that the filtrates contained a distinct factor, to which the name 'coenzyme' and later 'cozymase' was given.

Their work was simple but precise, and its very precision was perhaps a bar to their further elucidation of the phenomenon of phosphorylation. Harden perceived that inorganic phosphate was necessary for the rapid rate of fermentation, that is, the process of esterification was necessary; but it seemed that the ester formed (hexose diphosphate) could not be an intermediate, since it was only fermented very slowly by the juice. Harden and Young considered that a coupled reaction occurred:

$$2C_6H_{12}O_6 + 2HR_2PO_4 \rightarrow 2CO_2 + 2C_2H_6O + 2H_2O + C_6H_{10}O_4(PO_4R_2)_2$$

in which by the phosphorylation of one molecule of sugar the breakdown of a second molecule was induced; when all the inorganic phosphate was esterified, the rate of fermentation fell to the basal rate, dependent for a supply of phosphate on the slow hydrolysis of the phosphoric esters.

It was not until 1945 that Meyerhof showed that the two phases were due to a destruction of the adenylpyrophosphatase of yeast during the preparation of the juice, so that the coupled reaction:

3-Glyceraldehydephosphate + phosphate + cozymase $\rightleftarrows$ 1-3 diphosphoglyceric acid + dihydrocozymase

1-3 Diphosphoglyceric acid + adenosine diphosphate $\rightleftarrows$ 3 phosphoglyceric acid + adenosine triphosphate

came to a halt for lack of the phosphate-supplying mechanism of the apyrase:

Adenosine triphosphate $\rightarrow$ adenosine diphosphate + phosphate

Harden's facts, however, were incontrovertible and induced an autocatalytic fermentation in the science of biochemistry the course of which need not be recapitulated here. Though he realized the fundamental nature of his work, he was habitually restrained and would have thought it regrettable hyperbole to say to his colleague in 1906: "This day we have lighted such a candle in England as I trust shall never be put out". But it is no exaggeration to say now that their work is the source, reflected and amplified by many later workers, of our understanding of intermediary carbohydrate metabolism and many other phosphorylation mechanisms in animals, plants and micro-organisms.

IMMUNOLOGICAL TOLERANCE

A MEETING was held on March 8 at the Royal Society on the subject of "Immunological Tolerance", under the leadership of Sir Macfarlane Burnet. Following the definition of Billingham, Brent and Medawar, immunological tolerance is a specific weakening or suppression of reactivity caused by exposure of animals to antigenic stimuli before the maturation of the faculty of immunological response. In his opening paper, Prof. P. B. Medawar (University College, London) referred to the experimental demonstration of tolerance against such varied antigens as the erythrocyte agglutinogens, the tissue antigens responsible for transplantation immunity, bacterial antigens and purified proteins. Marked differences are found between the first two of these antigens: the erythrocyte antigens are stable, cytoplasmic, and elicit a transient gamma-globulin response, whereas the unstable, nuclear, tissue antigens elicit a permanent state of heightened graft resistance mediated by leucocytes rather than serum.

In contrast to the suppression of reactivity brought about by agents such as cortisone or radiation, tolerance is specific: the response to one antigen is suppressed without altering the response to others. Another essential property is that the suppression is central, acting on the tissue producing the antibody. Tolerance differs in this respect from immunological paralysis, or the enhancing of tumour growth by antiserum or tissue extracts. A comparable specific and central suppression of the immunological response has been demonstrated by Chase in the inhibition of sensitization to simple organic compounds by prior oral feeding. Medawar then returned to the subject of the biological implications of immunological tolerance[1].

In a paper on "Erythrocyte Antigens and Tolerance Phenomena", R. D. Owen (California Institute of Technology) drew two conclusions from his earlier work on stable erythrocyte mixtures in twin cattle. From the observation that the antigenic types derived from each twin occur in equal proportions in the blood of each twin, it follows that no selective pressure is exerted in favour of hæmatopoietic tissue of native origin, and that tolerance is therefore complete. From the observation that no more than two types of cell are found in twins which differ by several antigens (with the exception of *J*), it follows that sub-cellular transformations do not occur, and that hæmatopoietic cells are in this sense fully autonomous. Attempts to mimic the chimerism of twin cattle in rats by means of parabiosis have been unsuccessful; but Ripley has produced a similar condition by injection of embryonic rats with embryonic liver and spleen cells through the chorionic blood vessels. Chimeras have also been produced in rats after injection of hæmatopoietic tissue into irradiated recipients, by Lindsley, Odell and Tausche. Owen then described his own work on acquired tolerance in man, where past exposure to *Rh* antigens *in utero* weakens the adult antibody response. *Rh*-negative women who complete three or more *Rh*-positive pregnancies without developing antibodies tend to have *Rh*-positive mothers. This tolerance is, however, not associated with a reduced incidence of erythroblastosis. Owen finally described an effect of injection of human erythrocytes into new-born chickens. The antibody response of the recipients as adults is delayed, weakened and tends to the production of incomplete antibody.

B. Cinader and J. M. Dubert (Lister Institute and Institut Pasteur) gave an account of their joint work on "Specific Inhibition of Response to Purified Protein Antigens". New-born rabbits were injected with highly purified human albumen, and litter mates left as controls. When challenged with the same antigen as adults, the controls produced antibody detectable by a gel-diffusion technique, and also by agglutination of tanned erythrocytes coated with antigen. The animals injected at birth failed to produce antibody, constituting an example of actively acquired tolerance. Tolerance of the injected animals

was also exhibited in experiments with human albumen labelled with radioactive iodine. The labelled protein was eliminated slowly and continuously from the tolerant animals, in contrast to the controls, which exhibited a sharp rise in the rate of elimination as the immune response developed. Tolerance in this instance was shown to be specific, by means of cross-tests with tobacco mosaic virus and also diazotized human albumen. The diazotized human albumen provides a refined demonstration of specificity, since it is an antigen which normally elicits antibodies of two distinct types, specific either for the diazo group or for the albumen. Those tolerant animals which responded to the diazotized human albumen produced antibody only against the diazo group, as could be shown by absorption tests with human albumen. In a single animal, administration of diazotized human albumen appeared to weaken the tolerance to normal albumen, indicating that the state of tolerance can itself be modified experimentally.

Applications of immunological tolerance were described in papers entitled "Tolerance of Ascites Tumour Cells", by H. Koprowski (Lederle Laboratories, New York), and "Acquired Tolerance of the Rous Sarcoma Agent in Turkeys", by R. J. C. Harris (Chester Beatty Research Institute). Koprowski was able to obtain, from two transplantable mouse lymphomas, lines that would grow in normally resistant mouse strains; and from a rat hepatoma he obtained a line which would grow in mice. The transformation was made by inoculation of tumour cells into unborn mice of the prospective host strain, thus inducing a state of tolerance which enabled the tumour to grow progressively. The tumour masses which developed after birth served to start the transformed line of tumour, if necessary re-inoculating fœtal mice to complete the transformation. The adaptation of the transformed tumour lines to their new hosts was incomplete, as judged by the dosage of tumour cells needed to kill the new hosts as compared with hosts of the strain of origin. The transformed mouse-tumour lines appeared to retain antigens characteristic of their strains of origin, as indicated by adoptive immunization tests. The rat tumour retained the characteristic rat *Y*-chromosomes, and could be transplanted back into rats. In tests with a variety of animal viruses, the transformed-tumour lines appeared to provide better hosts for virus multiplication than the original lines, and to be more susceptible to oncolysis by viruses.

Turkeys which had been rendered partially tolerant to chicken antigens were used by Harris, in an attempt to separate the Rous sarcoma agent from chicken antigens. If inoculated soon after hatching with chicken antigens, a proportion of turkeys are rendered susceptible to the Rous sarcoma virus and other non-virus chicken sarcomas. Live blood cells, blood cells killed by freezing or heating, or skin grafts, are all active for this purpose as chicken antigens. While growing in susceptible turkeys, the Rous sarcoma progressively loses its content of virus infective in chickens. This may indicate a conversion of the virus to the turkey antigenic type; but since virus assays were not also carried out in turkeys, it may instead indicate a decrease in the virus content of the tumour cells. After a single passage back into chickens, the sarcoma regains its full content of virus infective in chickens.

Parallel papers were presented by M. Hašek (Czechoslovakian Academy of Science) on "Tolerance Phenomena in Birds", and by R. E. Billingham and L. Brent (University College, London) on "Analysis of Tolerance induced in Newly Hatched Turkeys and Chicks". Work in London and Prague has shown that tolerance is readily produced in birds by the introduction of foreign cells into the embryo, intravenous injection and parabiosis being particularly effective methods. Hašek concentrated on the manifestation of tolerance as a suppression of hæmagglutinin production, and Billingham and Brent as a prolongation of the survival-time of skin grafts. In order to weaken or suppress reactivity to skin homografts, Billingham and Brent find that live, nucleated cells are essential. According to the criteria of hæmagglutinin suppression and prolonged graft survival, tolerance is produced more readily within than between species. The combinations of species tested were between chicken, turkey, duck, pheasant, goose, guinea fowl and pigeon. As expected on Darwinian principles, they find that tolerance produced between some strains of poultry is weaker than between others. The degree of tolerance which could be produced between species appeared to vary in accordance with their systematic relationship.

Induction of tolerance by intravenous injection of antigens into new-born chickens or mice was also described by Billingham and Brent. This method proved to be more economical than injection into the embryo. Nearly half the chickens injected with blood from another strain exhibited a degree of tolerance, although only a small proportion of skin homografts on new-born chickens take permanently. This discrepancy is ascribed to the delay in vascularization of the grafted skin.

[1] *Nature*, **176**, 852 (1955).

OBITUARIES

Prof. F. Riesz

The distinguished Hungarian mathematician, Friedrich (Frigyes) Riesz, died recently. He was born on January 22, 1880, at Györ, and studied at Zurich, Budapest, Göttingen and Paris, taking his doctor's degree at Budapest in 1902. In 1911 he was appointed to a supplementary professorship at Kolozsvár (Cluj), becoming Professor Extraordinarius in 1912 and Professor Ordinarius in 1914. In 1919 Riesz moved with his university to Szeged, and in 1945 he was appointed to a chair in Budapest. In 1922 he became editor of a newly founded periodical, the *Acta Scientiarum Mathematicarum* of Szeged, which quickly established a distinguished place for itself among the world's mathematical journals.

Riesz was one of the pioneers of functional analysis, and we owe to him many of the fundamental ideas of the subject, which were later incorporated in an axiomatic formulation by S. Banach and his collaborators. Riesz's principal contributions may be summarized as follows: the Riesz–Fischer theorem (1907) on the equivalence of Hilbert's space of sequences of convergent sum of squares with the space of functions of summable square, which is the mathematical basis of the equivalence of matrix