

# **Physiopathological and clinical studies of respiratory complaints**

## **Toxicology**

3rd Programme

Progress report on research  
programmes on industrial  
medicine, health and safety  
as at January 1, 1968







PHYSIOPATHOLOGICAL AND CLINICAL STUDIES OF  
RESPIRATORY COMPLAINTS

TOXICOLOGY

1000



Physiopathological  
and clinical studies  
of respiratory  
complaints

Toxicology

3rd Programme

Progress report on research  
programmes on industrial  
medicine, health and safety  
as at January 1, 1968





## FOREWORD

When taking over from the High Authority, the Commission of the European Communities expressed the wish to continue the work on the various research programmes already undertaken within the framework of the ECSC Treaty.

This paper outlines the stage reached with the physiopathological and clinical studies of respiratory complaints covered by heading A. a), 3rd programme, in the annexed table, which shows how these subjects fit into the ECSC overall promotion of research on industrial medicine, health and safety.

The principles guiding the Commission of the European Communities' methods are described in detail in the publication "High Authority policy for the promotion of study and research on industrial medicine health and safety".<sup>(1)</sup>

For readers unable to consult this document, the principles and methods applied can be summarized as follows :

- a) The promotion of industrial health and safety by the collection and distribution of information which can be applied :
  - (i) to the prevention of industrial illnesses and consequences;
  - (ii) to the treatment of their symptoms and consequences;
  - (iii) to the rehabilitation of workers who have been ill or injured.Exchanges of views and experiences and original research and studies are promoted and encouraged to this end.
- b) Use of the Community levy to finance research and other essential activities, under "Programmes" spread over a number of years and each directed to a specific field of research.
- c) Close co-operation with the employers' and workers' associations and government departments concerned, during the preparation and execution of programmes and the circulation of findings.

F. VINCK  
Director General

(1) Publications Department of the European Communities, Luxembourg, 1966.



## CONTENTS

	Page
Foreword . . . . .	7
Introduction . . . . .	11
<i>Basic research in the pneumoconioses</i> . . . . .	13
The elimination and the retention of dust by the lungs . . . . .	13
The injurious effects of siliceous dusts and mixed dusts on cells and tissues . . . . .	14
Substances which inhibit the toxic effect of dust . . . . .	16
The role of infection in the development of the pneumoconioses . . . . .	18
Factors which condition sensitivity and resistance to dust . . . . .	19
<i>Respiratory physiopathology</i> . . . . .	21
<i>Chronic Bronchitis and Emphysema</i> . . . . .	30
a) Aetiopathogenesis . . . . .	30
Epidemiological surveys . . . . .	30
Constitutional factors . . . . .	33
Functional data in chronic bronchitis and emphysema . . . . .	33
b) Prevention and treatment . . . . .	34
Research on the bronchial mucus . . . . .	34
Bronchodilators . . . . .	36
Respiratory cinesitherapy . . . . .	36
Anti-influenzal vaccination . . . . .	37

	Page
<i>Toxicology</i> . . . . .	38
a) Carbon monoxide . . . . .	38
b) Other toxic agents . . . . .	39
Effects of cristobalite, tridymite, and silica . . . . .	39
<i>List of research projects</i> . . . . .	41
<i>Synoptic table of research programmes sponsored</i> . . . . .	50

# Introduction

A sum of 3 million EMA-units of account was allocated for the 3rd programme of physiopathological and clinical research initiated by the ECSC in 1964. Starting in 1965, this programme now covers 86 current research projects, and total commitments so far amount to 75% of the full appropriation (see 15th General Report of the High Authority, Statistical Annex, Industrial Problems).

The programme covers four basic fields of research:

- A. Basic research on pneumoconiosis;
- B. Physiopathological and clinical research;
- C. Research on chronic bronchitis and emphysema;
- D. Toxicology : carbon monoxide, other toxic agents.

The pages which follow describe progress up to January 1, 1968 on the basis of the half-yearly scientific reports submitted to the Commission of the European Communities under agreements concluded with research institutes.



## Basic research in the pneumoconioses

Active prophylaxis is the only effective measure at present available against coalworkers' pneumoconiosis. To be fully effective it must be based upon an exact understanding of the mechanisms which produce the pulmonary lesions. The acquisition of such understanding calls for experimentation at cellular level, to find out how the different inhaled dusts act and what associated exogenous or endogenous factors may modify the reaction of the respiratory apparatus to aggression from mineral particles.

The research projects at present in operation under the third five-year plan (1965-69) for financial support to research are concerned with:

- the elimination and the retention of dust by the lungs;
- the injurious effects of siliceous dusts and mixed dusts on cells and tissues;
- substances which inhibit the toxic effect of dust;
- the role of infection in the development of the pneumoconioses;
- factors which condition sensitivity and resistance to dust.

Analysis of the work done during 1967 warrants a favourable judgement of these projects' progress and achievement. They have been conducted in conformity with the guiding plan established at the outset; more important still, they have added to knowledge of the physiopathological mechanisms which govern the evolution of the pulmonary lesions in pneumoconiosis.

### **The elimination and the retention of dust by the lungs**

The behaviour of inhaled dust during the processes of pulmonary scavenging, and the influence of its composition and quantity on its behaviour, had been established previously by statistical methods, and particle size of intrapulmonary dust in acute and chronic human silicosis had been determined. Submicroscopic studies had revealed no significant relation between particle size on the one hand and mineral particle concentration in total inhaled dust on the other, while microscopic studies had demonstrated the important part played by the lymphatic system in lung cleansing.

Prof. Thomas and Dr. Einbrodt (Göttingen) have shown that:

- dust particle size decreases from the lungs towards the intrapulmonary and extrapulmonary lymph nodes;

quartz particle size increases from the lungs towards the intrapulmonary and extrapulmonary lymph nodes;

quartz content increases markedly from the lungs towards the intrapulmonary lymph nodes, then falls in the extrapulmonary lymph nodes.

The potential practical usefulness of lymph node biopsy in the early diagnosis of pneumoconiosis is thus evident.

Animal experiments have proceeded *pari passu* with investigations in man. Prof. Schlipköter (Düsseldorf) has measured particle deposition and rate of particle elimination after prolonged and uninterrupted dust inhalation in various animals, including mice, hamsters, guinea-pigs, cats, and dogs. The amount of dust deposited varies in the species studied, while within a given species it increases in proportion to the size of the animal. For their size rats retain much dust and rabbits relatively little. The speed with which particles are eliminated from the lungs, on the other hand, is approximately the same in all the species, the only exception being guinea-pigs, in which it is especially slow. The real interest of this work lies in its possible application to man.

Prof. Ulmer (Bochum), likewise continuing animal studies on pulmonary cleansing, is observing the effects of administration of modifying substances such as adrenocortical hormones. Glucocorticoids depress the phagocytic capacity of the macrophages, a depressor effect which is reversible and disappears when the drug is withdrawn. The intimate mechanisms governing the mode of action of these hormonal substances are at present under study.

Prof. Thomas and Dr. Einbrodt (Göttingen) are conducting an *in vivo* investigation, based on sputum observation, of bronchial cleansing in coal-miners. There is every indication that the investigation will be a success and that it will yield valuable information.

### **The injurious effects of siliceous dusts and mixed dusts on cells and tissues**

The importance of the phagocytes, whose mission it is to block invasion by dust particles at the alveolar level, was demonstrated in the preceding research. To phagocytose quartz dust alveolar macrophages must be in the living state; quartz dust, once they have ingested it, rapidly damages and destroys them.

Working in this field, Prof. Gernez-Rieux and Prof. Voisin (Lille) have detected, by electron microscopy, important quantitative alterations in the intracellular lysosomes. To facilitate objective study of these lysosomal changes they have elaborated a new technique (by which free phosphatase is differentiated from intralysosomal phosphatase) for determining acid phosphatase. It permits objective and comparative observation *in vivo* and *in vitro* of the reaction of the lysosomes of the alveolar macrophages to different types of cellular aggression. Observation of *in vitro* phagocytosis of silica particles of various sizes has given interesting initial results. At varying doses of a given type of silica, intralysosomal phosphatase activity falls in proportion as the percentage of phagocytosis rises. Intralysosomal phosphatase activity also varies with the size of silica particles, being maximal with the largest particles.



The cytotoxicity of various forms of silica for other cellular systems is being investigated by Prof. Thomas and Prof. Strecker at Göttingen. They have confirmed that damage to erythrocyte membrane by quartz particles varies with both the shape and the purity of the particles. Unfortunately their technique has proved inapplicable to dust analysis in lungs extensively invaded by silicosis.

Prof. Reploh and Dr. Einbrodt (Münster) plan to study the effect of quartz dust on other cellular systems (such as bacteria, protoplasts, and spheroplasts) using as criterion estimation of nucleic acids set free during bacteriolysis.

Prof. Thomas and Dr. Strecker (Göttingen) are seeking to define the changes which quartz particles cause in lysosome membrane. It is too early to draw conclusions from the results thus far obtained.

Factors liable to modify the behaviour of the alveolar macrophages, which are responsible for phagocytosis and elimination of mineral particles, are also receiving attention in current research.

The Lille group are at present following up their earlier work on the effects of influenzal virus and of pathological bronchial secretions on guinea-pig alveolar macrophages with a study of changes in these latter cells consequent upon inhalation of spores of *Aspergillus fumigatus* by (a) non-dusted animals and (b) animals previously dusted with mineral particles. This investigation may have a bearing on a recent clinical observation that aspergillus infection not infrequently establishes itself in the lungs of miners with pneumoconiosis.

Massive inhalation of live spores of *Aspergillus fumigatus* provokes in the lung tissue of guinea-pigs an inflammatory reaction which recedes within 10 to 12 days. Counts of viable spores in the lung show complete disappearance of the fungus within this lapse of time, as a result of the phagocytic activity of the alveolar macrophages. If the macrophages are collected by Myrvik's technique within 24 hours to 20 days after spore inhalation and preserved alive *in vitro*, their fate can be followed by phase-contrast microcinematography, electron microscopy, and acid phosphatase determinations. Cell damage follows immediately upon phagocytosis of the live spores; plasmodia, intracellular pigment deposits, and myelin figures appear between the first and the sixth day; cell lysosome content (as reflected by free and masked acid phosphatase levels) then rises progressively. Prior immunization of the animals does not modify the dynamics of the pulmonary tissue's reaction to spore inhalation. The experiment is being repeated in guinea-pigs which have first been exposed to dust from pure coal; the initial results show no meaningful difference, when dust exposure has been brief, between their response and that of the non-dusted animals.

The reaction of lung tissue to aggression by quartz and by free crystalline silica continues to be probed in a series of research activities.

The death of cells loaded with quartz dust is a significant factor in the pathogenesis of silicotic fibrosis. Work in progress at Göttingen has shown how particle size and composition influence tissue reaction by determining the degree and the speed of onset of necrosis in the dust-laden macrophages. Quantitative data from chemical analysis and ultrahistological studies suggest that collagen formation in the silicotic granuloma may be looked upon as a "reaction of exaggeration" on the part of the pulmonary tissue. Such reaction would consist

in (i) defective breakdown of the debris of dust cells and the appearance of fibroblast-stimulating mediators and (ii) the release of substances, such as lysophosphatides, which act on the vascular system and thereby lead to hyalinization.

Prof. Mottura at Turin is working on experimentally-induced silicosis in animals. In a systematic study of rat pulmonary parenchyma in relation to varying duration of dust exposure and to different survival times, he has found that animals housed in revolving cages placed in dust chambers whose atmosphere contains 150 particles of quartz per ml need at least 24 hours' exposure for typical silicotic nodules to be discernible 18 months later.

In a further experiment now in progress, on the same lines but with animals killed at shorter intervals after dust exposure, no change in pulmonary and lymph node architecture is detected after three months; after six months large agglomerates of lymphoreticular cells and clusters of necrosing macrophages are present in the lung tissue.

The approach adopted by Prof. Fritze (Bochum) consists in observing the pyrogenic action of quartz and of other forms of silica, and is directed to exploring the role of the reticulo-endothelial system in the mechanisms controlling this action. The work has already shown that cristobalite and tridymite behave differently from rock crystal, and current experimentation is trying to explain this.

### **Substances which inhibit the toxic effect of dust**

The polymer polyvinylpyridine-N-oxide or P 204 has continued to be the object of much research and its high activity, both *in vivo* in animals and *in vitro*, remains unchallenged. Prof. Schlipköter (Düsseldorf) has found that if administered at the same time as quartz, or after, it arrests incipient experimental silicosis in rats, mice, rabbits, and guinea-pigs. The protective action is manifest when it is given subcutaneously, intraperitoneally, or intravenously. Prof. Ulmer's work at Bochum suggests that the best protective and therapeutic effects are obtained when it is given by the intravenous route. Specification of mode of administration is all the more essential because of its bearing on the important problem of determining toxicity. While absence of acute toxicity has been confirmed experimentally, the product's poor elimination has to be taken into account. Accumulation is substantial and prolonged in certain parenchymata, especially spleen, pancreas, and testicles, but relatively slight in liver and lymph nodes; in the lungs it increases progressively in parallel with the injections.

Initial experimentation suggested that P 204 was not so active when administered as an aerosol. However, Prof. Ulmer's more recent work has shown that the doses used had been too high, overloading the macrophages and exhausting their phagocytic capacity, so that the reverse of the desired protective effect was obtained. In the next experiments the polymer will be given in dosage equal to one-tenth of that used before.

Prof. Thomas's and Dr. Strecker's research work at Göttingen includes examination of the mode of action of P 204. That it acts at the beginning of the silicotic response seems to be confirmed. It opposes the detrimental effect of

dust on phagocytes, exerting its protective activity on the changes which quartz particles bring about in the lysosome membrane. It is possible that it may also be adsorbed onto dust itself, thus modifying the latter's physico-chemical properties, but whether a reaction between P 204 and the silicic acid which dissolves from the particles is an essential factor in its mechanism of action is not yet known. These findings link up with what has been learned about the release of acid phosphatase from phagosomes or phagolysosomes.

P 204 likewise inhibits the fibroblastic tissue reaction which follows administration of various dusts, including cristobalite, tridymite, lean coal, and kaolin. Finally, it greatly assists pulmonary and bronchial scavenging.

Prof. Vigliani (Milan) has conducted *in vivo* and *in vitro* studies of other polymers, preliminary results having suggested that other chemical groupings can endow macromolecular substances with protective properties.

The *in vitro* activity of N 57 and N 60 (polymers of the oxide-N-aliphatic group) has proved comparable to that of P 204 towards tridymite. The morpholinic polymers N 40, N 41, and N 42 do not exert their protective effect unless they are administered before the silica particles.

*In vivo* experiments have confirmed the protective properties of N 24; histological examination reveals no silicotic nodules but clumps of macrophages containing particles of tridymite and droplets of polymer. On the other hand, the protective potency of the polymers N 40, N 41, and N 42 has been found to be nil *in vivo*, and that of N 60 less than *in vitro*. Oxyproline determinations now being performed will probably confirm these results.

Other substances capable of modifying the silicotic reaction are at present under study at Prof. Mosinger's Institute at Marseilles. Previous work, aimed at influencing the third phase of the tissue response to quartz (that is, the formation of connective tissue) showed that adrenal hormones both stimulate the alveolar macrophages and encourage discharge of dust via the lymphatics and the blood stream. The present work compares the action of oestrogens with that of P 204. Oestrogens protect rat and guinea-pig macrophages from necrosis *in vivo*; they stimulate proliferation of the alveolar macrophages, leading to a condition which may justifiably be termed "silico-oestrogenic pneumopathy"; their antisilicotic properties, however, are weaker than those of P 204.

Experiments are being conducted at present (i) to determine the frequency with which these protective substances cause pulmonary neoplasms and (ii) to find a means of preventing the stimulant action of oestrogens.

Prof. Ulmer's experimentation at Bochum with rats first exposed to dust from a mixture of quartz and coal in equal proportion and then treated with aluminium chloride, aluminium hydroxychloride, and P 204, is now terminated. Analysis of the histopathological findings (on both light and electron microscopy) will not be completed for some months; it will guide the decision as to which of the substances tested will be used in the next experimentation, which is to be conducted with monkeys.

## **The role of infection in the development of the pneumoconioses**

The Cerchar<sup>(1)</sup> group at Paris are studying this complex problem, and are approaching it in several ways.

The research undertaken previously to evaluate the influence of pulmonary dust load on the evolution of tuberculous infection is now finished. The results have been subjected to statistical analysis and show that the extent and the seriousness of the tuberculous foci increase in proportion to the quantity of dust present in the lungs, be it fibrogenic dust or not. The aggravation is reflected anatomically by the greater extent of the lesions and bacteriologically by greater multiplication of the organisms. Moreover, when the quantity of dust oversteps a certain limit, pulmonary lesions which are normally regressive cease to be so. The nature of the dust—pure coal or a coal-quartz mixture containing 15% of quartz—has minimal impact on the results.

The influence of the duration of infection (by *Mycobacterium kansasii* W<sub>12</sub>) on the effects of a single short exposure to dust has been observed in guinea-pigs. Although little dust is retained in the lungs, the tuberculous lesions are more widespread, more numerous, and more mutilating in animals both dusted and inoculated than in those only inoculated. Infection seems to make no appreciable difference to the expulsion of inhaled dust from the lungs but histological examination reveals a change in its distribution, the interstitium being more heavily loaded with particles in infected animals than in controls; in these latter the dust is confined to the alveoli.

Another line of research is study of experimentally-induced tuberculous lesions at their early stage in guinea-pigs lightly exposed to coal dust. Electron microscopy reveals little dust in the tuberculous foci, a pronounced septal reaction (which, by determining the degree of destruction of the alveoli, governs the evolution of the lesions), non-specific involution of the blood capillaries, dedifferentiation of the epithelial lining, and the advent of rows of cuboidal cells.

The sequence of events in the development of the alveolar lesions is as follows : pathological changes in, followed by disappearance of, the blood capillaries; invasion by lymphocytes; disappearance of the air-space which gradually becomes filled with macrophages, lymphocytes, and polynuclear cells; and, finally, rupture of the basal membrane heralding complete destruction of the alveolus and its incorporation in the diffuse connective-tissue granuloma. Analysis of the nodules so formed reveals simultaneous intervention of tissue-destructive and tissue-constructive processes (appearance of fibroblasts and immunologically competent cells).

The influence of inoculation route upon the development of tuberculous infection in the dusted lung is also being investigated. Subcutaneous injection of organisms of the *Mycobacterium kansasii* W<sub>12</sub> type has not proved an effective means of

(1) Centre d'Etudes et Recherches des Charbonnages de France (Research Centre, French Coal Industry).

systematically producing pulmonary lesions. An apparatus for infecting animals by bacterial aerosol is now ready for use and will enable air-borne contamination to be studied in dusted subjects.

Finally, a series of research projects are being directed to the effects of exposure to dust on BCG vaccination. According to the initial results, dust does not cause reactivation but does intensify the pulmonary and lymph node reactions to the vaccine, reactions which are especially evident where the latter has been given intravenously, and which are never tuberculous in appearance. Additional studies have been started to find out if vaccination influences the formation of dust aggregates.

### **Factors which condition sensitivity and resistance to dust**

Research to assess the influence of immunological reactivity on silicotic fibrosis is being conducted at Paris under the direction of Dr. G.A. Voisin and has contributed to understanding of this subject. Determination of the effect of a purified antigen, siderophilin, on the fibrogenic potency of quartz prepared the way for guinea-pig studies of the chronological relations and the associations between the different types of hypersensitivity observed. Interpretation of the experimental findings being rendered difficult by the intervention of anaphylactic hypersensitivity and of hypersensitivity of Arthus type, supplementary work has been done to elucidate the nature of such intervention, and its results will be published very shortly.

The mechanisms concerned in hypersensitivity reactions liable to be implicated in silicogenic fibrosis have been analyzed from the point of view of vascular permeability in the Arthus phenomenon. Changes in vascular permeability are known to be a central feature in the initial stage of the inflammatory reaction, of which fibrosis is the final stage.

Research on the influence of delayed hypersensitivity on quartz fibrogenesis was initiated in guinea-pigs, but it was found that these are not ideal animals for such investigation. This important subject will therefore be taken up again in a fresh series of experiments, this time in the rat, an animal whose satisfactory fibrogenic potentialities are known and have been classified.

An additional activity in the immunological sphere is that of Professors Vigliani and Pernis (Milan) who are using the *in vitro* macrophage migration test in an endeavour to appraise the consequences of delayed-type hypersensitivity reactions on silicotic fibrosis. Experimental work in guinea-pigs was planned but has been temporarily delayed. A further study now in progress consists in administering a single intratracheal injection of silica to rats which had previously received serial injections of horse serum.

Prof. Fritze (Bochum) is performing comparative immunoelectrophoretic analysis of, respectively, normal lung and the pseudotumoral masses of human silicosis. The results appear to indicate that pneumoconiotic tissue contains antigenic substances not present in normal pulmonary tissue. Attempts to isolate basic polypeptides from pseudotumoral tissue have led to separation of three protein fractions which may be histones. This line of research is being pursued.

That the third programme of basic research in silicosis is progressing very satisfactorily emerges clearly from the above scrutiny of the results obtained during 1967. It confirms that the projects entrusted to the different research centres are fully integrated, and that there is every likelihood of their uncovering new factors in the genesis of coalworkers' pneumoconiosis. It may thus be hoped that the near future will see a decisive advance in the effective protection of the health of workers.

## Respiratory physiopathology

The following pages summarize the most important work performed during the past year in the centres engaged on research in respiratory physiopathology.

Attention should be drawn from the outset to the significant progress that has been made in these research projects in most of the centres concerned. Many of the projects are in process of completion and the results of some have been published.

Profs. Ulmer, Worth, and Maugeri have studied the development of silicosis and conducted comparative assessments of respiratory function in coalworkers and in normal subjects.

Prof. Ulmer (Bochum) has completed part of his research programme and has published the results under the title "Comparative clinical and functional investigations in miners with and without silicosis and in workers not exposed to dust".

In another group of miners—500 in number, with radiographic evidence of pneumoconiosis, and selected at random from among men known to have this condition—Prof. Ulmer has followed the evolution of the functional pulmonary deficit and compared it with evolution in pulmonary function in over 4,000 healthy people from a centre of population in the Ruhr. The results of this survey were communicated at the Münster Congress on the pneumoconioses and will be published in the Proceedings of that Congress.

The same observer and his team are at present submitting miners with severe silicosis to a battery of functional tests in order to find out if they have a higher incidence of bronchitis and emphysema than the mean of the population.

Prof. Worth (Moers) has followed several lines of research. In the hope of throwing fresh light on the aetiopathogenesis of chronic bronchitis and emphysema, he has investigated—by case histories based upon the ECSC questionnaire, clinical examination, radiology, electrocardiography, and tests of function—132 labourers in the metalworking industry and 146 employees and workmen belonging to an administrative service and to a transport company.

He has also conducted a comprehensive assessment of function in 219 miners suffering from incipient silicosis, who had been investigated four years previously and had not worked in the mines since. The examinations they have undergone will show whether removal from a dusty site suffices in itself to prevent silicosis from developing into a chronic, obstructive respiratory disease, or whether additional measures are needed. The results will be published shortly, after having been subjected to statistical analysis.

Seeking to identify the factor limiting strenuous physical exercise, he measured cardiac, circulatory, respiratory, and metabolic parameters in some 20 highly trained athletes who were made to perform increasing grades of exercise up to an energy expenditure level of 400 watts on the bicycle ergometer. The results assigned the limiting role to the cardiovascular system.

Prof. Worth reports two facts of importance in treatment. First, he has experimented with two bronchodilator drugs and found them to have a duration of effective action of over eight hours. Second, during treatment with saluretic agents in patients with disorder of pulmonary gaseous exchange, he has noted the early appearance of metabolic alkalosis accompanied by rise in  $P_{a,CO_2}$  and later by restoration of acid-base balance. In all patients so treated the alveolar-arterial gradient of oxygen tension fell while the  $P_{a,O_2}$  tended to rise.

Continuing their studies of respiratory function in workers in the iron and steel industry examined at their place of work, Prof. Maugeri and Prof. Pezzagno (Pavia) have carried out lung function tests in 41 subjects exposed to dust and in 42 volunteers working in the same industry but not exposed to dust. The tests used were: spirometry, with estimation of residual volume by the closed-circuit method; measurement of pulmonary diffusing capacity for carbon monoxide by a rebreathing technique; continuous monitoring of carbon dioxide in expired gas and recording of the values in the form of a tracing (capnigram); and, finally, helium wash-in; the last two procedures mentioned are performed with the Visser katapherometer.

Although the investigators have as yet insufficient data for statistically significant conclusions or for interpretation of the carbon dioxide and helium expiration curves, they have noted that spirometer values are frankly abnormal in some workers exposed to dust and that diffusing capacity is reduced in most. This investigation continues.

Four research groups have studied pulmonary permeability to carbon monoxide, and three of them have compared different ways of estimating  $D_{L,CO}$ .

Prof. Maugeri (Pavia) has estimated  $D_{L,CO}$  by the three classical methods—single-breath (breath-holding), steady-state, and rebreathing—in a large series of subjects, some healthy, some sick, the latter suffering from reticular silicosis, nodular silicosis, or chronic bronchitis. The single-breath (breath-holding) method used was that of Ogilvie and associates, and the steady-state method that of Filley and associates. In the rebreathing method, the subject rebreathes for 12 to 18 seconds into a bag containing carbon monoxide (about 0.25%) and helium (about 10%) in nitrogen; the carbon monoxide is measured in an infra-red analyzer and the other gases by chromatography. In neither the healthy nor the sick groups was a significant difference found between the  $D_{L,CO}$  values measured by the single-breath and rebreathing methods respectively. In both groups, on the other hand, the  $D_{L,CO}$  was significantly lower when measured by the steady-state method than when measured by the other two methods. Using these three techniques, Maugeri has begun determinations of pulmonary capillary volume and diffusing capacity of the alveolar capillary membrane in normal persons.



Dr. Billiet (Louvain) intends to adapt each of these three methods to the study of carbon monoxide transfer factor in artificially ventilated dogs. His interest is focused on the effect of unevenness of ventilation on  $D_{L,CO}$  determination. This research calls for the elaboration of complicated equipment, in particular construction of a plethysmograph in which the animal will be enclosed while the measurements are being made, and of a respirator mobilizing gaseous mixtures at variable volumes and frequencies. The carbon monoxide will be measured by means of a rapid infra-red analyzer.

The Cerchar (Paris) are estimating  $D_{L,CO}$  by the single-breath and steady-state methods, the latter (based on Bate's technique), being applied at rest and during exercise involving energy expenditure of 50 watts. They have measured  $D_{L,CO}$  by these methods in 300 subjects—193 silicotics at different radiological stages and 107 patients with cardiac or other pulmonary conditions. The theoretical  $D_{L,CO}$  values for the single-breath method are calculated by Cotes' formula depressed by the standard deviation; the values for the steady-state method had already been established by the Cerchar.

The results have been classified in four groups according to whether the  $D_{L,CO}$  values are in concordance or not. The two concordance groups include the values which are normal or significantly lowered irrespective of the method used, and the two discordance groups those which are normal when estimated by one method and reduced when estimated by another.

The concordance groups comprise 58.7% of the cases. Of the 123 cases classified in the discordance groups, most (117) had reduced  $D_{L,CO}$  by the steady-state method and normal  $D_{L,CO}$  by the single-breath method. The researchers are reserving their physiopathological interpretation of these observations.

Prof. Galy (Lyons) used the single-breath method to assess diffusing capacity in 34 silicotic patients and 123 patients suffering from pure, irreversible, adult-type, chronic obstructive respiratory insufficiency. He expressed the  $D_{L,CO}$  values in relation to alveolar volume ( $D_{L,CO}/V_A$ ). In the 34 silicotics, this ratio was lowered in nine out of 10 with pseudotumoral silicosis but in only eight of 24 with the reticulo-micronodular or reticulo-macronodular forms of the disease. The 123 nonsilicotic patients fell into three groups : (i) 35 with a reduced  $D_{L,CO}/V_A$  ratio and radiological evidence of diffuse emphysema; (ii) 42 in whom both the  $D_{L,CO}/V_A$  ratio and the chest radiographs were normal ; (iii) the remainder, with no radiological signs of diffuse emphysema but a lowered  $D_{L,CO}/V_A$  ratio.

To sum up: in all patients with chronic obstructive respiratory insufficiency and radiological signs of emphysema the  $D_{L,CO}/V_A$  ratio is lowered. In patients in whom this ratio is normal the chest radiographs show no evidence of diffuse emphysema. Finally, in a substantial number of patients the  $D_{L,CO}/V_A$  ratio is lowered but there are no radiological signs of emphysema.

Prof. Lavenne (Louvain) has continued his research on diffusing capacity ( $D_{L,CO}$ ) and on alveolar-arterial pressure gradients for oxygen and for carbon dioxide in coalworkers with pneumoconiosis.

He has introduced technical changes and improvements. Thus, the respiratory circuit used for measuring  $D_{L,CO}$  by the single-breath method has been provided with electromagnetic valves based upon those used in Cotes' apparatus. A prototype rapid-acting electrode for estimation of oxygen in expired gas has been studied and calibrated. Direct estimation of alveolar  $PO_2$ , otherwise calculated from an alveolar equation, will thus be possible.

The  $D_{L,CO}$ , at rest and during exertion, and the capillary volume have already been determined in several dozen coalworkers with pneumoconiosis and in normal subjects. In addition, the alveolar-arterial gradients for oxygen and for carbon dioxide have been measured, at rest and during exertion, in coalworkers and in controls, under a variety of conditions—ambient air, hypoxia (13% of  $O_2$ ), and hyperoxia (50% and 100% of  $O_2$ ).

Prof. Deenstra and Dr. Serra (Utrecht) have pursued the work begun by Deenstra and Visser in 1961. Their objective is to define the effect which changes in the distribution of air in the lungs exert on the alveolar-arterial gradients for oxygen and carbon dioxide. Since the alveolar  $CO_2$  concentration depends on the  $\dot{V}_A/\dot{Q}_C$  ratio, and the alveolar  $O_2$  concentration on the  $\dot{V}_A/\dot{Q}_C$  and  $\dot{Q}_C/D$  ratios, analysis of the shape of the alveolar expiratory plateau for  $CO_2$  and  $O_2$ , supplemented by analysis of that for expired He, supplies useful information on the distribution of the two ratios; especially when ventilation itself is unevenly distributed.

This research activity has been carried out on two planes, technical and physiopathological.

The investigators first effected technical improvements in their rapid analyzer for  $O_2$  and  $CO_2$ . It had been fitted with needle valves and these were replaced by diaphragms. Better control of gas output was secured by placing a short-circuit system in parallel to the measuring block. These modifications improved the apparatus in many ways: flux regulation became more accurate; the expiration curves were no longer distorted by water vapour and atmospheric impurities; and response time remained rapid even at very low gas outputs. A future activity planned by the Utrecht group is to determine the influence of carbon dioxide on oxygen expiration curves, although physiologically this appears to be negligible.

Using this improved apparatus, Deenstra and Serra have successfully performed instructive physiopathological experiments, including recording of the helium and carbon dioxide expiration curves for each lung separately in dogs in which lung transplantation had been carried out. The shape of the curve for expired helium from the healthy lung appears to suggest an obstructive deficit and that from the operated lung a restrictive one. In addition, the  $P_{A,CO_2}$  from the transplanted lung is reduced, as is also the oxygen consumption. Taken together, the functional and morbid anatomical data point to pleural adhesions and reduced alveolar vascularization on the operated side.

In another project they have recorded the curves for expired oxygen, carbon dioxide, and helium in 150 patients and 200 manual workers. Analysis and comparison of these curves provide mutually complementary data. In some cases marked arterial desaturation, depending on the distribution of the factor  $\dot{Q}_C/D$  or, more exactly, on the  $\dot{V}_A/\dot{Q}_C/D$  ratio, can be detected by comparing the slopes of the curve for expired oxygen, carbon dioxide, and helium.

Prof. Ulmer (Bochum) and Prof. Cara (Paris) have continued with success their efforts to standardize certain ventilatory tests.

Prof. Ulmer has compared the values for residual volume measured by the helium-dilution technique and by whole-body plethysmography respectively. The latter gives more accurate and higher values, but the former yields readily reproducible values provided certain conditions are fulfilled. The results of this work will be published shortly.

The objective of another of Prof. Ulmer's research activities was to assess the reproducibility, over a period of one year, in normal volunteers, of measurements of airflow resistance by plethysmography during spontaneous respiration. The experimental part of this work is terminated. Analysis of the results will provide reference values for the plethysmography method for measuring airflow resistance during spontaneous respiration.

Prof. Cara has contributed to the standardization of certain respiratory tests and to the dissemination of information on the scientific work sponsored by the Community.

He is engaged in the codification of:

- (a) rapid respiratory tracings (of which certain have been selected and will be used for reference);
- (b) exercise tests, with special attention to rectangular and trapezoidal tests; a common terminology for exercise tests has been proposed;
- (c) measurement of residual volume and of intrapulmonary gas-mixing.

The same worker has also drawn up a supplement to the *aide-mémoire* on the performance of pulmonary ventilatory function tests by spirometry.

In addition, he made a communication at the Prague Congress on the scientific basis, the experimental aspects, and the clinical results of the activities of the ECSC experts during the last ten years. Finally, he did the preparatory work for several meetings of the committees on standardization.

Prof. Denolin (Brussels) has studied two fundamental problems, (i) the application of functional tests in pathological conditions of the heart and lungs and (ii) re-appraisal of the interpretation of the physical capacity tests used in industrial medicine.

Working on problem (i), he has re-examined various aspects of the reactions of cardiopulmonary invalids during effort.

In a review of techniques and of interpretation in electrocardiography, he has compared tracings recorded during exercise intensified at five-minute intervals with those obtained during exercise intensified gradually according to the method of Bonjer. He has re-analyzed the non-specific changes in the phase of repolarization at rest and the tracings taken during and after effort. Electrocardiograms recorded after exertion enable potential coronary insufficiency to be detected and the physical capacities of patients with angina pectoris or previous myocardial infarction to be determined.

He has made a special study of cardiopulmonary adaptation during the early stages of exertion; differences between oxygen consumption at the beginning of effort and after its termination will no doubt throw light on the physiopathological significance of oxygen debt. His work has also included estimation of cardiac output by injection of cardio-green, observation of changes in the blood volume and in the corpuscular and plasmatic constituents of the blood during effort, and re-study of arterial tension as measured at the brachial artery. His research has given sharper definition to the concept of lean body mass, a biometric parameter which is likely to promote better definition of physical capacity. The clinical validity of some of these procedures has already been tested in patients suffering from various cardiopathies.

Work on the second of Denolin's problems, interpretation of physical capacity tests, is well advanced and some conclusions may already be drawn. Determination of pulmonary ventilation, oxygen consumption, and heart rate in 61 volunteers (fitters in a motor-car assembly chain), (i) at work and (ii) in the laboratory on the bicycle ergometer, has revealed a high degree of correlation between cardiovascular response in workshop and laboratory respectively. In 16 of the volunteers, continuous telemetric recording of the heart rate during prolonged exertion (three hours) made it possible to estimate the total cost to the heart of the work performed. The results are in process of publication. A comparative study of energy expenditure (i) while at their work in the factory and (ii) in the laboratory on the bicycle ergometer is at present being conducted in a group of steelworkers exposed to intense noise. Pulmonary ventilation, oxygen consumption, heart rate, and blood pressure are estimated.

The haemodynamic repercussions of silicosis, of chronic bronchitis, and of emphysema have been the subject of many research projects.

Prof. Fritze (Bochum) has initiated pulmonary scintigraphy studies in sufferers from pneumoconiosis. He believes that this may prove to be a useful complementary investigation in reviewing the functional and radiological status of these patients.

Prof. Reale and Prof. Venturini (Rome) are using radioactive krypton ( $^{85}\text{Kr}$ ) to evaluate the severity of certain vascular anomalies in the lungs. In cases of arterio-venous fistula they inject  $^{85}\text{Kr}$  into the pulmonary artery and take a blood sample from the brachial artery. In arterio-venous shunts other than those due to angiomas, the  $^{85}\text{Kr}$  is injected through a small catheter introduced into the superior vena cava; at the same time two blood samples are withdrawn from a branch of the pulmonary artery and from the brachial artery. Radioactivity measured in the arterial blood is expressed as a percentage of that found in the

pulmonary circulation. Patients with pulmonary arteriovenous fistula and with mitral stenosis have already been investigated by this procedure, and it is planned to examine others suffering from chronic pneumopathies.

Prof. Casula (Cagliari) is exploring means for detecting the onset of pulmonary hypertension at as early a stage as possible and is studying the effects of this condition on the chambers of the right heart in the chronic pneumopathies.

In pursuance of these investigations he has performed cardiac catheterization and recorded various parameters at rest and on effort in a large series of patients, who underwent in addition clinical and radiological examination, electrocardiography, and respiratory function tests. In some of the patients these procedures, in particular the cardiac catheterization, were repeated at varying intervals. Special attention was devoted to the electrocardiographic changes associated with right heart failure; tracings were taken both in the resting state and during exercise on the bicycle ergometer. Finally, this investigator has undertaken a comparative study of the values for cardiac output obtained (i) by the Fick method and (ii) by the dye injection method.

Prof. Gunella (Bologna) has already assembled data on the effects of mechanical ventilation on the haemodynamics of the lungs.

He uses three methods of artificial ventilation. The first, intermittent positive pressure ventilation, is operated by an MSA machine. In the second, alternating positive and negative pressures are produced by a Bird respirator Mark 8. The third method also depends on positive-negative pressure, but in addition the inspiration time: expiration time ratio can be modified at will; an SF4 apparatus is used. These three techniques have been tried in 15 patients (each technique in five patients) suffering from silicosis or from bronchitis and emphysema and whose  $S_{a,O_2}$  and  $P_{a,CO_2}$  were normal at rest. Finally, intermittent positive pressure ventilation has been tried in a fourth group of five patients, comparable to the other 15, during cardiac catheterization. Initial results suggest that mechanical ventilation, whatever the technique, has very few haemodynamic consequences.

Dr. Van de Woestijne (Louvain) has sought to assess the effect of various sources of error on measurements of intrathoracic pressure by the oesophageal balloon technique.

The influence of the mediastinal organs on intraoesophageal pressure was elucidated in experiments on dogs examined in different positions before and after opening the thoracic cage; it is a complex influence and was found to vary with the situation of the balloon in the oesophagus and with the position of the body. The mediastinum is largely responsible for the pressure gradient measured in the oesophagus, in the erect posture; this gradient is probably unrelated to the similar gradient measured in the pleura. Moreover, the mediastinum modifies pulmonary elastance.

In another investigation, conducted in human subjects, this researcher made a radiological study of the influence of the respiratory movements on the movements of the oesophagus.

An important cause of false intraoesophageal pressure readings is pulsation originating in the heart. The morphology of the resultant "cardiac artefacts" in oesophageal pressure tracings varies at different levels of the oesophagus and

at different stages of respiration. The errors of measurement to which they give rise may be substantial. Prof. Van de Woestijne has evaluated these errors in man and proposed a means of eliminating them; this consists in studying states of cardiac isocontraction, that is, in relating variations in oesophageal pressure to the stage of ventricular diastole. During this research he detected a second source of error, namely, displacement of air within the balloon. He has been able to demonstrate the impact of these two factors—cardiac artefacts and air displacement—on measurement of (i) pressure variation in the axis of the oesophagus (“intraoesophageal pressure gradient”) and (ii) static pulmonary compliance. This work has been the subject of many publications.

Prof. Bretschneider (Bochum) has continued his studies of coronary blood flow by means of inert gases.

Before beginning observations in humans, he developed certain complicated apparatus and techniques, in particular, a chamber for extracting the blood gases and a method for the chromatographic separation and estimation of argon. Various models of extraction chamber were tried and modified as necessary to achieve greater efficiency; their effectiveness was tested with liquids of different viscosity and with dog and human blood. The technique for chromatographic analysis of argon was simplified and improved: adjustment of the most important parameters facilitated linearization of the calibration curve; addition of sodium dithionite so modified the chemical binding of the oxygen in the blood sample that the oxygen produced only a single small, but constant, peak; the dithionite had the further advantage of enabling the chromatographic analysis to be performed at 50°C; finally, addition of a trace of octyl alcohol checked foam formation during rotation of the magnetic stirrer of the extraction chamber.

That the inhalation of high concentrations of argon in oxygen apparently evokes no reaction in the circulatory or respiratory systems was seen when these gaseous mixtures were administered to conscious men and to anaesthetized dogs.

Bretschneider has estimated coronary blood flow in dogs both by the argon method and by the classical method of coronary sinus catheterization, and has found good agreement between the results thus far obtained by the two procedures. Coronary vasodilator drugs greatly increase coronary blood flow, and here again the two techniques have given concordant results. After trials in animals Bretschneider hopes soon to be able to apply the argon method in man and thereby to obtain accurate data on coronary blood flow. The results of his work on the extraction chamber and on chromatographic analysis have been published.

Dr. Wassner (Bremen) has recorded and analyzed the tracings of ventilatory response to carbon dioxide in 20 normal subjects and 29 patients with silicosis, bronchitis, emphysema, and neoplasms. He has not yet enough data to draw conclusions.

Finally, reference should be made to the revival of a technique which may give useful service.

In order to evaluate and measure changes brought about in the lungs by certain pathological processes, in particular chronic bronchitis and emphysema, Prof. Galy (Lyons) has initiated a study of isolated lungs. The anatomical specimens

are obtained from necropsies and surgical operations. The visceral layer of the pleura has to be intact. To study the elasticity of the isolated lung, the investigator uses a thick-walled transparent box connected (i) to a suction pump which has a adjustable flow rate and by which the pressure in the box can be lowered, and (ii) to a water manometer. The lung is attached by a bronchus to an orifice in the lid of the box, which orifice communicates with a spirometer. This technique, based on that of Christie, reveals any loss of pulmonary elasticity. It is interesting to compare its results with those of the classical function tests.

# Chronic bronchitis and emphysema

The ECSC's present research programme in chronic bronchitis and emphysema has, as we know, a threefold orientation aetiopathogenesis, prevention, and treatment.

The following current research projects are focused on aetiopathogenesis: epidemiological surveys in large population groups (conducted in 11 centres in the Community); studies (in two laboratories) of the possible role of certain factors in the aetiology of these conditions; an investigation (by two teams of experts) into their functional background; and an examination (in three research centres) of their anatomical correlations.

In prevention and treatment, three laboratories are exploring the effects of mucolytic drugs and two others are testing the effectiveness of various forms of bronchodilator therapy. An investigator is studying the effects of respiratory cinesitherapy on respiratory function. Finally, an inquiry begun several years ago into the impact of preventive anti-influenzal vaccination on absenteeism in chronic bronchitis has been continued at a research centre.

## **a) Aetiopathogenesis**

### *Epidemiological surveys*

The initial results of a longitudinal study carried out in Lorraine under the direction of Prof. Sadoul stress the seriousness of the outlook in bronchitis, even in patients leading fully active lives at the time of diagnosis. In 1960, 248 unselected metalworkers, aged 45 to 64 years, were examined clinically, radiologically, and by spirometry. Six years later they were reviewed by the same doctors and the same methods; it was then appreciated that both mortality and sickness absence rates had been significantly higher ( $P > 0.0001$ ) in the subjects in whom bronchitis was detected at the first examination than in those found healthy at that time. This study confirmed the prognostic value of the presence of airway obstruction, although in some cases the spirographic method proved inadequate for surveillance since disordered blood gases could co-exist with normal spirographic readings.

The limitations of spirometry in this field are recognized by many workers, who tend in consequence to use for their surveys a wide spectrum of lung function tests. Thus, Prof. Valentin at Erlangen conducts measurements of respiratory mechanics using, in particular, body plethysmography. In preliminary



work, he made a critical study of the value of this technique, identified the phenomena (such as temperature, relative humidity of the inspired air, shape of the mouthpiece, and buccal malformations) liable to interfere with its results, and correlated its findings with those obtained by spirometry, more especially as regards measurement of residual volume. The method thus worked out is at present used routinely in the investigations for which Professor Valentin is responsible.

Dr. Jongh's epidemiological research at the IJmuiden steel works is centred on chronic bronchitis in welders, utilizes the ECSC questionnaire and, with a view to specific identification of the cause of respiratory disease in the workmen concerned, includes measurements of air pollution in work premises. It had been noted in a previous investigation that respiratory function in welders seemed to deteriorate towards the end of the working day, a fact which might incriminate welding fumes. The present study, however, has as yet produced no evidence that such fumes are in fact detrimental to pulmonary function.

Another epidemiological study being carried out in the Netherlands (by Dr. van der Lende under the direction of Prof. Orie) concerns a large control group (2,065 men at Meppel, 2,143 men and women at Vlagtwedde, and 1,194 men and women at Vlaardingen) of persons not exposed to the harmful effects of work in coal pits or steel works. The findings in those aged 40-to-64 or -65 were published recently. They showed that cough and expectoration were much influenced by tobacco smoking, perhaps also by place of residence, and only slightly by age. Dyspnoea, on the other hand, appeared to depend chiefly on age and, to a less extent in women, on place of residence, but practically not at all on smoking habits. These tendencies were confirmed by objective examinations which revealed a correlation between age and spirometry values but not between age and quantity of sputum as measured in samples handed in by the patients at the time of examination.

Prof. Symanski's team have continued their epidemiological surveys in the iron and steel works of the Saar Basin. Following up a line of inquiry suggested by their previous investigations, they are devoting special attention to the effects of certain sociological factors which may influence selection for employment in steel works and which might thereby cause erroneous conclusions to be drawn from the results of these observers' epidemiological research. The Saar studies have emphasized the importance of non-occupational factors, in particular tobacco smoking, in the aetiology of bronchitis.

Professor Symanski is at present re-examining 800 workmen aged between 40 and 60 who were first examined between 1959 and 1961.

A similar longitudinal study is being carried out in Sardinia by Prof. Casula. He examined 2,000 coalworkers a year ago, on the basis of the ECSC questionnaire, and is now re-examining them for comparison.

Data from a field survey conducted by Dr. Minette at Lanaken are at present being recorded on punched cards. The survey concerns 262 miners chosen at random from the mining population of the locality and the results will be compared with those obtained in a control group of similar size composed of

male subjects following other occupations. The findings of a four-year longitudinal study in 4,000 workmen in the Houthalen collieries are being subjected to statistical analysis. Facts emerging from these two investigations will be scrutinized in the light of observations in 1,298 workmen with bronchitis of varying severity examined at the Lanaken Institute on several occasions over periods varying from two to eight years.

In order to gain further insight into the evolution of bronchitis in colliers, Prof. Crepet at Padua has conducted serial examinations in 289 workmen over periods ranging from four to nine years, by a variety of techniques, including a standard questionnaire, radiology, and searching functional tests. The results are being reviewed statistically.

Also in Italy, Dr. Zanini is working on the incidence of chronic respiratory affections in workers in blast furnaces and steel works, in particular those exposed to dust during deseaming operations. Measurements of the dust present in the atmosphere of work places and experimental research on the effects of such dust in mice, conducted in conjunction with this observer's epidemiological research, have yielded confirmatory evidence that the most dust-producing operation in these industries is the cleaning of premises normally sheltered from rain, for much dust is raised in the process. The dust collected has been found to contain from 5 to 6% of silica by weight and in certain special premises silica has constituted 4% of the total number of particles.

Another important epidemiological study, designed to explore the effects both of dust and of the sulphur dioxide given off in the auto-oxidation of pyrites ore, is being carried out at the Gavorrano pyrites mine by Professors Sartorelli and Pernis. Begun several years ago, it is based on the first version of the ECSC questionnaire, but also utilizes a battery of complementary radiological and functional investigations. The observers have perceived the expediency of the patients' complaints being recorded by two experienced doctors; data can thus be cross-checked and replies are more likely to be objective. The findings are being compared with those in a control group of 300 non-miner manual workers.

Dr. Brinkmann, in collaboration with the Institute for Medical Statistics of the University of Mainz, is at present conducting a similar investigation comprising longitudinal and cross-sectional studies into the respiratory repercussions of dust in mines. This work, based upon the ECSC questionnaire and upon pulmonary function tests such as blood gas analysis and respiratory resistance determinations, is not directed solely to the dust hazards specific to the coal and steel industries, but seeks also to explore the potentially noxious effects of the dusts, gases, and vapours associated with typical dust-polluted atmospheres.

Other researchers have adopted a morbid anatomical approach to ascertaining the prevalence of pulmonary emphysema. Thus, Dr. Otto at Erlangen has found that this affliction is apparently much less frequent in Germany than in Wales; necropsy revealed 85 cases of emphysema in 282 adults aged between 30 and 90 at Cardiff and only 92 cases in 722 adults at Erlangen. The reason for the difference is not clear. In both localities the necropsy material was drawn from working-class populations. Possibly the higher incidence at Cardiff is conditioned by general climatic factors.

### *Constitutional factors*

Work on the possible role of certain "constitutional" factors in the aetiology of chronic bronchitis is being done at two centres.

At Bochum Prof. Fritze has been looking for evidence of respiratory hypersensitivity in 300 miners exposed to dust, but has so far found no difference in this respect between them and non-dusty groups.

At Lanaken Dr. Minette made a similar study in the course of the epidemiological survey carried out there under his direction. The miners and non-miners included in the survey were fully investigated from the allergic standpoint—skin sensitivity tests to a wide range of allergens, eosinophil counts in the circulating blood, and pharmacodynamic broncho-constrictor tests. A smaller group of 25 miners were also tested with allergens prepared from moulds and plants found at the bottom of the mine. The results are being analyzed but the preliminary data do not suggest that sensitivity factors have much to do with colliers' bronchitis.

The part played by certain hormonal factors in chronic bronchitis has also received attention from a group of experts. Prof. Regniers and his associates at the University of Ghent are working out techniques, applicable to physiological studies on chronic bronchitis and emphysema, for estimating plasma testosterone.

Marginal to these general studies on aetiopathogenesis is Dr. Zimmermann's important work at Homburg on evaluation of the pathogenicity of the micro-organisms present in the bronchial tree of bronchitics. The work is based on the notion that under normal conditions pathogenic organisms are bound to act as antigens and that it should therefore be possible to detect their presence by demonstrating specific antibodies in the blood. Although these investigations have not as yet revealed high antibody titres in bronchitics they have confirmed the very high incidence of *Streptococcus viridans* and of *Neisseria* in their bronchial tree. Next in order of frequency, but five to eight times less frequent, are *Haemophilus influenzae* and *Staphylococcus aureus*. The results of this work, and their interpretation, are still under study.

### *Functional data in chronic bronchitis and emphysema*

This problem has been studied clinically by Prof. Worth at Moers and Prof. Caccuri at Naples, and clinicopathologically by Prof. Giese at Münster, Prof. Könn at Bochum, and Dr. Brille at Paris.

The objective of Prof. Worth's research has been to obtain comparative data on lung function in workmen exposed to dust and workmen suffering from silicosis. The results have shown pulmonary diffusing capacity in miners to be significantly lower than in workmen in dust-free occupations. No significant difference in pulmonary ventilation has been found between miners and non-miners. In a practical and theoretical study of body plethysmography Prof. Worth has noted serious practical and theoretical difficulties in the way of quantitative expression in resistance diagrams, difficulties which are such that the suitability of the method for comparative (for example, epidemiological) studies becomes questionable.

Prof. Worth has also conducted important and successful comparative investigations into certain statistical problems, such as the normal distribution of the partial pressures of oxygen and carbon dioxide at the end of expiration, and the arterial gradients for oxygen and carbon dioxide, likewise at the end of expiration. In so doing he has observed a significant correlation between the haematocrit values and the arterial oxygen gradients at the end of expiration. The higher the haematocrit values the greater were the gradients.

Prof. Caccuri has studied changes in the electrocardiogram, atrial vectorcardiogram, and pulmonary rheogram, and conducted measurements of maximal exercise tolerance, in 20 normal subjects, 32 patients with various bronchopneumopathies, and 148 silicotics; the results are being analyzed at present. The same battery of investigations was performed in welders, and has revealed changes in static and dynamic respiratory volumes. Professor Caccuri has devoted special attention to pulmonary compliance in welders and has attempted to determine the doses of toxic substances to which they are exposed in their work.

In clinicopathological studies, Prof. Giese has endeavoured to assess the importance of the glandular changes in the bronchi of chronic bronchitics and to establish a method for identifying the stage of the disease by observing these changes. Applying the index proposed by Lynne Reid for this purpose, he concluded that the index is open to various causes of error, and that in particular it takes no account of glandular fields which may hypertrophy and make their way through the cartilage to the adventitia. He therefore prefers the more time-consuming but more accurate method consisting in making drawings of sections of the bronchi on cardboard of uniform thickness, then cutting out and weighing the glandular fields.

Prof. Giese has also continued his work on functional values, measured in the isolated lung. He has perfected his apparatus and hopes for results towards the middle of 1968. At the present stage of the work Professor Giese has come to the conclusion that the mixing time is not a true parameter of intrapulmonary gas mixing. The mixing volume (that is, the product of the ventilation per minute by the mixing time) on the other hand, is in much closer correlation with the functional residual capacity and this makes it a good index of pulmonary mixing efficiency.

Prof. Könn has used necropsy material from 72 subjects for a study of heart changes in chronic bronchitis, and his results are being analyzed. Analogous data from non-bronchitic subjects will be used for comparison.

A correlative clinicopathological study, directed more specifically to the lesions of the obstructive bronchopathies, is being carried out under Dr. Brille at Paris. Assemblage of the necessary necropsy specimens is proceeding satisfactorily.

## **b) Prevention and treatment**

### *Research on the bronchial mucus*

Changes in the bronchial mucus and means of influencing these changes are of interest to many investigators at the present time. Research in this field is being pursued, with the aid of ECSC grants, under Prof. Voisin at

the University of Lille, Prof. Crepet at the University of Padua, and Prof. Sartorelli and Pernis at Milan.

Developing his work on the sulphated glycoproteins of bronchial origin, Prof. Voisin has shown that these can be isolated from the fibrillary structures of the sputum. They are present together with two other glycoproteins of glandular origin, (i) the blood group-specific substances and (ii) a glycoprotein whose acid character is related to the presence of sialic acid residues at the terminal position of the polysaccharide units.

Affinity for staining by basic dyes such as toluidine blue, or by the Schiff reagent after oxidation with periodic acid, depends on degree of sulphatization and on sialic acid content, and these vary from one pathological mucus to another.

Using histological techniques, Professor Voisin has also demonstrated a very active sulphatization process in the serous cells of the mixed glands and in the calyciform cells of the surface epithelium of the human bronchial mucosa. The metabolism of the mucous cells is oriented especially towards production of sialoglycoproteins or of blood-group substances.

The mechanisms responsible for regulating the equilibrium of the bronchial milieu are not at present known. Professor Voisin has no doubt that the sulphoglycoproteins are a fundamental factor in maintaining local water-electrolyte balance, in particular the high calcium and potassium content of the fibrillary mucus.

Work at the Pasteur Institute, Lille, on the effect of benztropine citrate, administered orally or by suppository, on expectoration in chronic bronchitis, has shown that this compound does in fact reduce expectoration quickly and substantially. The reduction is accompanied by biochemical changes, consisting in (i) increase of the trypsin inhibitors and (ii) alterations in the composition of the fibrillary mucus, namely, decrease of the DNA fraction and increase of the blood-group substance type of glycoprotein. The increased content of blood-group substance reflects diminished incorporation of sulphates in the structure of the bronchial mucins, and may be a local anti-inflammatory action of the same type as occurs in corticotherapy.

The central feature of Prof. Crepet's research work on the bronchial mucus is quantitative estimation of the immunoglobulins in the serum of miners with or without chronic bronchitis. G-globulin was increased in 89% of bronchitics, A-globulin in 79%, and M-globulin in 22%. No correlation was found between the severity of pneumoconiosis and serum immunoglobulin levels. On the other hand, a correlation was found between the severity of chronic bronchitis and A-globulin levels, patients in whom the latter were raised being more seriously afflicted than the others.

Prof. Sartorelli and Pernis too are working on immunoglobulins in the bronchial secretion of chronic bronchitics. In a one-year study of the bronchial secretion of 15 patients at different stages of bronchitis but all with copious mucopurulent sputum, they found A-globulin in most and (a point of major interest, confirming their previous findings) G-globulin in nine. It was to G-globulin that their attention was chiefly directed, for it is rarely if ever present in the mucus of healthy bronchi. Difficulty was experienced in collecting and preparing samples of mucus and the intention is to obtain mucus in future by bronchoscopy and bronchial lavage.

These researchers plan to extend the scope of their investigations to include comparison of the characteristics of mucopurulent and non-infected secretion respectively.

### *Bronchodilators*

Dr. Minette at Lanaken and Prof. Crepet at Padua have been investigating the effects of bronchodilator substances.

The purpose of the Lanaken work is to compare the bronchodilators at present available commercially. In a communication at the Stresa symposium Dr. Minette reported an important statistical study demonstrating that orciprenaline (administered from a calibrated bottle) and atropine methonitrate (administered as an ordinary aerosol in a dose of 3.2 mg) are potent bronchodilators. Both compounds produce side-effects; these are not severe (at least not in the case of orciprenaline taken moderately) but may limit their use. Dr. Minette's subsequent research has been on a new hydroxyphenyl derivative of orciprenaline, Th 1165a, put up, like orciprenaline, in calibrated bottles. In a dose of 600  $\gamma$  it exerted a more powerful and more prolonged bronchodilator action than 1500  $\gamma$  of orciprenaline or 400  $\gamma$  of isoprenaline. Its results in 54 miners, observed systematically by a standard procedure, warrant its inclusion among the major bronchodilators. Its side-effects are similar to those of orciprenaline. This research has confirmed the interesting activity, previously reported, of atropine methonitrate.

Associated with these problems is a current study of a new product, FLP 670, which has the property of blocking certain antigen-antibody mechanisms and may therefore be effective in some forms of spastic bronchitis with hypersensitization. Preliminary results are encouraging, although precise definition of the indications seems difficult.

Dr. Minette's work on standardization of aerosols has continued in co-operation with the Hygiene Institute of the Hasselt Collieries; its status has been reported to the ECSC's committee on standardization of function tests.

Prof. Crepet has been investigating mainly the action of orciprenaline administered as an aerosol in doses rising from 2 to 10 mg. He has evaluated the effects by determining vital capacity and forced expiratory volume per second, and his results have confirmed this drug's important potentialities.

### *Respiratory cinesitherapy*

In research on this subject at the St. Antoine Hospital, Paris, Dr. Brille computes the work of breathing by measuring the area of the pressure-volume loop. Comparison of ventilatory work before and during exercise respectively should provide an indication of the real effectiveness of cinesitherapy. Evaluation of total ventilatory work raises technical problems in patients so treated, in whom total lung compliance curves may be difficult to obtain. These problems are at present under study.

### *Anti-influenzal vaccination*

The Lanaken Institute has for some years been doing important research work in this subject in the Campine Basin (Belgian Limburg). An initial mass campaign in 4,995 workers in a colliery in the winter months of 1965-66 had no effect on their respiratory sickness absence rate during that winter.

A fresh attempt was made in the 1966-67 season, this time in two collieries, and the workmen vaccinated were followed-up until the autumn of 1967. The results of these trials are now being analyzed.

# Toxicology

## a) Carbon monoxide

Prof. Rubino at Turin is doing research on acute carbon monoxide poisoning. The problem selected for study is the effect of exposure to carbon monoxide on the cardiovascular and nervous systems in experimental animals. Dogs of both sexes have been submitted to serial haemodynamic determinations—during exposure, during reanimation, and subsequently—the parameters studied being heart rate, systolic arterial pressure, pulmonary arterial pressure, cardiac output, coronary output, and pulmonary vascular resistance. The results are under analysis.

Clinical research on carbon monoxide poisoning is being conducted by Prof. Pancheri and Prof. Franchini. The present phase of Prof. Franchini's work is devoted mainly to defining the histological lesions in brain, kidneys, liver, and lungs, but he has also examined the immunoelectrophoretic behaviour of the blood proteins in acute poisoning. In addition, he is carrying out two epidemiological studies. The first, based on 51 cases, is designed to elucidate the clinical and medico-legal significance of coefficient of intoxication in acute carbon monoxide poisoning. In the second, which as yet comprises only a small number of subjects, it is planned to follow the morbidity and the incidence of invalidity in a group of workmen exposed over periods of years to the carbon monoxide hazard.

A comprehensive investigation (including attention to the physiopathological, psychological, psychopathological, and social and occupational aspects) in individuals who had suffered acute carbon monoxide poisoning one year previously is being made by Dr. Veil in Paris. Of 156 case histories reviewed, 17 only were accepted for inclusion in the survey and these are now being studied.

Dr. Heim at Erlangen has continued his work on these same problems and is at present observing the effects on cerebral metabolism of repeated exposure to low concentrations of carbon monoxide. He has found that if white mice are exposed nine hours per day for seven weeks to 0.1% of carbon monoxide in air, about one-third of their haemoglobin is converted into carboxy-haemoglobin. The consequent cerebral hypoxia often leads to increased glycolysis with resultant significant increase in pyruvates and lactates (products of carbohydrate catabolism). Blood sugar being used up, blood sugar levels fall. In spite of the increased glycolysis the brain's needs in energy-rich bonds are not fully covered and, although normal ATP concentrations are maintained, cerebral creatinine phosphate levels are significantly lowered.



In a second research series, Dr. Heim has found the metabolic disorders consequent upon carbon monoxide poisoning to be only slowly reversible, recovery being still incomplete 15 hours after withdrawal from the contaminated atmosphere.

Prof. Caccuri has undertaken a study of the effects of toxic fumes emanating from welding operations. In observations in 50 welders, he found that there is a real risk of carbon monoxide poisoning when welding is carried out at a short distance from the electric arc, and in another 46 that ocular lesions are rare in this trade provided preventive measures are applied. Investigating the absorption of iron via the respiratory tract in 50 welders he found it to be slight; in particular, none showed radiographic evidence of siderosis. Finally, Prof. Caccuri has been attempting to determine the manganese content of the ambient air at welding sites. This research continues.

## **b) Other toxic agents**

### *Effects of cristobalite, tridymite, and silica*

Prof. Santi is proceeding with his research on the toxic effects on pulmonary tissue of various dusts, in particular cristobalite and tridymite, produced in metallurgical operations. This investigation has been conducted in laboratory animals. Preliminary studies, designed to work out the most effective experimental method, revealed that (i) the sensitivity of rat pulmonary tissue to the dusts under suspicion makes it eminently suitable for the investigation envisaged, and (ii) intubation is a better way of introducing the dusts than inhalation in a dust chamber.

The experiments proper have consisted in intubation of two batches of 40 rats, one with cristobalite, the other with tridymite, both substances being given in 5% suspension in normal saline after sterilization in an autoclave. Half the animals of each batch subsequently received intraperitoneal injections of benzopyrene to find out if this compound aggravates or possibly even exerts a carcinogenic action on the pulmonary lesions caused by the silicogenic substances.

The initial results of this work may be summarized as follows:

- (a) both cristobalite and tridymite gave rise to a discrete histiocytic reaction in the walls of the alveoli within 10 days; after 30 days multiple silicotic nodules, already partially confluent, were visible in the pulmonary tissue;
- (b) the confluent silicotic masses produced by tridymite were more extensive than those produced by cristobalite;
- (c) benzopyrene worsened tridymite silicosis, causing increased granuloma formation, a pronounced fibroplastic reaction, and abundant production of collagen fibres;
- (d) in the rats intubated with cristobalite the productive lesions, which contained atypical cells, were also more extensive after administration of benzopyrene; these responses are still under study.

Work aimed at a better understanding of the interactions of benzpyrene and tridymite is proceeding at present, and consists in introducing benzpyrene directly into the trachea at the same time as the tridymite. A companion study will be intratracheal administration of benzpyrene alone.

Animal experimentation with industrial dusts is also being carried out by Prof. Schlipköter at Münster. He has become interested in the mixed dusts arising from the mixtures of sand and resin currently used for making moulds in foundry work, and has observed that dusts of particle size below 5  $\mu$  contain less quartz when their source is a sand-resin mixture (55%) than when it is pure sand (91%).

This research was carried out in two batches of 50 rats, each of which had received 30 mg of the dusts in question suspended in 1 ml of distilled water.

The rats were killed 120 days later and the following investigations made:

- (a) determination of lung weight and of size of tracheobronchial glands;
- (b) histological examination of the tissue reactions;
- (c) chemical determination of oxyproline;
- (d) chemical determination of  $\text{SiO}_2$ .

Oxyproline levels were highest in the animals injected with dust from pure-sand moulds; tissue reactions and glandular changes were least pronounced in those which received dusts from moulds of mixed composition.

The work just described was complemented by experiments with dusts collected from the air of work premises situated close to where the moulds were made, since the industrial operations related to mould formation might be expected to alter the toxic properties of such dusts. Chemical analysis of dust collected at different work sites did in fact reveal differences in the quartz content of the air between one workshop and another—25% where cores were made, 75% at the moulding site, and 24% where sand mixed with resin was used. Tests in animals, analogous to those in the first set of experiments described above, again indicated that dust from sand-resin mixtures is less fibrogenic than dust from pure sand. These research activities are being actively pursued at the present time.

Finally, in conjunction with his epidemiological studies on bronchitis, Prof. Symanski is devoting attention to the hazards to which scarfers, fettlers, and grinders are exposed in various steel works in the Saar. All necessary precautions are taken to eliminate possible interference from the casual changes of occupation which are common in those industries.

Prof. Symanski's investigation comprises radiology of chest. It also takes extrapulmonary risks, into account, in particular joint involvement (hands, elbows, shoulders) in men operating compressed-air hammers; in certain categories of workers audiometric tests are performed. Up to the present these studies have been carried out in 400 subjects, including controls.

# List of research projects

## Basic pneumoconiosis research

021	Prof. Ulmer Bochum	Dust detoxicants
023	Prof. Ulmer Bochum	Lung cleansing and retention of dust in the lungs, with special reference to the alveolar macrophages as protective aerosols
024	Prof. Schlipkötter Düsseldorf	Dust detoxicants
025	Dr. Brockhaus Düsseldorf	Lung cleansing and retention of dusts in the lungs
063	Prof. Reploh Münster	The harmful effect of silicic acid dusts and dust mixtures on cells and tissues
065	Prof. Reploh Münster	Dust detoxicants
066	Prof. Thomas Göttingen	Lung cleansing and retention of dusts in the lungs
067	Prof. Thomas Göttingen	The harmful effect of silicic acid dusts and dust mixtures on cells and tissues
072	Prof. Fritze Bochum	(a) Quartz pyrogenicity in animal experiments and its relation to the RES and bacteria deposited therein (b) Substances inhibiting quartz pyrogenicity
073	Prof. Fritze Bochum	The serum protein pattern in quantitative immunology assays and the complement titre of the serum in miners exposed to dust and in silicosis patients
075	Prof. Fritze Bochum	Immuno-electrophoretic analysis of indurated tissues of the human lung in silicosis as compared with normal lung tissue

035	Prof. Lavenne Hasselt	Experimental silicosis of dogs. Examination of the protein composition of the serum and of the silicosis nodule. Research on changes in the lung vessels
033	Dr. Voisin Paris	Immuno-pathology of silicosis
049	Prof. Gernez-Rieux Lille	The effect of quartz dusts and mixed dusts on the alveolar macrophages (in vitro and in vivo). Investigation of factors capable of changing cell behaviour
053	Cerchar Paris	The role of infection in the development of pneumoconiosis
003	Prof. Mottura Turin	Research on the development of experimental silicosis caused by minute amounts of quartz
012	Prof. Vigliani Milan	Silicosis prophylaxis by means of synthetic polymers
039	Prof. Pernis Milan	Research on the pathogenesis of massive progressive fibrosis due to mixed dusts
007	Dr. Molitor Luxembourg Prof. Mosinger Marseilles	Research on dust detoxicants affecting lung cleansing and the causative mechanism of dusts

### **Physiopathological ABD clinical studies**

014	Prof. Worth Moerse	Epidemiologic, clinical, X-ray and functional research in the Community. Research on the standardisation of functional cardio-respiratory tests (residual volume, cardio-respiratory function)
016	Prof. Ulmer Bochum	Epidemiologic, clinical, X-ray and functional research in the Community with reference to collective samples selected on the basis of jointly determined criteria with a view to establishing the exact degree of breathing capacity and the development thereof in ECSC workers
017	Prof. Ulmer Bochum	Research on the standardisation of functional cardio-respiratory tests (residual volume, cardio-respiratory function)

- 079 Prof. Fritze  
Bochum  
Standardisation of cardiac function tests and their prognosis value for healthy and trained subjects, as well as for silicosis, bronchitis and emphysema patients
- 119 Prof. Bretschneider  
Bochum  
Experimental research on the improvement of foreign-gas methods of determining blood irrigation by gas chromatography and the semi-automatic extraction chamber
- 143 Dr. Wassner  
Bremen  
Research on respiratory system ailments of pulmonary origin in chronic lung diseases, especially silicosis and chronic bronchitis
- 170 Prof. Loeschke  
Bochum  
Development of an electrode for measuring CO<sub>2</sub> pressure of the blood
- 034 Prof. Lavenne  
Hasselt  
Comparison between alveolo-arterial oxygen and carbon dioxide gradients and the CO diffusing capacity (D<sub>CO</sub>) in coal-miner's pneumoconiosis; the use of D<sub>CO</sub> as an index of incapacity.
- 036 Prof. Lavenne  
Hasselt  
Standardisation of pulmonary haemodynamics. Study of the effect of pneumoconiosis on the pulmonary circulation and its application to incapacity
- 122 Dr. Vanroux  
Charleroi  
Development of a rapid method of investigating the overall function of the resting and working lung from the viewpoint of ventilation and respiration
- 135 Prof. Lequime  
Brussels  
Development of new techniques of assessing the functional capacity by measuring the total hemoglobin and the cardiac volume. Comparison of multiple parameters during exertion of varying intensity and duration. Telemetric study of the heart rate during work for establishing the occupational needs and the value of functional tests in the laboratory
- 141 Prof. Gyselen  
Louvain  
Experimental research on the effect of unequal ventilation on the diffusion capacity measured by three methods using carbon dioxide: single inhalation, state of equilibrium, reinhalation
- 142 Prof. Gyselen  
Louvain  
Research on lung elasticity measured by means of the oesophagus probe technique

055	Cerchar Paris	Determination of respiratory system disorders of coal-miners by alveolo-capillary CO diffusion methods during eupneic breathing and apnoea
085	Prof. Cara Paris	Standardisation of respiration tests, utilisation of results and standardisation of techniques (residual volume, exertion test)
091	Prof. Galy Lyons	Epidemiologic, clinical, X-ray and functional research in the Community with reference to collective samples selected on the basis of jointly determined criteria with a view to establishing the exact degree of breathing capacity and the development thereof in ECSC workers (including pneumoconiosis cases observed in the steel-making industry)
152	Prof. Sadoul Nancy	Research with a view to improving methods of examining and interpreting results for the better assessment of the functional capacity by specialists and industrial physicians (cardio-respiratory function)
102	Prof. Maugeri Pavia	Research on functional disorders related to distribution and diffusion in ECSC steelworkers
111	Dr. Venturini Rome	Hemodynamic study of patients suffering from pulmonary hypertension due to chronic bronchitis, emphysema or silicosis Research on radioactive krypton diffusion
130	Prof. Maugeri Pavia	CO diffusion. Comparative study of steady state and unstable phase methods. Comparison of results after applying both methods to a group of normal subjects and a group of workers not suffering from respiratory system disorders but exposed to a polluted atmosphere (as in a foundry)
150	Prof. Casula Cagliari	Systematic, clinical and functional research on prodromes of cardio-pulmonary complications in chronic pneumoconiosis cases with a view to early diagnosis and full and effective treatment
151	Prof. Gunella Bologna	The study, by various techniques, of the effect of mechanical ventilation on pulmonary and general hemodynamics in chronic pulmonary cases and silicosis cases in particular

042 Prof. Deenstra  
Utrecht Continuation of research 11,330 : differentiation between cardiovascular and respiratory causes of reduced ability to work and diffusion disorders

### **Bronchitis and emphysema research**

005 Prof. Giese  
Münster Epidemiologic research on emphysema, bronchitis and dust deposits in the lungs of the population as a whole and miners; the role of bronchitis and dust in the pathogenesis of focal emphysema; asymmetric and infectious forms of pneumoconiosis

009 Prof. Symanski  
Saarbrücken Community epidemiologic, clinical, X-ray and functional research on emphysema

015 Prof. Worth  
Moers Community research on various pneumoconiosis therapies. Research on etio-pathogenesis. Community research on epidemiology

032 Dr. Brinkmann  
Recklinghausen Résumé : a sentence typifying the research topic, quoted by the DG PTAR : "Besides the specific pulmonary reactions to dust, are there any generalised obstructive lung diseases arising from external factors?"

061 Prof. Valentin  
Erlangen Community research on the epidemiology of bronchitis and emphysema in ECSC workers

076 Prof. Fritze  
Bochum The incidence and significance of tuberculous infection on the one hand and the presence of rheumatic factors on the other in miners before entering the industry and after varying periods of work

077 Prof. Fritze  
Bochum The role of allergic reactions in the etiopathogenesis and epidemiology of chronic bronchitis and emphysema

109 Prof. Symanski  
Saarbrücken The harmful effect of fettling operations

110 Dr. Brockhaus  
Düsseldorf-Beurath Research on the action of materials used for lining ingot moulds and ladles

- |     |                                |                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 116 | Prof. Otto<br>Erlangen         | Anatomo-pathological studies on a group of 1,000 patients having an obstructive pulmonary syndrome. A comparative study of a batch of subjects exposed and a batch not exposed to dust; the incidence of emphysema cases. Technique: histopathological study of large area sections (according to Gough)                                                                                                                       |
| 163 | Dr. Zimmermann<br>Homburg/Saar | Serological and bacteriological research on the etiology of chronic bronchitis                                                                                                                                                                                                                                                                                                                                                 |
| 164 | Prof. Giese<br>Münster         | Etio-pathogenetic research on chronic bronchitis and pulmonary emphysema; comparative clinical and post-mortem functional research on ventilation disorders and respiratory activity                                                                                                                                                                                                                                           |
| 169 | Prof. Könn<br>Bochum           | Comparative clinico-radiological and anatomo-pathological research on different stages of silicosis, on emphysema and chronic bronchitis, and the effects of these disorders on the respiratory function and heart                                                                                                                                                                                                             |
| 071 | Dr. Minette<br>Lanaken         | Result of anti-tuberculosis therapy in the prevention of progressive confluent pneumoconiosis                                                                                                                                                                                                                                                                                                                                  |
| 082 | Dr. Minette<br>Lanaken         | The importance of anti-influenza vaccination of bronchitis cases among coal-miners                                                                                                                                                                                                                                                                                                                                             |
| 083 | Dr. Minette<br>Lanaken         | Problems of bronchodilators and their applications to bronchitis cases among coal-miners                                                                                                                                                                                                                                                                                                                                       |
| 113 | Dr. Van der Straeten<br>Ghent  | Research on cortisol and corticosterone metabolism in cases of aspecific chronic respiratory system disorders<br>Research on the role of androgens in pathogenesis and development<br>Research on the effect of sympathicomimetics, antihistamines and corticosteroids on the aspecific hypersensitivity of the bronchi<br>Research on aldosterone metabolism in chronic cor pulmonale due to silicosis or pulmonary emphysema |
| 133 | Prof. Bastenier<br>Brussels    | Research on the pathogenesis, symptoms and detection of cardio-circulatory complications in chronic pulmonary cases                                                                                                                                                                                                                                                                                                            |
| 037 | Dr. Brille<br>Paris            | Etio-pathogenesis and physiotherapy of chronic bronchitis and pulmonary emphysema                                                                                                                                                                                                                                                                                                                                              |



050	Prof. Gernez-Rieux Lille	Biochemical research on the bronchial secretions of coal-miners. The effect of their macromolecular structure on the development of microbial and virus infections. Its application to the etiopathogenesis, treatment and prophylaxis of coal-miner's bronchitis
086	Dr. Pham Nancy	Epidemiology of chronic bronchitis of Lorraine steelworkers and research on the etiological factors with a view to prophylaxis
087	Prof. Sadoul Nancy	Therapeutical treatment of respiratory insufficiency in chronic bronchitis
090	Prof. Sadoul Nancy	Epidemiology and development of pneumoconiosis and broncho-pulmonary disorders of iron-ore miners
124	Prof. Galy Lyons	Comparison between functional tests of excised lungs of broncho-emphysema and pneumoconiosis subjects. Anatomic study of large Gough sections. Research on the differences between broncho-alveolar obstructions with and without inhalation of dust Anatomo-pathological research
010	Prof. Zannini Genoa	Research on respiratory system disorders due to the use of firebricks in blast furnaces and steelworks
011	Prof. Zannini Genoa	Research on respiratory system disorders caused by sinter in sintering plants and blast furnaces
040	Prof. Vigliani Milan	Clinical and pathological research on bronchitis and pulmonary emphysema in mineworkers
045	Prof. Crepet Padua	Research on the constitution factor in chronic bronchitis and on the effect of mucolytics on bronchitis and emphysema
103	Prof. Casula Cagliari	Community research on the etiopathogenesis, epidemiology prophylaxis and therapy of bronchitis and emphysema; research on the respiratory functions and their development in ECSC workers
106	Prof. Zannini Genoa	Research on the harmful effect of fettling

- |     |                         |                                                                                                                                                                                                                           |
|-----|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 126 | Prof. Caccuri<br>Naples | Functional, radiologic, therapeutical and prophylactic research on cardio-circulatory functions in chronic pulmonary cases                                                                                                |
| 168 | Prof. Santi<br>Genoa    | Cristobalite silicosis. Investigation of the bronchial impairment of silicosis cases. Connections between silicosis and lung cancer, research on possible precancerous broncho-pulmonary conditions in silicosis subjects |
| 081 | Prof. Orie<br>Groningen | Research on the etiopathogenesis, including constitution, and different kinds of therapy of bronchitis and emphysema in ECSC workers                                                                                      |

### **Toxicology**

- |     |                                                         |                                                                                                                                                                            |
|-----|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 156 | Prof. Heim<br>Erlangen                                  | Research on the nature of the sequelae of acute carbon monoxide poisoning                                                                                                  |
| 108 | Prof. Fournier<br>Paris                                 | Research on the effect on the human organism of toxic fumes produced by welding operations                                                                                 |
| 114 | Dr. Veil<br>Paris                                       | Overall psycho-socio-physiopathological pattern twelve months after acute monoxide poisoning                                                                               |
| 105 | Prof. Caccuri<br>Naples                                 | The effects on the human organism of toxic fumes produced by welding operations                                                                                            |
| 149 | Dr. Molinari                                            | Clinical research on cases of acute CO poisoning with reference to the presence and character of possible sequelae                                                         |
| 155 | Prof. Rubino<br>Turin                                   | Experimental research on the sequelae of acute monoxide poisoning of the cardio-vascular and nervous systems                                                               |
| 159 | Prof. Carnevalerici<br>Milan                            | The effects of noxious gases and materials; the cochleovestibular apparatus in carbon monoxide, tetraethyl lead, lead, carbon disulphide and triethylamine, etc. poisoning |
| 162 | Prof. Franchini<br>Genoa                                | Effects of noxious gases and materials; research on the nature of the sequelae of acute carbon monoxide poisoning                                                          |
| 107 | Dr. Molitor<br>Luxembourg<br>Pr. Mosinger<br>Marseilles | Effects of welding operations on the human organism                                                                                                                        |

- 154 Dr. Molitor  
Luxembourg/  
Pr. Mosinger  
Marseilles
- 099 Dr. Van Zuilen  
T.N.O.  
The Hague
- Research on the nature of the sequelae of acute poisoning, especially by carbon monoxide
- Research on the harmful effects of welding fumes

## Synoptic table of research programmes sponsored

in industrial medicine, health and safety

(as at December 31, 1967)

Field and title of programme	Approved on	Financial assistance (E.M.A. units of account, rounded figures)	
		Total amount allocated	Committed
<b>A. Industrial medicine and health</b>			
a) Physiopathology and clinical medicine			
1st programme (Industrial medicine)	Oct. 5, 55	1,200,000	1,200,000
2nd programme (Industrial medicine)	April 7, 60	2,800,000	2,700,000
3rd programme (Physiopathology and clinical medicine)	April 28, 64	3,000,000	2,300,000
b) Traumatology and rehabilitation			
1st programme (Rehabilitation)(1)	Dec. 5, 57	500,000	500,000
2nd programme (Traumatology and rehabilitation)	June 19, 64	1,800,000	1,100,000
3rd programme (Burns and scalds)	May 18, 66	1,500,000	6,000
<b>B. Industrial physiology and psychology</b>			
a) Human factors and safety			
1st programme (Human factors and safety)(1)	Dec. 5, 57	1,000,000	1,000,000
2nd programme (Human factors and safety)(2)	Nov. 4, 64	1,200,000	600,000
b) Ergonomy			
1st programme (Industrial physiology, psychology and job organization)(2)	Nov. 4, 64	2,000,000	800,000
<b>C. Industrial Health</b>			
a) Dust prevention and suppression in mines			
1st programme (Dust prevention and suppression in mines)(1)	Dec. 5, 57	900,000	900,000
2nd programme (Dust prevention and suppression in mines)	Dec. 21, 64	6,000,000	4,300,000
b) Dust prevention and suppression in the iron and steel industry			
1st programme (Dust prevention and suppression in the iron and steel industry)(1)	Dec. 5, 57	600,000	600,000
2nd programme (Dust prevention and suppression in the iron and steel industry)	June 14, 67	4,000,000	1,000
c) Sundry research projects			
Converter gases (Brown smoke)	July 18, 61	1,000,000	800,000
Converter gases (Brown smoke)	June 19, 64	1,825,000	1,000,000
Climatic factors in mines	March 16, 66	116,000	116,000
Defluorization of fumes	March 16, 66	66,000	66,000
Total		29,507,000	17,989,000

(1) Part of a single financial aid programme under the general heading of "Safety", comprising four programmes.

(2) Part of a single financial aid programme under the general heading of "Human factors and ergonomics", comprising two programmes.

PUBLICATIONS DEPARTMENT OF THE EUROPEAN COMMUNITIES

4609/5/69/1