nents of the bronchial wall apart from the mucous glands and cartilage) was measured in numerous bronchi from each lung. This was done by tracing each component at a suitable magnification on a Projectina microscope, and then measuring the traced area on an image analyser. The bronchi were then divided into four groups of the following external diameters: (1) 3-3.99 mm, (2) 4-4.99 mm, (3) 5-5.99 mm, (4) 6-6.99 mm. Significant differences ($P < 0.01$) were found in the mean areas of the mucous glands in the control and obstructed patients in groups (3) and (4), and of the mean area of cartilage in groups (1) and (2). The latter probably indicates that dividing the bronchi into groups by size rather than generation leads to comparison of different generations of bronchi, and the implication of this on luminal size will be discussed.

Lung Cancer in Young Adults

A. KENNEDY (*Sheffield Royal Infirmary and University of Sheffield*)

This is an account of 36 cases in which the diagnosis of lung cancer was established histologically before the age of 40 years. The dominant feature of the pathology is that two-thirds of the tumours were oat cell carcinomas, and that all but one of the patients under 33 had oat-cell tumours. Only three patients were known to be non-smokers; four tumours arose in lung scars but no other aetiological factor was evident. Of the 10 women in the series three were pregnant at the time of appearance of the tumour or its metastases. There was a high death rate which is attributable to the large proportion of oat-cell tumours. The only long-time survivors are patients who had tumours other than of the oat-cell type and who were seen early enough for radical surgery. One of the patients had a pulmonary blastoma but she is alive 14 years after pneumonectomy and 11 years after the appearance of metastases.

Glandular Metaplasia and Mucin Production in Transitional Cell Carcinomas of Bladder

A. M. WARD (*Department of Pathology, University of Sheffield*)

Three hundred and forty cases of transitional cell carcinoma of bladder seen in the Urological Unit, United Sheffield Hospitals, between 1967 and 1970 are reviewed. Of these 340 cases, 25-30% show evidence of mucin production, and a similar, but not necessarily identical

percentage show some form of adenomatous metaplasia or glandular configuration. Mucin production and adenomatous metaplasia do not affect the grading of any particular tumour, and are seen with equal frequency in low, intermediate, and high grade tumours. There is no relationship to infection or prior instrumentation, and the changes have no apparent prognostic significance. Tumours showing mucin production and adenomatous metaplasia emphasize the metaplastic potential of the urothelium; they will behave biologically as transitional cell carcinomas, and should be treated as such.

Ultrastructural Evidence of Secretion in Hormonally Active Oat-cell Carcinomas: Origin of One Such Tumour in the Pancreas

B. CORRIN, E. D. GILBY, MARY MCMILLAN, J. PATRICK, AND H. SPENCER (*St. Thomas's and Lewisham Hospitals, London*)

An electron-microscopical study of 48 lung tumours identified characteristic cytoplasmic granules in oat-cell carcinomas and bronchial carcinoid tumours, but not in large cell anaplastic carcinomas. The granules were similar to those found in the cells of many endocrine glands. Sparse cells containing such granules were also identified in normal bronchial epithelium. These resembled intestinal Kulchitzky cells and are believed to represent the cell of origin of both the bronchial carcinoid and oat cell carcinoma (Bensch, Corrin, Pariente, and Spencer, 1968). If this is so, why do oat-cell carcinomas not arise in the gastrointestinal tract, and what is the fine structure of oat-cell carcinomas associated with inappropriate endocrine activity?

Two cases of oat-cell carcinoma associated with ectopic ACTH production are presented, one arising in the lung, the other in the pancreas. Electron microscopy of the pulmonary neoplasm showed that the cytoplasmic granules were more plentiful than in non-secretory tumours, supporting the suggestion that they represent secretory activity, even in those tumours in which hormonal activity is not clinically manifest, and that all oat-cell carcinomas may be regarded as latent endocrine neoplasms. In the second case necropsy showed that the tumour was limited to the tail of the pancreas, local lymph nodes, and the liver. Detailed examination of the lungs disclosed no new growth although histologically the tumour was a typical oat cell carcinoma. McKeown (1952) has reported two oat-cell carci-

nomas arising in the oesophagus, and it would appear that although an extrapulmonary origin is rare these tumours are not restricted to the lung.

References

- Bensch, K. G., Corrin, B., Pariente, R., and Spencer, H. (1968). Oat-cell carcinoma of the lung. Its origin and relationship to bronchial carcinoid. *Cancer. (Philad)*, **22**, 1163-1172.
McKeown, Florence (1952). Oat cell carcinoma of the oesophagus. *J. Path. Bact.*, **64**, 889-891.

Asbestos in Tumours

C. GOLD (*M.R.C. Pneumoconiosis Unit, Penarth, Glamorgan*)

Epidemiological evidence suggests that the four main types of asbestos, although all carcinogenic in animals, do not appear to be equally implicated in the causation of human tumours. Furthermore, in the three types of asbestos-related malignant lesions there are obvious site and behavioural differences between lung carcinoma and mesotheliomas of pleura or peritoneum. Variable factors such as type and source of asbestos, fibre characteristics, site of deposition, cellular, chemical and physical reactions, and total dose of dust may be all, or in part, responsible. Thus it would seem important to establish among other things if human neoplasia are related only to certain types of asbestos or if there is a dose-response relationship.

Bronchial carcinomas tend to have a high lung asbestos content while a pleural mesothelioma lung can contain relatively little asbestos. On the other hand, in peritoneal mesotheliomas the lungs may have an intermediate value or sometimes a considerable amount of asbestos in them without having a pleural or intrapulmonary tumour. With these apparent paradoxes a correlative investigation of both the dust and the histopathological changes seem justified. This approach is illustrated by results in selected referred human lung cancers and mesotheliomas.

The simple KOH extraction method yields a concentrated dust residue suitable for quantitative and morphological study with the light microscope and useful for the identification and typing of asbestos in the electron microscope. In experimental animal work with pure exposures to the individual types of asbestos very high fibre counts can be obtained and virtually pure dust reclaimed.

Experimental Tumour Induction in the Rat Nervous System by N-Ethyl N-Nitrosourea

E. L. JONES, W. THOMAS SMITH, AND C. E. SEARLE (*Departments of Pathology and*

Cancer Studies, University of Birmingham) In recent years several carcinogenic N-nitroso-compounds have been discovered that induce a remarkably high incidence of malignant tumours of the nervous system on direct systemic administration to experimental animals. An indirect technique has also been described that makes use of the transplacental passage of a selective resorptive carcinogen ethylnitrosourea (ENU) and results in a high yield of neural tumours in the offspring.

Exposure of both newborn Wistar strain albino and newborn hooded rats to a single postnatal injection of ENU in a dose of 10 mg/kg body weight resulted in the appearance of a wide variety of tumours of the peripheral and central nervous system in 85% of animals 200-500 days later. Certain sites of predilection for tumour growth were demonstrated and a provisional histopathological classification is suggested.

Six months after injection of ENU malignant neuroblastomas of spinal and cranial nerve ganglia developed. Nine to 12 months later a wide variety of tumours were found including malignant schwannomas and multiple gliomas (oligodendrogliomas, mixed astrocytomas, and ependymomas of the brain and spinal cord).

These ENU-induced tumours of rat nervous system show a remarkable similarity to human brain tumours and provide a valuable experimental model for further investigations of the biological properties of such tumours.

The Pathological Anatomy of Chronic Obstructive Lung Disease

W. THURLBECK (*McGill University, Montreal*)

The different diseases which may produce chronically increased resistance to airflow in the lungs are chronic bronchitis, pulmonary emphysema, bronchiectasis, bronchiolitis, and asthma. The first is defined in clinical terms; the last is indefinable, but all can be recognized, and can perhaps be defined, by anatomical criteria.

Chronic bronchitis is defined as chronic excess sputum production and is recognized by enlargement of the bronchial mucous glands. However, the distribution curve of mucous gland size is a normal one and thus there is a gradual transition from normal subjects to those with chronic bronchitis. Severity of chronic bronchitis can be assessed by the severity of mucous

gland hyperplasia and this has important clinical implications.

Emphysema is defined as abnormal enlargement of the gas exchanging portion of the lung, accompanied by destruction. There are several types of emphysema, and each may have a different aetiology, pathogenesis, and clinical effect. Bronchiectasis is defined as permanent abnormal enlargement of the bronchi and, in common with emphysema, may have widely differing aetiologies. The major source of airway obstruction in bronchitis, emphysema, and bronchiectasis is in the small airways and in all the most significant cause is mucous plugging in the airways.

Asthma, by contrast, is primarily a disease of central airways and can be recognized by a variety of anatomical changes. Quantitative measurements of bronchial muscle have been developed recently and these have shown an increase in muscle in patients with atopic asthma and in bronchitics with unusual degrees of bronchospasm. A case can be made for defining asthma by increase in bronchial muscle, and atopic asthma can probably be distinguished by various features which include basement membrane thickening, eosinophilic infiltration, characteristic plugs, and a normal Reid index.

The Bacteriology of Chronic Bronchitis

D. C. TURK (*Radcliffe Infirmary, Oxford*)

Bronchi damaged by this disease cease to be self-sterilizing and are liable to colonization by bacteria—especially by *Haemophilus influenzae* and pneumococci. When the sputum is mucoid such bacteria are probably doing no harm, but *H. influenzae* in particular is found far more frequently when the sputum is purulent. In such cases its eradication or suppression by chemotherapy is nearly always accompanied by reduction in sputum purulence and by improvement in the patient's clinical state. With the reappearance of *H. influenzae* in the sputum these changes are usually reversed. No other bacterial species has been shown to have the same close correlation with sputum purulence in this disease.

Because there are wide differences in bacterial content between consecutive sputum samples from a chronic bronchitic and also between different parts of the same sample, haemophili are likely to be missed unless repeated specimens are examined and are homogenized before culture. It may be that the importance of *H. influenzae* in a given patient can be more reliably established by serological

means (May's H₁ precipitin lines) than by bacterial culture.

Rational chemotherapy of chronic bronchitis depends on clear distinctions (a) between patients who will not benefit from it, those who need intermittent therapy and those who need continuous therapy or chemoprophylaxis, and (b) between regimes aimed at bactericidal effect and those that are merely bacteriostatic. Ampicillin and tetracyclines remain the most important agents, but sputum concentrations of ampicillin are largely dependent upon the degree of inflammatory reaction prevailing in the bronchi.

Deficiency of α_1 -Antitrypsin

J. R. HOBBS (*Westminster Medical School*)

Serum α_1 -antitrypsin (mol wt 54,000, normal range 180-280-510 mg/100 ml) is the chief of some 10 α_1 -globulins, accounting for 90% of the antitryptic activity of human serum. Released from many tissues its level rises with the non-specific response to inflammation. Fagerhol has identified eight allotypes known as F, I, M, S, V, X, Z, and W. Of these two result in severe lowering of the α_1 -antitrypsin level (to under 60 mg/100 ml) and then only in their homozygous state, ZZ or SS. The inheritance of such deficiency is thus autosomal recessive (Laurell and Eriksson).

Homozygous deficiency, found in 22 of 35,000 Hammersmith adult patients, provides a soil where the seeds of infection, smoking, and atmospheric pollution can precipitate panlobular emphysema at an early age (20-40 years), predominantly affecting the lower lobes of the lungs (19 patients had this). It is also associated with familial cirrhosis of childhood (Sharp *et al*, 1969) and I have seen it in three patients with acute nephritis, requiring transplant. It accounts for some 6% of all emphysema (5% ZZ, 1% SS, or SZ) and is found in Europe, USA, and in one native I saw in Chandigarh, India.

Heterozygous deficiencies (S or Z with another allele) result in serum levels 50-180 mg/100 ml not obviously predisposing to emphysema (? 1/200 as against expected 1/1,000). Genetic counselling can thus be practised in studies of affected families and prospective spouses.

The predisposition is ill understood, but if papain is repeatedly instilled into the bronchial tree of rats, panlobular emphysema results. This experiment needs repeating with excess α_1 -antitrypsin protection. Early onset emphysema can be screened by serum electrophoresis of