution in the quantity of transmitter which is liberated by the impulses. Thus the postsynaptic excitatory action of the impulses is diminished not by any interaction at the level of the postsynaptic membrane (the postsynaptic inhibitory mechanism), but as a consequence of a diminution of the transmitter liberation, there being thus a smaller excitatory response from an otherwise unaltered postsynaptic membrane.

POSTSYNAPTIC INHIBITION

Integrative functions of postsynaptic inhibition; the Renshaw cell system

When motoneurons discharge impulses to muscles, they also activate Renshaw cells via motor axon collaterals (Renshaw 1946). These Renshaw cells in turn inhibit the motoneurons and so tend to suppress the motoneuronal discharge (Eccles, Fatt and Koketsu 1954). The more intense the motoneuronal discharge, the more intense is the activation of Renshaw cells and the consequent inhibition of motoneurons. Thus the Renshaw cell system operates as a negative feedback to motoneurons. When studied in detail, it is found that the negative feedback from any particular impulse is not at all selective to the motoneuron that discharges that impulse, nor

to the whole population of motoneurons that supplies the same muscle, nor even to the whole assemblage of motoneurons supplying muscles of comparable function, *e.g.*, flexion or extension. All that can be stated is that the Renshaw inhibition from the motoneurons of any muscle is more powerful on the motoneurons in close proximity, and in particular on the motoneurons of slow tonic muscles (Fig. 1; Granit *et al.* 1957; Eccles, Eccles, Iggo and Ito 1961). Possibly this selective distribution serves to stabilize the frequency of motoneuronal discharge to tonic muscles

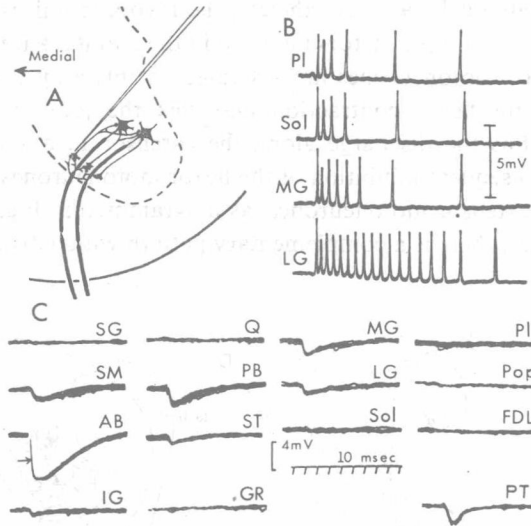


Fig. 1

A: diagram showing synapses from two motor axons onto three Renshaw cells whose axons in turn make inhibitory synaptic connections onto the two motoneurons. Note microelectrode in position for recording extracellularly from one Renshaw cell as in *B*.

B: responses of a Renshaw cell evoked by single maximal antidromic volleys in the motor nerves to various muscles. Pl — plantaris; Sol — soleus; MG — medial gastrocnemius; LG — lateral gastrocnemius. All other antidromic volleys were ineffective.

C: intracellular recording from an anterior biceps motoneurone, showing the responses evoked by single maximal antidromic volleys in the motor nerves to various muscles as indicated by symbols. SG — superior gluteal; Q — quadriceps; MG — medial gastrocnemius; Pl — plantaris; SM — semimembranosus; PB — posterior biceps; LG — lateral gastrocnemius; Pop — popliteus; AB — anterior biceps; ST — semitendinosus; Sol — soleus; FDL — flexor digitorum longus; IG — inferior gluteal; GR — gracilis; PT — posterior tibial. Note that the anterior biceps volley evokes an antidromic spike potential of the motoneurone with a subsequent after-hyperpolarization that is superimposed on the Renshaw IPSP. The arrow marks the approximate size of the IPSP alone.

during maintenance of postures (Granit *et al.* 1957). An alternative suggestion is that it serves to suppress all discharges from tonic motoneurons during the rapid movements of running or jumping. This suppression is functionally desirable, else the slowly contracting and relaxing tonic muscles would impede the rapid movements (Denny Brown 1928; Eccles, Eccles, Iggo and Ito 1961). Apart from this special action on tonic motoneurons, the general action of the Renshaw cell system is to produce an unspecific limitation on the activity of motoneurons regardless of their function.