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

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 or

Partigen¹ plates. It is possible a normal α_1 -antitrypsin level by these methods may be without antitryptic activity, so biological assay should be considered in such patients with diminished lower lobe perfusion.

References

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¹Partigen α_1 -antitrypsin plates and a standard serum can be purchased from Hoechst Pharmaceuticals, Hoechst House, 50, Salisbury Road, Hounslow, Middlesex.

The Correlation of Structure and Function in Chronic Obstructive Lung Disease

G. CUMMING (Department of Medicine, University of Birmingham)

The anatomical changes seen in lungs which have been the seat of airways obstruction range from widespread destruction of the greater part of the lung parenchyma (panacinar emphysema), destruction of a small volume of lung parenchyma located at a functionally strategic part (centriacinar emphysema), no destruction at all (bronchitis), and lastly complete obstruction of a proportion of very small airways (bronchial asthma).

The functional consequences of each of these disease processes are similar and include airways obstruction, hyperinflation, and poor mixing of inspired gas. Bronchitis and asthma have an additional feature in that the latter may be completely reversible and the former partially so.

Explanation of the airways obstruction is possible in each disease though the mechanism is not similar, the first two having the site of obstruction in the large airways and the latter two in the small airways, with some contribution from the larger ones. Hyperinflation may be a consequence of airways obstruction and of changes in elasticity.

The gas mixing defect produced by centriacinar emphysema may be readily explained, as may that seen in panacinar. In the absence of anatomical changes impairment of gas mixing is less readily explained but a general hypothesis explaining this functional defect will be described.

Radioimmuno- and Related Assays: Applicability to All Branches of Pathology

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During the last decade a large number of

radioimmunoassays have been developed, based on the progressive saturation of specific antisera by the compound to be assayed. This technique owes its success to the large number of samples that can be assayed; its specificity, which is a feature of all antigen-antibody reactions; and its sensitivity, often in the femtogram or low picogram range, which results from the use of an isotopically labelled tracer.

Introduced for insulin by Yalow and Berson, radioimmunoassay was applied initially to the larger peptide hormones such as growth hormone. More recently the technique has been extended to the smaller peptides, including angiotensin and vasopressin; to non-hormonal proteins such as the lipoproteins; and, of especial importance, to the detection of tumour specific antigens. Conjugation to synthetic or natural proteins of all types of molecule, as haptens, has enabled the development of radioimmunoassay for aldosterone, oestradiol, and other steroids. A similar approach to the assay of digoxin and cyclic AMP indicates the wide applicability of this technique in pharmacology and biochemistry. Concomitantly, a variety of procedures have been introduced which employ specific circulating or tissue-binding proteins instead of antibodies. Vitamin B₁₂, folic acid, thyroxine, and cortisol are among the compounds that can be assayed by such techniques.

It seems likely that the next decade will witness a still more explosive increase in the use of radioimmuno- and related assays, and their incursion into many different and, as yet, unexplored fields such as virology and bacteriology.

Book reviews

The Nucleus and Cytoplasm 2nd ed. By Henry Harris (Pp. xviii + 181; illustrated. £1.90 board, 90p paper.) London: Oxford University Press. 1970.

This book is based on a series of lectures given by the author at the University of Oxford setting out his views on the control of mammalian cells. He builds up lucid arguments on the nature of cytoplasmic nuclear relationships drawing on the results coming from the rapidly expanding fields of molecular biology, nucleic acid chemistry, and cell science. His approach is critical, first reviewing the classical experiments on the giant unicellular algae, acetabularia that have given many important clues. The Jacob Monod theory is then discussed and its wider implication considered. The history of the search for messenger RNA is followed by a chapter on the transcription of genetic information. The author's own study of the formation and function of hybrid eukaryotic cells (heterokaryons) produced by the action of the Sendai virus has been a most enlightening line of research that has had considerable impact on our present-day knowledge of nuclear activation and inactivation and the flow of genetic information from the nucleus to the cytoplasm. Finally, he considers the problems of cell differentiation in the light of observations from a wide range of experimental systems.

The printing of a second edition of this book is a mark of its previous success; it can be recommended to pathologists as excellent reading if they desire to learn more of the fundamental basis of cell behaviour and given them an insight into the way biological science is making inroads into topics that eventually may give us a new understanding of pathology. For experimentalists there are many points of real interest and value. The frequent use of the personal pronoun leaves the reader in no doubt that the author is prepared to accept responsibility for his statements and not hide behind the vague anonymity of a less personal style. Moreover, you can get all this for a moderate price.

EDWARD H. COOPER