MEDICAL RESEARCH AT DALHOUSIE

Article 2. — Department of Physiology

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It is traditional in a department of physiology that original research be carried out. In no other way can the frontiers of knowledge be pushed forward and it seems to be a fundamental urge to explore the unknown. The religions, the philosophies, the sciences are all exploring the unknown in their respective fashions using, if one may greatly oversimplify, the emotional, reason and the factual approach to the problem. Even though much research inevitably fails to do more than to illuminate some tiny segment of the unknown yet the very attempt keeps alive a healthy investigative spirit and helps one to avoid a too casual acceptance of the pronouncements of authority.

However in a teaching department it is also necessary to design or invent methods whereby fundamental phenomena may be successfully demonstrated in class. This frequently involves a considerable amount of experimentation which sometimes could be called research though it is of an applied character and does not usually elucidate new fundamental knowledge. Several of our experiments are unique, some in their entirety and some only in part. The majority of the experiments have some novel feature or have been modified from the classical description to fit our conditions. Furthermore some of the laboratory exercises have been used for the collection of new data. For example useful and publishable information has been gathered in respect in man to taste thresholds, pitch discrimination, color vision, respiratory reserve, diuresis, pain thresholds, reaction times, and other values.

In addition, from time to time, equipment and techniques of our laboratories are helpful in the hospital in unusual cases requiring special investigation. As examples of this and in addition to the loan of many items of equipment to a hospital, we have often taken the apparatus and have done the determinations ourselves. For example the measurement of respiratory reserve of polio patients in and out of the respirator, proved to be an interesting problem. Our skin temperature meters have been valuable in the differential diagnosis of incipient gangrene. Our stimulators have been useful in paralytic and in accident cases in neurological diagnosis. B.M.R. determinations have been done and a study of B.M.R. methods was asked for. Before the metabolism and biochemistry laboratories of the V.G.H. set up the method, we carried out those pregnancy tests that were asked for. Many chemical and spectroscopic studies have been made of unusual blood pigments, or more com-

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monly of bloods suspected of containing unusual pigments. These studies can hardly be called research but they are small investigations and they do help to keep the work of the department slanted toward the clinical.

As to original research it has long been the policy of the department for members of the staff to develop and pursue their own fields of interest. For this reason, over the years since I have been at Dalhousie a surprisingly large variety of topics have been research subjects. Among others, significant contributions in knowledge have been made and published in the following fields.

Intestinal Obstruction: The cause of the dramatic, almost shock-like state, resulting from 'high obstruction' was studied by the closed loop method ond was shown to be partly neurogenic in origin. The hemoconcentration and dehydration, though a serious matter, is really a secondary matter, resulting from the vomiting.

Hemoglobin: A comparative study was made of hemoglobin methods and the rate of hemoglobin regeneration after repeated blood letting followed in man and in animal.

Hemolysis: The term 'Anti-hemolytic value' of serum was coined and the effect on it studied of various substances:- e.g., lysolecithin, saponin, heparin, lipemia.

Capillary Fragility: It was shown that vitamin C which had been implicated, had less effect on the capillary fragility in man than did vitamin D.

Pneumothorax Gases: The analysis of gases from pneumothoraces was shown to be a useful clinical procedure. The finding of a pneumothorax with a high CO_2 content and a low O_2 content is indicative of an inflammatory condition of the pleura, and is suggestive of an empyema.

Aqueous Humor: The permeability of the blood-aqueous barrier to inorganic and to organic substances was studied with reference to the method of formation of the humor.

Colchicine: It was shown to have a stimulating action on the pituitary and to sharply increase the rate of ovulation in the frog.

Fish: Metabolic rate determinations were done on fish (oxygen consumption) and the species difference noted on the effect of water temperatures and oxygen tension etc.

Gastric Secretion: By gastric fistulae and pancreatic duct fistulae in dogs the relation between histamine and acetyl choline was studied. It was found that some anaesthetics alone caused profuse secretion.

Motion Sickness: It was shown that men giving an extreme response to a standardized cold caloric test were more prone to seasickness and those giving no response were less prone than those giving a normal response. However the correlation was was not consistent enough to warrant using the test as a screening procedure.

Immersion Foot: A study of the feet of rabbits and rats exposed to conditions simulating those experi-

enced by shipwrecked mariners revealed histological evidence of nerve fiber degeneration in the feet prior to the development of lesions.

Pulmonary Fat Embolism: Heparin was not found to be a useful aid in the control of this condition which was a serious war injury hazard. Oil globules were found to be a most normal phenomenon in alveolar lung capillaries in cats but they did not cause any symptoms.

My current research program started some years ago with the finding that minute intravenous doses of heparin dramatically cleared the opacity of a lipemic serum. It has led to a widespread study of the nature and composition of chylomicrons and the lipo-protein complexes of the blood. We have shown that the clearing of the lipemia is due to an abrupt increase in the dispersion of the lipid particles rather than to a removal of the lipid from the blood. It involves both the protein and the lipid fractions; there is a shift in the binding of the lipid from Beta globulin to Gamma globulin to albumin and it is possible that esterases are implicated. The dramatic effect of the heparin is noted only in vivo and it is not a direct action, the heparin causing liberation by the tissues of a clearing factor (the antichylomicronemic factor) which can then act in vitro. We have shown that the clearing factor, which seems to act enzymatically, can be liberated by most tissues of the body with the possible exception of the liver. Recently we have found that the clearing factor consists of at least two components and present work is towards elucidating this aspect.

The field is very broad and complicated and it has attracted many workers in other parts of the world, not only because of its intrinsic fascinations but also because of its clinical implications. It is currently believed that greater knowledge in this field will throw a flood of light on the major clinical problems of atherosclerosis and the mechanisms of the vascular degenerations.

Research Programme of the Laboratory of Cell Physiology

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In the years between 1915 and 1930, classical investigations of the physiology of the cancer cell were undertaken by Otto Warburg and his collaborators at the Kaiser Wilhelm Institute for Cell Physiology in Berlin. These studies, which won a their energy by means of an anaerobic glycolysis, akin to alcoholic fermentation of yeast, even in the presence of an excess of oxygen, whereas, as all Physiology I students will surely recall, normal cells obtain their energy in the presence of oxygen by total combustion of glucose to CO_2 and water, that is, by cell respiration. Since this discovery, there has been no single major advance in our knowledge of the intimate details of the life of the cancer

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cell, despite the millions of dollars and man-hours spent on this problem, which may also be why there has been no truly fundamental advance in the clinical management of this most frightening of diseases.

In the Dalhousie Laboratory of Cell Physiology, which nestles tranquilly in the bowels of the Forrest building, we have been attacking the problem of the structure of enzymes within normal and abnormal cells. We have discovered that certain enzymes within the yeast cell may be converted by suitable physical or chemical agents into a much more highly active condition than they normally possess. At the same time that these enzymes are activated (and, by the way, many of their other properties are also changed), the respiratory physiology of the cell is modified: there is an abrupt change in the cytochrome spectrum (the reader will recall that the cytochromes are the complex of cell enzymes concerned with fixing the oxygen transported to the cell by hemoglobin of the blood) coupled with a disruption of the mechanism whereby the cell passes electrons to Nobel prize in Physiology and Medicine for Warburg, established the fundamental fact that the major difference between cancerous and non-cancerous cells within the same tissue was in their respiratory physiology: the cancerous cells obtained these respiratory enzymes for flushing down the metabolic toilet, which is, after all, the ultimate function of oxygen. There are many striking analogies between our system (that is, the change in enzyme structure and respiratory function of the yeast cell) and the transformation of normal cell to cancerous cell. However, it is too early to say whether or not our yeast studies bear directly on the cancer problem; it is certain that they contribute to a knowledge of the structure and function of normal cells, and thus, in any case, may contribute to an understanding of the transformation which occurs when a normal cell becomes malignant.

Our work has diverged of necessity into two separate, but ultimately confluent, pathways. The first is a study of the change in properties of intracellular enzymes which we have dubbed enzyme alteration, and a study of the changed respiratory character of the cell which accompanies enzyme alteration. We believe that the change in enzyme properties is due to desorption of the intracellular enzyme protein (catalase is the one most intensively studied to date) from some interface existing within the cytoplasm—in much the same way, for example, as yolk proteins exist at the olive oil-water interface in a good, home-made mayonnaise (an interfacial system which seems to be passing from the culinary scene, replaced alas, by a disgusting, commercial product of the same name which spoils all with which it comes in contact). The interested reader will find reference to our earlier papers in this field in our most recent publication, to appear in a forthcoming number of the Journal of General Physiology.

The second of these pathways has been the necessary companion study of the properties of proteins at interfaces, in order to establish whether

an enzyme at an interface such as we envisage, would in fact possess the properties required by our hypothesis of enzyme alteration discussed immediately above. Several studies of the surface chemistry and biology of proteins have been published, reference to which may be found in our most recent paper (Journal of Biological Chemistry, 1954, 210, 57).

In the past, some of the outstanding leaders in the field of general physiology have been medical men: such names as Jacques Loeb, Leonor Michaelis, Albert Szent-Gyorgy and Evart Gorter (the Dutch paediatrician, the best-known of the modern workers in the field of protein surface chemistry confirm the truth of this statement. It is to be strongly hoped that some of the brighter of today's young medical graduates will be sufficiently interested in fundamental research to attack some of the challenging problems in this field.