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Selective Vulnerability of the Brain in Hypoxaemia

A symposium organized by
THE COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES
established under the joint auspices of
UNESCO & WHO

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CHAIRMEN'S OPENING REMARKS

The medical world is fully alive to the benefits of the modern scientific symposium, and we who have been invited to take part in this present one are indeed privileged and grateful. Every one of you, however, has contributed substantially to our knowledge on the effects of the hypoxic state on the central nervous system, and so you are here to speak of your latest work, to contribute to the discussion, to ventilate ideas, and to suggest lines of research to be pursued when this meeting is over.

We are a small group and our sessions will be entirely informal. We have a responsibility, however, to see to it that the substance of our deliberations is conveyed to the Fourth International Congress of Neuropathology in Munich, to which this Symposium is tied, and also to that wider circle who will read the proceedings to be published as soon afterwards as is possible.

This Symposium has been organized by the Council for International Organizations of Medical Sciences and is sponsored and supported jointly by them and by the National Aeronautics and Space Administration of the United States of America. The Council was established in 1949 under the sponsorship and with the support of UNESCO and the World Health Organization, mainly for the co-ordination and support of international congresses of medical sciences: it now has fifty-five member societies, all of them international in scope. Its activities are primarily of an interdisciplinary nature, and apart from a mission to improve the efficiency of international congresses, it is concerned with the organization and publication of reports of selected meetings, such as this, on important scientific subjects not in the realm of the regular WHO programme.

During the last 40 years, the pursuit of the subject of hypoxia hazards has been gaining momentum. Modern interest in the subject can be dated to a paper by Joseph Barcroft in *The Lancet* for 1920 and his important work has since served as a useful basis for classification of the hypoxias. The subject, however, was greatly complicated by the recognition, a decade later, of the presence of respiratory enzyme inhibitors. Hypoxia ceased then to be a factor solely extrinsic to the cell, and now we are confronted both with extracellular and intracellular

aspects of reduced oxygen tension. Strughold (1954), however, has rightly insisted that the term hypoxia refers only to a physical state and that the pathophysiological state brought about by it should be called hypoxidosis. In the title of the Symposium we have used the term hypoxaemia to denote the basis of the hypoxidosis on which we are centring our discussion because it is rather more restrictive and is of particular interest. It is not our intention, however, to limit discussion too strictly to hypoxaemic hypoxidosis.

In planning this meeting, we have felt it desirable to stress certain features of hypoxidosis at the expense of others. In doing so we may be accused of being one-sided but we have aimed to concentrate upon those aspects of the subject which are still little understood and upon which as yet not a great deal of work has been published. Our knowledge, for instance, of the effects of hypoxia on various enzymes is still rudimentary, and it is our hope to encourage the pursuit of research in this particular field. We hope by the time our meeting is over that we shall have clearer views as to where future work should lie. That this work will be of increasing importance none of us can doubt. Man is spending more and more of his time in sealed cabins travelling at great speed in a wide range of oxygen tensions; some work in bathyscaphes, others in the near stratosphere. So far there are few cosmonauts but already we are alive to the many problems which face the physiologists who are responsible for their survival.

Our discussions will range over a variety of topics, some of them highly controversial, such as the interdependence of the neuron and glia. On some subjects our views are in the *Gestalt* stage but we will be reminded of the observation made by Ramòn y Cajal that it is while listening to discussion and taking part in debate that an important idea appears in a flash, sparked off by the impact of one intellect on another as in the clash of two well-tempered swords.

It is most appropriate that this Symposium should be dedicated to Professor Willibald Scholz who has devoted so much of his life to the subject of hypoxidosis and particularly to the problem of selective vulnerability. It is indeed most fitting that the words 'selective vulnerability' figure in the title of our programme. The congress in Munich will be the crowning point in the outstanding career of our well-loved colleague and we are therefore all so glad that he is with us in Baden to enjoy what we hope for him will be a relatively restful few days before his busy time in Munich. We, for our part, shall have the benefit of his wide experience, good counsel and valued judgment.

location for the meeting, and we are indeed grateful to him and to Madame Lüthy for all the arrangements they have made on our behalf and which promise so well.

W. HAYMAKER
W. H. MCMENEMEY

Baden b/Zürich
28 August 1961

CLOSING REMARKS

W. HAYMAKER and W. H. MCMENEMEY

We shall not attempt to summarize the work and the views which have been presented during the last 4 days but certain deductions may be advanced with some measure of confidence.

The human patient continues to provide us with an endless variety of problems in the field of hypoxidosis. Many of our contributions this week have been prepared from human material and important conclusions have been drawn with the aid of clinico-pathological correlations. The human nervous system, in its diseased state, will certainly continue to be our main source of instruction. Although the laboratory animal provides the much more strictly controlled experiment, this enviable advantage is to some extent offset by the fact that its brain, after all, is not human. In spite of this, with increasingly strict criteria demanded by the investigator for the study of hypoxidosis and with careful and thorough analyses of the data of the human nervous system, animal experimentation remains our best hope for the elucidation of the basic principles involved in the dynamics of hypoxidosis.

As time goes on, the respective roles of pathoclisis and circulatory disturbances in the production of hypoxidosis become clearer. We have been presented with a thesis, strongly supported by well-documented human material, that selective vulnerability can be a function of circulatory disturbances, often arterial, sometimes venous, and occasionally both. But equally compelling evidence has been provided in support of the concept of nerve-cell pathoclisis. In illustrating the solidity of this concept, Professor Scholz showed us a section from a cerebellum in which Purkinje cells had wholly vanished up to a clearly defined level whereas granule cells in the affected region had only partly disappeared; the Golgi cells, on the other hand, had survived.

The seemingly opposing viewpoints of a circulatory factor and a nerve-cell pathoclisis are not as irreconcilable as appears. Actually, they form a spectrum in pathogenesis, the complexity of which still needs to be fathomed. Oscar and Cécile Vogt pointed to the evidence that 'pathoclisis' applies not only to nerve cells but also to glia and blood vessels.

We shall be closer to an understanding of the nature of hypoxidosis when we have learned more about vasculo-glial functional relations and how nerve-cell feeding processes are maintained, and also more about the respective vulnerability in various parts of the brain of each of the three essential elements to which Hortega referred as the 'vasculo-glial-neuronal unit'. It is here that we look to the electron microscopist to help us. We have been shown convincing electron micrographs of these cell arrangements and of their changed state in hypoxidosis, but we are all too well aware of the fact that electron microscopists have also their problem in interpretation. For example, they are not yet completely agreed as to which neuroglial cell is the dark cell and which is the light. It is interesting that 20 years after the advent of the electron microscope the neuroglial cell, like a villain, should have aliases!

Moreover, it would be too hasty to accept as the last word the electron microscopists' denial of the existence of an extracellular space sufficient for conduction of metabolic exchanges. We do not need to be reminded that they are looking at fixed material which may present some basic error as far as preservation of exact volume dimensions *in vivo* is concerned.

There is also that question of a potential space which under certain circumstances, could develop. This brings us to the extremely important problem, so frequently mentioned during the past few days, of cerebral swelling and oedema. There is an urgent need to elucidate the nature and mechanics of these shifts in water balance which undoubtedly may lead to severe pathological alterations in the structural components of the tissue.

A remarkably impressive contribution to our Symposium has come from the physiologists, and the bearing of their work on aeronautic, cosmonautic and bathynautic problems is only too evident. The physiologist must always teach the pathologist and point the way in the study of man's reaction to unusual physical environment. We cannot understand the pathological implications of unfavourable environment until we are familiar with the physiology.

The basic problem of O_2 transfer by the circulation and through the tissue, has been discussed, and beautiful new techniques for measuring local blood flow, local O_2 consumption and ionic movements within specific areas of the brain have been described. The application of these methods to the quantitative evaluation of some of the factors which may determine selective vulnerability promises well.

Yet between the data presented and those which we need for the

proper evaluation of the O_2 supply to the tissues there is a gap: we need to know the ratio between the minimal metabolic rate required to maintain cell integrity and the blood supply under both normal and hypoxic conditions. Beyond this there are still the unsolved problems of local metabolic reserves and of differences between local enzyme activities. Between the facts established by morphological investigations and the tentative explanations of local vulnerability offered by the physiologist, there stretches a wide territory, largely unexplored. Even the new physiological methods do not permit us to study metabolism of individual types of brain cells *in vivo*.

The gap between physiology and biochemistry on the one hand and the studies of the electron microscopist on the other, needs no further emphasis. But it is as much a purpose of our meeting to draw attention to and define the gaps in knowledge and thus to stimulate investigation as it is to reach agreement on the meaning of observed facts. If the success of a meeting is best judged by the questions posed which cannot be answered, then this meeting *has* been a success. It has been an exceedingly fruitful experience to have the physiologists, electron microscopists and neuropathologists mingled together around this table in an attempt to elucidate some of the mechanisms of hypoxidosis as it affects the central nervous system.

To CIOMS and the National Aeronautics and Space Administration we should like to express our gratitude for making this conference possible. We should like to thank Madame T. Taussig for the excellence of the arrangements and the smooth running of the meeting and Professor and Mrs Lüthy for their hospitality and for those admirable and refreshing social occasions, the memory of which we shall always cherish.

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