# MEETING OF BIOCHEMISTS IN SPAIN

DURING July 28–31 the third general meeting of Spanish biochemists was held at the University of Oviedo, organized by the Spanish Society of Biochemistry and sponsored by the Ministry of Education and the University of Oviedo. The Minister of Education, Prof. M. Lora Tamayo, himself a biochemist, was the honorary president of the meeting.

At the opening session, Dr. A. Sols and Dr. J. R. Villanueva, president and secretary, respectively, of the Spanish Society of Biochemistry, gave a short historical review of the Society including its progress as shown through the programme of these meetings and other activities. Prof. F. Grande Covian, of the University of Minnesota, spoke in representation of the scientists coming from abroad, and finally the acting rector of the University expressed his pleasure at being with the Spanish biochemists.

The meeting centred about three symposia: (*a*) "Enzymatic Regulation"; (*b*) "Microbial Metabolism"; (*c*) "Hormonal Metabolism". The first symposium held was under the chairmanship of Prof. S. Grisolía, of the University of Kansas, and Dr. Gertrudis de la Fuente (Madrid) described the work on the allosteric effects in hexokinases, followed by M. L. Salas, who discussed the allosteric regulation of the yeast phosphofructokinase. C. Gancedo (Madrid) described some results on the allosteric yeast fructose-1,6-diphosphatase and the regulation of gluconeogenesis. Dr. Gertrudis de Torrontegui (Madrid) described the level of pyruvate carboxylase and related enzymes in micro-organisms grown on different carbon sources. Prof. S. Grisolía presented the work carried out in collaboration with Dr. Torralba and J. Tecson at the University of Kansas on the reversible transformation of phosphoglyceromutase in diphosphoglycerate phosphatase. J. Salas (Madrid) described results of the stability and synthesis of the liver glucokinase *in vitro* and *in vivo*. Finally, A. Sillero described the induction and turnover of the glucokinase in liver. The session was followed by a general discussion, and at the end Drs. A. Sols and S. Grisolía summed up the more important points of the symposium. This session was followed by a lecture by Prof. J. Oró, University of Houston, on recent researches on hydrocarbons of biological origin found in Pre-Cambrian sediments and meteorites.

In the second symposium, under the chairmanship of Dr. C. Asensio (Madrid), Dr. D. Vázquez (Cambridge) described investigations of the effect of some antibiotics inhibiting the synthesis of proteins at the ribosomal level. Prof. R. Parés (Barcelona) described work on amino-acid excretion by a coliform. Dr. E. Muñoz (Liège) described recent work carried out in collaboration with Drs. Ghuysen and Petit on the structure of glucopeptides of the bacterial cell wall. Dr. Concepción García Mendoza (Madrid) described the purification and chemical analysis of the cytoplasmic membrane of yeast, and finally Dr. J. R. Villanueva (Madrid) reviewed the ways in which information about yeast cell wall structure has been obtained and described some results obtained by his group at the Institute for Cell Biology. At the end of this symposium a discussion on "Unity and Variety in Microbial Biochemistry" was held, the main discussants being Drs. Losada, Mayor, Montoya, Parés, Regueiro, Sols and Villanueva. The session was followed by an address by Dr. M. Losada, director of the Institute for Cell Biology, CSIC, Madrid, who described the mechanism of the photosynthetic reduction of nitrate to ammonium.

In introducing the third symposium, Prof. F. G. Valdecasas, rector of the University of Barcelona, made some comments on the importance of the subject of hormonal metabolism. Dr. J. Gómez Acebo (Madrid) showed a collection of electron micrographs of pancreas cells during the process of insulin secretion *in vitro*. Dr. C. López Quijada (Madrid) reported the effects of iodoacetate and cystein on the antigenic power of insulin. Prof. C. Osorio (Granada) described the process of secretion of thyroxin in bile of monkeys. Dr. J. A. Sanchez-Martin (Madrid) discussed the action of thyrotrophic hormone on the intra-thyroid metabolism of the propylthiouracil. Dr. E. Herrera (Madrid) discussed the problem of experimental goitrogenesis, Dr. A. Colás (University of Oregon) described the biosynthesis of the oestriol during pregnancy, and finally Dr. A. Oriol-Bosch (Madrid) described the metabolism of tritiated progesterone by the adrenal cortex of the guinea-pig. The session ended with an address by Prof. J. L. Rodriguez Candela, director of the Marañón Institute, CSIC, Madrid, who described investigations of his group and discussed the regulation of the insulin secretion. The symposia were followed by sessions where short communications were read. In all, about forty papers were presented.

During the closing session of the meeting, Prof. F. Grande Covian gave a lecture on the role of the dietetic factors in the regulation of the plasma lipids.

Several social events were also organized, including receptions in the University and the Town Hall, and an excursion to the beautiful resorts of the Asturias coast. Nearly two hundred people attended this meeting, including a notable group of Spanish research workers from abroad and many young research students. The meeting was very successful, especially in encouraging the strong development of biochemistry in Spain, which has been proceeding during the past five years. The next general meeting of the Society will be held in the University of Granada in the autumn of 1966.

The whole of the Oviedo University meeting made an important contribution to the way in which science, and in particular biochemistry, is growing in Spain. The progress has been strongly stimulated by the marked interest taken in biochemistry by some distinguished professors and research workers from the Consejo Superior de Investigaciones Cientificas and the University. Recently, increasing attention has been directed in Spain to the means of developing scientific policy and the mechanisms of scientific advice.

J. R. Villanueva

# LUNG TUMOURS IN ANIMALS

AN international conference on "Lung Tumours in Animals" was held at the Division of Cancer Research, University of Perugia Medical School, during June 24–29. The conference brought together many geneticists, physiologists, pathologists, virologists and biochemists, whose main interests lay in basic cancer research.

Following the opening of the conference by Prof. G. Ermini (Rettore Magnifico of Perugia University), L. C. Strong (San Diego, U.S.A.), addressing the audience as the representative of the doctors 'honoris causa' of the University of Perugia Medical School, said that the contributions of that small select group of scientists to the human knowledge of cancer had indeed been great—and that no small part of these contributions had been made, and would presently be made, at the Conferences of the Division of Cancer Research, Perugia.

H. L. Stewart (Bethesda, U.S.A.), speaking as the representative of the National Cancer Institute, Bethesda, commented that the conference should contribute much to our knowledge of the comparative pathology of pulmon-

ary tumours and help to decipher some of the puzzles that remain obscure about cancer of the lung in human beings.

Prof. L. Severi, in an introductory talk, commented that, because of the apparent increase in human lung cancer attributed to atmospheric pollutants and, on the basis of statistical investigations, especially to smoke, the conference was most timely. He pointed out, however, that lung cancer occurs in animals, which do not smoke, and that no conclusive evidence was available to show that tumours could be induced in them either with smoke or with the products of tobacco.

Lectures were given at the conference to emphasize important aspects of pulmonary carcinogenesis in animals as a whole, and a number of papers were presented. Of special interest was the brief address of Prof. W. I. B. Beveridge on the World Health Organization's programme in comparative oncology.

From Heston we learnt that lung tumours in the mouse are the most suitable for genetic study. There are sub-strains with high- and with low-pulmonary-tumour incidence. The genes which influence the development of induced tumours have the same effect on the development of the so-called spontaneous tumours. These are tumours with a high degree of heritability, and at least 10 known genes are connected with the increase or decrease in pulmonary tumours. After discussing the anatomy, histology and electron microscopy of the lungs of the animals most used in experimental research on lung tumours, Peacock directed attention to the double exposure of alveolar epithelium to carcinogens, on one hand, through the air breathed, and on the other through blood, which is responsible for conveying fat-soluble substances directly from the alimentary canal.

As the environment (broadly speaking) would seem to be important in pulmonary carcinogenesis, which may be supposed to overcome the body's defences, Bell examined the protective physiological mechanisms of the lung in small laboratory animals and birds, the respiratory physiology of which is little known or studied. Kinosita reviewed recent progress in research on pulmonary carcinogenesis, and pointed out that many newly discovered causative agents for various species of animals have been introduced. The neoplasms are apparently alveolar and bronchiolar in origin, often undergoing squamous metaplasia. Even minute doses of the agents, given to pregnant or nursing mothers or to the progeny at birth, can be shown to produce lung cancer in mature age.

According to Roe, mice are not ideal for research on lung cancer in man, especially because of differences in airway size and mucus production; they represent, however, a valuable tool in that they make possible the study of a large number of animals and the rapid induction of pulmonary tumours. Such tumours are induced more easily with techniques which prevent the rapid elimination of the carcinogen from the pulmonary tissue. From this fact Shabad developed the theory that, in man, disturbances in the defence mechanisms of the lung could promote the deposition and the retention of carcinogens and the induction of tumoral proliferation. By histological analysis of pulmonary tumours of a number of different animals, by comparison between the lung tumours of the various species and comparison of these with human lung tumours, and by considerations of tumour classification, H. L. Stewart has been led to the conclusion that these are for the most part tumours that have not been studied in depth.

## Spontaneous and So-called 'Spontaneous' Lung Tumours

Evidence points to the belief that spontaneous pulmonary tumours in animals are rare. In cattle they are exceptional (Migaki and Brandly; Montroni and Barboni), about 50 cases having been described (Owen); in the cat, according to Stünzi, they represent 12 per cent of all carcinomata; in the dog, where they do not seem to be on the increase (Cohen), they occur in between 0·2 and 0·6 per cent of the autopsy material, respectively, at Richland (Washington) (Clarke *et al.*) and Storrs (Connecticut) (S. W. Nielsen). In both domestic animals (Dahme) and in captive wild mammals and birds (H. L. Stewart), the cases are usually of adenocarcinomata and squamous-cell carcinomata; alveolar-cell carcinomata are infrequent and are divided into unicentric and multicentric—the latter corresponding (Dahme) to pulmonary adenomatosis in sheep (jaagsiekte).

Because lung adenomatosis or foetalization frequently occurs in many circumstances and due to many causes, care (Schiefer) must be taken in formulating the diagnosis of adenomatosis, strictly defined, in sheep; its real nature is still doubtful, since the possibility of its being inflammatory cannot be excluded (Cohrs). Perhaps, in this regard, it is appropriate to consider the 'jaagsiekte complex' (Marsh) which consists of two morbid entities: (*a*) pulmonary adenomatosis in sheep (jaagsiekte), which may be a tumour capable of metastasising; (*b*) progressive chronic pneumonia, to which 'maedi' belongs. This latter disease (Gudnadottir) has appeared in sheep in Iceland in the past twenty-six years. It is a generalized infection which produces pulmonary lesions, lesions in the lymphatic system and probably in the central nervous system; it would seem that it may be transmitted to healthy animals by the coughing of affected animals. It is a virus disease, the fundamental characteristics of which we have now learned (Thormar).

Pleuropneumonia-like organisms have been shown in a series of sheep with adenomatosis, both serologically and culturally (Mackay). A lesion similar to adenomatosis in sheep (jaagsiekte) is found in man, and this is an alveolar carcinoma of the lung, which has a peculiar clinical progression (Cunningham). The so-called spontaneous lung tumours in mice (the lung tumours of inbred strains) are dependent on many factors, genetic and extragenetic. Johnson and Strong showed that, in all probability, it is possible to control the incidence of lung tumours, a genetically controlled biological characteristic, with selection on a maternal age basis. Rabotti reported on the biology of lung tumours in *BALB/cN* mice, a sub-strain of intermediate lung tumour incidence, and presented data on incidence (which can vary by extragenetic influence), progression and the findings by electron microscopy and tissue culture.

## Induced Lung Tumours

It is possible to induce hyperplastic, metaplastic and/or tumoral lesions in the respiratory apparatus of animals in many ways.

(1) *Ionizing radiation.* After a review of lung carcinogenesis by ionizing radiation (Cember), papers were read on the possibility of obtaining tumours: (i) in the dog, with plutonium particles (Park *et al.*; Clarke *et al.*) and with X-rays (Andersen and Guttman); (ii) in the rat, with β-rays (Kuschner *et al.*); (iii) in the mouse, with X-rays at high altitude (Mori-Chavez).

(2) *Viruses.* Squartini *et al.* found indications that viruses and hormones might be involved in lung carcinogenesis in mice (*BALB/c/Cb/Se* sub-strain). Rabotti found viral particles in spontaneous lung tumours in mice of the *BALB/cN* sub-strain. The virus involved might be regarded as a possible environmental extragenetic factor in the development of lung tumours in mice of this sub-strain. Smith and Miller carried out research to show a virus in a transplantable tumour of mouse lung origin. In the hamster, with cultures of a human lymphoma containing a virus, S. E. Stewart obtained pulmonary lesions. Leuchtenberger and Leuchtenberger concluded from experiments on mice with influenza virus, and with influenza virus in combination with cigarette smoke, that influenza virus would appear to be an 'infectious' RNA virus, which under certain conditions may be implicated in malignant transformation

of cells. Such a conclusion supports the hypothesis that influenza virus may be a co-factor in the development of bronchogenic carcinoma. Harris and Negroni, in a series of experiments, similarly exposed mice to influenza virus and also to influenza virus in combination with cigarette smoke. The results with influenza virus alone gave a low incidence of malignant lung tumours developing rather late in the life of the mice; preliminary results with the combination of influenza virus and cigarette smoke indicate that tumours appear earlier. Of particular interest in the latter series of experiments is the appearance of a squamous cell carcinoma not unlike the lung tumours observed in human smokers. The authors do not regard their findings as conclusive.

(3) *Atmospheric pollutants.* Tumours: (1) in the rat, with nickel carbonyl (Sunderman), and with asbestos (in the pleura, mesothelioma) (Wagner); (ii) in fowls, with asbestos (axillary air-sacs) (Peacock); (iii) in the hamster, with asbestos (in the pleura, mesothelioma) (Smith), with benzo(*a*)pyrene by means of dust particles (Saffiotti *et al.*), and with cigarette smoke (metaplastic and papillary processes in the trachea and bronchi) (Dontenwill and Wiebecke).

Experiments in mice have yielded the following results: (i) with denicotinized tobacco smoke condensate (decrease in the development of pulmonary tumours by 3,4,9,10-dibenzpyrene) (Homburger and Treger); (ii) by the inhalation of tobacco smoke (after a year a single pulmonary tumour) (Harris and Negroni); (iii) with tobacco tar fractions (no increased incidence of pulmonary tumours) (Orr and Woodhouse). From the point of view of human pathology, Carnes and Moses reported that epithelial lesions have been studied, in autopsies, in relation to three forms of atmospheric pollution: (*a*) smoking history; (*b*) residence, classified by size; (*c*) occupation. Epitholial lesions of the trachea and bronchi proved to be more severe in those cases with a smoking history. According to Kreyberg, cigarette smoking, and to a lesser extent pipe smoking, may be considered to be particularly responsible for lung cancer.

(4) *Chemicals.* Tumours: (i) in the rat, with *N*,*N*′-2,7-fluorenylene*bis*acetamide and related aromatic amines (Morris), 9,10-dimethyl-1-2-benzanthracene, 3,4-benzpyrene and 3-methylcholanthrene (Crocker and B. I. Nielsen), 20-methylcholanthrene and 3,4-benzyprene (Laskin *et al.*), *N*-methyl-*N*-nitrosourethane (Schoental); (ii) in the mouse *N*-nitrosodiethylamine and *N*-nitrosodimethylamine (Takayama and Oota), 4-nitroquinoline-*N*-oxide (Kinosita), 3-methylcholanthrene and 4-nitroquinoline-*N*-oxide, new-born and adult (Tsubura and Kimura), urethane (Tannenbaum; Ribacchi and Giraldo; at high altitude, Mori-Chavez), 'Imferon' (Langvad), hydrazine (Biancifiori *et al.*) and its derivatives (Clayson *et al.*); (iii) in the hamster, with diethylnitrosamine (Dontenwill and Wiebecke); (iv) in the white Pekin duck, with methylcholanthrene (Rigdon).

In the rabbit, Griciute produced adenomatosis with dimethylbenzanthracene, and Moran showed that cortisone, administered after pulmonary lesions had been produced by chemicals, resulted in temporary hyperplasias of the epithelial type. In the pulmonary tumours of the rat by dimethylnitrosamine and diethylnitrosamine, changes occur in the protein-levels which seem to reflect systemic alterations in the whole organism (Hoch-Ligeti). The various degrees of alkylation of nucleic acids in the lungs and in other organs of the mouse, hamster and rat after treatment with carcinogenic nitroso compounds were studied in relation to the susceptibility of the organ to the carcinogen (Magee).

Briand and Kieler investigated the carcinogenic and co-carcinogenic effect of various oxygen tensions on murine lung cells grown *in vitro*. Nitrosamines may be contained in cigarette smoke even though they have not been demonstrated; it is possible, however, that they disappear rapidly (Boyland and Roe). Urethane may act as an accelerator only (Bentvelzen and Szalay) and, according to Boyland, by means of *N*-hydroxyurethane. It has been shown in the rat that even a serious lesion in the pulmonary tissue is not sufficient for the development of a cancerous growth in the presence of a weak carcinogen (Stanton and Blackwell). Boeryd and Mellgren reported on the influence of heparin and epsilon-amino-caproic acid on pulmonary metastases of malignant tumours in mice.

## Summary

In the final session of the conference, under the chairmanship of Lord Florey, Prof. Severi gave a summary of the contributions to the scientific programme. Little is known of the epidemiology, the biological behaviour and the pathology of spontaneous lung tumours in animals. The World Health Organization's programme in comparative oncology certainly is welcome. Attempts to induce tumours in the respiratory system by means of physical, viral and chemical agents must be developed extensively, so that research in the field of pulmonary carcinogenesis can be widened. On this point, Balò considered drugs capable of producing lung tumours in animals while Sprunt reported that, by irritation of the pulmonary epithelium with non-carcinogenic substances, lung tumours can be produced in the rabbit. The last mentioned is perhaps an important step for the understanding of pulmonary carcinogenesis. The results reported on experimental carcinogenesis by tobacco did not extend our knowledge beyond the known facts: that smoke condensate is a complete carcinogen, if a weak one, for the skin of the mouse and the rabbit, for the mouse cervix, for the subcutaneous tissue of the rat and also for the trachea of the dog. Nothing is known for sure of its carcinogenic action on the bronchial epithelium, perhaps because of the technical difficulties. A great deal is known about lung cancer in man, and a very great deal about so-called 'spontaneous' and induced lung cancer in animals, but the cause of lung cancer in man or of spontaneous lung cancer in animals remains obscure.

Prof. Severi agreed with Hockett that much systematic, methodical, step-by-step research with animal models must be done. So far as man is concerned, what is not understood cannot be prevented. For this reason there is little to expect from preventive medicine, but much to hope for from basic research.

The *Proceedings* of the conference will be published, as usual, by the Division of Cancer Research, P.O.B. 167, Perugia, Italy.

L. Severi

# PLANNING A NEW MEDICAL SCHOOL

In July 1964 the Minister of Health informed Parliament that a new medical school was to be established in the University of Nottingham, with an intake of 100 students a year, in conjunction with a new teaching hospital of 1,200 beds. For three years before this announcement, the University had been engaged in negotiations, during which much thought was given to the problems involved. In October 1964 the University Council, at the request of the Senate, decided to set up a Medical School Advisory Committee to offer advice and recommendations to the University on medical education, teaching and research, on the best arrangements for the nature and lay-out of the buildings required, and on the University's administrative relations with other bodies concerned. The Com-