GULBENKIAN FOUNDATION, LISBON

GRANTS FOR 1958

THE Trustees of the Calouste Gulbenkian Foundation, Lisbon, have announced a list of grants made during 1958 and amounting in total to nearly £1 million. The two previous lists of grants, issued in April and November 1957, totalled £1½ million. Out of this year's grants the British Isles and the Commonwealth overseas receive more than £200,000.

The list of grants includes: £42,000 to the Old Bodleian Library, Oxford, for restoring the fabric of this building, begun in the fifteenth and completed in the seventeenth century; £30,000 to Fort Jesus, Mombasa, for the restoration of the sixteenth century Portuguese fort and its conversion into a museum of East African history and archaeology under the care of the Royal National Parks of Kenya; up to £6,000 over three years to the International Institute for the Conservation of Museum Objects; £1,500 to the Welsh Folk Museum for recording equipment for a survey of Welsh oral traditions of the countryside, including the domestic, agricultural and craft vocabularies, before they disappear under the impact of modern technology; £32,500 to the Centre for Nuclear Energy Research, Portugal, for equipment, and running costs for three years, for its mass spectrometry and isotope section; to the University of Coimbra, (a) the Chemical Laboratory, £12,430 for a spectrophotometer and expensive books, (b) the Physics Laboratory, £6,200 for analyser and other equipment for atomic energy research, (c) the Galenic School of Pharmacy, £3,020 for apparatus for electrophoresis and chromatography, (d) the Institute of Geophysics, £1,750 for scientific equipment; £14,375 to the Bento da Rocha Cabral Institute for Scientific Research for equipment and three years research expenses; £12,850 to the Centre for Research in Infectious Diseases, Portugal, for capital and running costs for three years; £11,250 to the Centre for Economics and Statistical Research, Portugal, over three years, for seminars and training of future research workers; £4,170 to the National Agronomy Station, Portugal, for books for the library; £3,750 to the Egas Moniz Research Centre, St. Mary's Hospital, Lisbon, for fellowships; £2,000 to the University of Lisbon Botanical Garden and Laboratory, for micro-film reader, microscopes and transport for field-work; £1,250 to the Organic Chemistry Laboratory, Higher

Technical Institute, Lisbon, for equipment; £1,080 to the Hospital of Dona Estaphania, Lisbon, for scientific meetings organized by the head of the Department of Child Health.

Scholarships and other grants for education or study at home or overseas for the year 1958-59 include: £112,500 for Portuguese students and scholars, £20,000 for Armenian students, and £10,000 for scholars, research workers, etc., and £15,000 for Middle East students. In the United Kingdom £4,030 was spent in 1958.

Other grants include £50,000 to Churchill College, Cambridge, to endow three Gulbenkian studentships for graduates of universities outside the United Kingdom; up to £3,750 to the Institute of Archaeology, University of Coimbra, and other archaeological bodies; £3,000 to the Department of Education, Oxford, directed by Mr. Alec Peterson, to enable a study to be made of specialization in schools and its real relevance to university requirements, and then to attempt to draft an ideal syllabus and timetable for a combined arts and science sixth form; £350 a year for three years to the Egypt Exploration Society and Ashmolean Museum, Oxford, for a technician to be trained (by the reader in papyrology in the University of Oxford) in the technique of piecing together fragments of ancient papyri by matching the fibres instead of the text; £600 over two years to Prof. Christopher Hawkes (University of Oxford) for visits to Portugal at the invitation of the Ministry of National Education to collaborate with Col. Mario Cardoza of Guimarães in the excavation of early Celtic *castros* and in the training of Portuguese archaeologists in the latest techniques of excavation; £700 to the Department of Economics, University of Bristol, for a study of the 'employability' of workers who have suffered long-term unemployment due to ill-health. Out of funds set aside in 1957, the Foundation has assisted one undergraduate scientific expedition this year, namely, the Westminster Hospital Medical School's expedition to the Belgian Congo. In addition, the Royal Geographical Society, London (which already lends surveying instruments to expeditions), has accepted £1,200 for a pool of other instruments and equipment for loan to university expeditions.

BIOCHEMICAL RESPONSE TO PHYSICAL INJURY

A SYMPOSIUM on "The Biochemical Response to Physical Injury" was held at Semmering, Austria, during September 7-12 under the aegis of the Council for the Organization of Medical Sciences with the assistance of the Wellcome Trust and the International Union of Biochemistry. Radiation injury was excluded from discussion.

Dr. D. P. Cuthbertson (Scotland) acted as chairman and Dr. H. B. Stoner (England) was technical secretary. The general and local arrangements were

respectively in the hands of Dr. J. F. Delafresnaye (Council for the Organization of Medical Sciences) and Dr. F. G. Wewalka (Austria).

F. A. Fuhrman (United States) opened with a description of "Electrolytes and glycogen in injured tissues". He pointed out that we know more about the electrolyte pattern and its control in skin and skeletal muscle—which constitute 70 per cent of the mass of the soft tissues of the body and which are more frequently injured than other tissues—than in

any other. The main difficulty, however, is our inability to determine precisely the size of the extracellular space in injured tissue. The replacement of intracellular potassium by sodium following injury is of very great interest and appears to be due to failure of the sodium pump rather than to death of cells. It is not known how long intracellular sodium must be present to be harmful; or, indeed, whether it ever does become harmful. At least eight different enzymes are activated by potassium and inhibited by sodium. Abnormal carbohydrate tolerance has been demonstrated in potassium-deficient animals in which part of the intracellular potassium was replaced by sodium. But much more information is necessary before the electrolyte changes in complex injuries can be causally related to alterations in physiological function.

J. Trémolières and R. Derache (France), in "Metabolism of nucleotides and phosphate in injured tissue", described the uniformity of the local response to injury as exemplified by the fact that the changes in the acid-soluble phosphorus compounds go on in nearly identical ways whatever the injury (radiation excepted). There is a reduction of energy-rich compounds (phosphocreatine and adenosine triphosphate) as in anaerobic conditions. Beyond a certain point cellular lesions become irreversible. These investigators then described the state in anoxic ischaemia and of revascularization. They suggest that local oedema can be explained by a fall in the protein-adenosine triphosphate complexes which are able to select between potassium and sodium. Necrosis and irreversible proteolysis can be related to the structural functions of adenosine triphosphate in mitochondria and proteins.

"The endogenous substances inducing pathological increases in capillary permeability" were considered in two papers by A. A. Miles and D. L. Wilhelm (England), who discussed the activation of endogenous substances increasing capillary permeability (Miles), and the evaluation of the role of endogenous permeability (Wilhelm). They emphasized that among the early responses to injury, the inflammatory reaction is paramount. In their view, in our present state of knowledge it is almost impossible to analyse the factors operative in a long-lasting and severe inflammation, and progress in this field is most likely to be achieved by studying the essential reactions of inflammation induced by minimal stimuli. Judging from the large number of relatively simple substances which can increase permeability, it is possible that the tissues use one or several of a variety of endogenous substances as mediators, and that these differ according to the type of injury. In certain circumstances and certain animals, histamine and 5-hydroxytryptamine appear to be mediators. These workers could not subscribe to the view that, since endogenous leukotaxine, globulin permeability factor and so forth are there, they must in consequence play some part in permeability changes, otherwise they would not be there. Their view is that even supposing all endogenous substances in the body have their proper and necessary role in the living tissues, the biological activities in terms of which we choose to identify and explore them may be wholly irrelevant to the function they fulfil in the body.

A. Fannesu (Italy) described "Changes in energy transformations as an early response of the cell to injury". The well-known histological picture of cloudy swelling is the morphological result of these changes—a condition described by Rudolph Virchow

in 1871 as a kind of acute hypertrophy with tendency to degeneration. The features of this condition are as follows: (1) an alteration of the mitochondria which follows, or is followed by, a partial inhibition of phosphorylation coupled with oxidation; as a consequence, aerobic glycolysis increases; (2) increased protein synthesis. Assuming the mitochondrial alteration is the first response of the cell to injury, this may be the cause of an increase of aerobic glycolysis and an increase of inhibition. No answer can be given as to how impairment of oxidative phosphorylation can lead to an enhancement of an endoergic process such as protein synthesis. Other conditions, in pathology, are known in which the uncoupling of oxidative phosphorylation is accompanied by an increase of both glycolysis and protein synthesis.

Concerning the more general response to injury, "The effect of limb ischaemia on carbohydrate distribution and energy transformation" was analysed by H. B. Stoner and C. J. Threlfall (England). It appears that during the period of limb ischaemia and for the first part of the survival period afterwards, the brain, liver, heart and uninjured muscle are adequately oxygenated and the metabolic changes in these organs cannot be attributed to hypoxia. The secretion of the adrenal medulla in response to the injury is the main cause of the altered carbohydrate distribution. The mechanism of the changes in energy transformations which occur at this time is not yet understood.

In the estimation of these investigators the ability of the animal to withstand the injury is probably decided during this early period and it is possible that the biochemical changes which occur are part of a defensive mechanism. If the animal is unable to withstand the injury, oxygen transport fails during the later part of the survival period and the resulting tissue hypoxia leads to the terminal changes in energy (heat) production and carbohydrate metabolism.

A. G. B. Kovách (Hungary), in a paper on "Metabolic responses to injury in the cerebral tissues", described the favourable effect of perfusion of the brain with normal blood in haemorrhagic and ischaemic shock. The functional changes as tested by electrocorticographic investigations support the hypothesis that impairment of the nervous system plays an important part in the development of shock. The oxygen consumption of the brain—its oxygen requirement—does not decrease during shock, in fact it rises, in spite of the fact that the circulation in the head is deficient. Unlike muscle where the glucose uptake is lessened after shock, the brain remains unchanged in this respect, to the terminal stage, when it diminishes. The hexokinase activity in the brain of the animal in shock increases, whereas in muscle it is slowed up. On the other hand, cerebral anoxia (stagnant or arterial) lowers the brain hexokinase activity. These and other changes—particularly in phosphorus compounds—might be attributable to an increase in intracellular potassium ions. The mechanism of this can only be determined by further experiment.

R. Fåhræus (Sweden) described the "Tissue injury due to the reduced filtrability of the erythrocytes". The intravascular aggregation of the erythrocytes in rouleau formation (termed by Knisely 'sludging') implies a mechanism which is advantageous for the circulation of the blood in certain aspects of the vascular system. This aggregation of the

erythrocytes favours their transport at the expense of the plasma and decreases the relative viscosity of the blood. But such rouleau formation may give rise to circulatory disturbance.

Determination of the filtrability of the erythrocytes at different blood pressures indicates that a large fall in blood pressure must have a more serious prognosis when the suspension of the blood is strongly reduced. In clinical cases with great aggregation of the erythrocytes the circulation *sub finem vitae* ceases earlier.

In reviewing the "Effect of physical injury on lipid metabolism", E. J. Masoro (United States) dealt mainly with the effects of cold injury and the inter-relationship of energy generation and the intermediary metabolism of lipids. At the moment the greatest barrier to the understanding of the effect of physical injury on lipid metabolism is still the absence of certain key data.

D. P. Cuthbertson (Scotland) contributed by discussing "The disturbance of protein metabolism following physical injury". He pointed out that the increased metabolism and urinary excretion of nitrogen, sulphur, phosphorus, potassium and creatine are the main energy and material losses to the body following moderate to severe physical injury such as the fracture of a femur. These alterations in catabolism reach their peak about the third to eighth day in man. There is also generally a slight rise in body temperature and pulse-rate. Comparable changes in nitrogen metabolism are found in the rat, sheep and, as Needham has shown, even in Crustacea. This rise in the surviving organism succeeds an initial depression of vitality following receipt of the wound. In the animal depleted in protein there is no increase in protein catabolism and in heat production following injury. The degree of response is related to the previous nutritive state.

Injury to an animal leads to lessened activity and lessened activity usually results in a diminished food and water intake. The necessity to heal is urgent and Dr. Cuthbertson's view is that the injury done sets in motion a chain of events to meet both the exigencies of repair and of maintenance. This involves changes which may even affect the internal milieu. The rise in heat production which is traceable to the protein oxidized will undoubtedly affect the rates of biochemical reaction.

A. Pekkarinen (Finland) gave a well-documented account of "The effect of operation and physical injury on the adrenal glands and the vegetative nervous system in man". The excretion of adrenaline, noradrenaline and total 17-hydroxycorticosteroids increases markedly after certain operations, thus showing a close relation between the vegetative nervous system and the pituitary-adrenocortical system, at least functionally. The rises might be regarded as of therapeutic benefit, promoting the adaptation of the organism to the stress of operation. The highest urinary excretions of noradrenaline and adrenaline correspond to liberation of 5 mgm. noradrenaline and 8.4 mgm. adrenaline. In most patients the excretion of these substances becomes normal during the first three days after operation. It may also be assumed that the secretion of steroids by the suprarenal cortex may decrease owing to the increased circulatory 17-hydroxycorticosteroid inhibiting the secretion of adrenocorticotrophic hormones from the pituitary gland.

An interesting finding is the significantly higher excretion following injury of adrenaline, noradrenaline

and total 17-hydroxycorticosteroids in men compared with women.

The part played by aldosterone secreted by the adrenal cortex in the regulation of the humoral equilibrium during operations is yet unknown.

"Fluid, electrolyte, and plasma protein disturbance in shock" were dealt with by R. C. Millican (United States). He pointed out that this kind of study is important, for circulatory collapse occurs in normal animals in which there are losses of fluid, electrolyte, and protein to the extent observed in shock arising from hæmorrhage or swelling at the site of physical injury. Under certain conditions death from shock can be prevented by administration of fluids, electrolytes, and proteins. In untreated shock associated with a swelling of the injured areas of about 4-5 per cent of body weight, the fluid accumulation within the injured area occurs at the expense of the injured tissues.

The total sodium accumulation in the injured area of mice following application of a tourniquet to the hind legs is equivalent to the entire sodium in the circulating blood, or approximately 25 per cent of the extracellular fluid.

Dr. Millican considered that as substantial amounts of potassium were liberated from injured tissues this was an important factor in shock when combined with the fluid and sodium loss. Doubt is cast on the importance of plasma protein in shock in mice by the lack of effectiveness of protein solutions when administered in the absence of electrolytes. Survival response is closely related to the sodium content of the administered fluid.

V. Wynn (England) took up one aspect of the clinical side in his paper on "Some problems of water metabolism following surgery". He considers that the common finding of a low plasma osmolality for several days after the trauma is explained by water retention in excess of electrolytes. Since renal function may be otherwise normal, present evidence suggests persistent antidiuretic hormone secretion as the cause of the oliguria. It seems that the supra-optic-hypophyseal system is made more sensitive in some way by trauma, so that a variety of stimuli provoke secretion of antidiuretic hormone; and the primary function of osmo-regulation by the system is seriously impeded or lost. An inhibitory effect upon aldosterone production is a secondary consequence of the water retention. This leads to renal loss and aggravates the hypotonicity of the body fluids.

In a discussion on the "Influence of environment on the metabolic response to injury" R. E. Haist (Canada) described his experiments, which indicate a prolongation of the survival time of rats, previously exposed to cold, and shocked by a clamping technique, over controls not so exposed. An increased blood volume due to the exposure may also be a factor. Sodium is retained by such cold-acclimatized animals. Previous cold-acclimatization does not alter the changes in muscle chemistry and temperature during and following ischaemia, or the hepatic blood flow after ischaemia, but does lead to a lesser hepatic temperature.

It was clear from H. Smith's (England) account of the "Biochemical response to bacterial injury" that infection with a number of bacteria and injection of different bacterial products can lead to a response in the host physiologically and biochemically similar to that produced by physical injury. The stimulus to this response appears to be a loss of circulating

blood volume either from extravasation into tissue spaces locally or generally, for example, in shock produced by anthrax, or from a peripheral pooling of the blood and a decrease in venous return as, for example, in shock produced by staphylococcal and meningococcal toxins. The possible biochemical mechanisms whereby different bacterial products affect blood vessels is a relatively untouched field for research.

W. W. Spink (United States), in his paper on "Brucellosis as a model for metabolic studies on bacterial shock and inflammation," directed attention to the increasing interest shown in recent years in the peripheral vascular collapse caused by endotoxins of Gram-negative bacteria. There is vasoconstriction of the small vessels, which causes ischaemia of the tissues, and changes in cellular function result. This is followed by vasodilation and stagnation of blood, increased vascular permeability, and oedema and haemorrhage. There is reduced cardiac output because of peripheral pooling of blood. Renal failure occurs because of the compensatory vasoconstriction, which results in ischaemic tubular necrosis.

The metabolic response of the host to bacterial invasion includes alterations in hormonal activity. The adrenal cortex is stimulated, as reflected by increased concentrations of adrenocorticoids, especially cortisone. The thyroid stimulates the activity of the adrenal cortex. Some doubt was expressed as to the wisdom of giving the large amounts of exogenous corticosteroids advised by Dr. Spink during the initial critical period of endotoxin shock. It was of interest that he had found that triiodothyronine accelerated the lethal action of endotoxin.

"The bacterial factor in traumatic shock" was discussed by J. Fine, E. D. Frank, H. A. Ravin, S. H. Rutenburg and F. B. Schweinburg (United States), who found evidence of a toxin appearing in the blood of animals in haemorrhagic shock, such toxin having many of the hallmarks of a bacterial endotoxin. They consider that it is the cause of the irreversibility to transfusion in their standardized preparations. A toxin with similar properties to the one in the blood in haemorrhagic shock is apparently present in the blood of the animal in tourniquet shock and in non-bacteraemic septic shock. The source of this toxin appears to be such Gram-negative bacteria as may be present in the animal's tissues, and the endotoxins normally present in the gastro-intestinal tract, which appear to enter the circulation at a

steady rate, if only in trace quantities. It is thought that when shock, however produced, becomes unresponsive to therapy, the refractory state of the peripheral vessels is due to unneutralized endotoxins through impairment of the reticulo-endothelial system. The protective effect of reserpine and of dibenamine given prophylactically lend strength to the view that the endotoxins act adversely on these vessels by intensifying the local action of adrenaline or noradrenaline.

S. M. Rosenthal and H. Tabor (United States), in their paper on "Some aspects of therapy of injury", described the survival effects of administering isotonic sodium salts to mice subjected to what would otherwise be one lethal dose of burn trauma, tourniquet trauma or haemorrhage. In their estimation, sodium and fluid depletion are the major factors in the cause of shock. Saline or plasma in amounts of 5 per cent of body-weight (50 ml./kgm.) is inadequate. These authors have been able to demonstrate a specific effect from the sodium ion in shock. Potassium salts behave in an opposite manner to sodium and are quite toxic. In shocked mice there is an eightfold increase over the toxicity in normal. Glucose and colloid solutions containing no sodium were relatively ineffective in the therapy of shock. The concept that plasma proteins exert their osmotic effects by being held rigidly in the vascular bed must be modified by the demonstration of Wasserman and Mayerson in 1952 that a complete extravascular circulation of the plasma proteins occurs every 20 hours.

In haemorrhage and haemorrhagic shock where there is a large loss of red cells, the striking efficacy of administering red cells has been clearly demonstrated, but there is little evidence to substantiate its value in shock from burn or other local trauma. In experimental burns and tourniquet shock whole blood is no more effective than plasma or saline solutions.

In studies on burned children in Peru a small but statistically significant benefit from plasma above that from saline was observed. The important problem of late deaths following severe burns is also being studied in Peru by Drs. Rosenthal and Millican.

This, the first main symposium covering this field of investigation to be held in Europe since the Second World War, was of great value to the participants. The papers contributed and the discussion which followed will be published in due course by Blackwell Scientific Publications, Ltd.

D. P. CUTHBERTSON

FREE RADICAL STABILIZATION

FREE radical chemistry began with the discovery of the stable aromatic free radicals by Gomberg in 1900. The second stage of the subject developed more gradually as the occurrence and importance of unstable free radicals became increasingly apparent and as kinetic and spectroscopic methods for their study in the gas phase and in solution were perfected. During the past few years a third chapter in free radical chemistry has been opened with the realization that even the most reactive of radicals can readily be stabilized for indefinite periods by trapping them in a rigid matrix at low temperatures.

An informal discussion of the Faraday Society on this subject was held in the Chemistry Department of the University of Sheffield on September 4 and 5. The meeting was attended by about one hundred and eighty scientists, half of whom were from Britain, fifty from the United States and Canada, and forty from other countries. Twenty-one papers, covering nearly all aspects of the subject, were presented and discussed.

The three principal methods of preparation of stabilized radicals are: (1) by irradiation of a rigid solid or solution at low temperatures; (2) by elec-