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

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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

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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

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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