with one of the linear accelerators already familiar in radiotherapy departments.

Some unsolved biological problems remain. Small early tumours are probably adequately nourished and unlikely to contain anoxic cells. What is not known is whether a tumour large enough to have an anoxic core will already have initiated metastatic spread and so be beyond the reach of effective treatment by local irradiation. But it is possible that anoxic cells are destroyed to some extent by existing techniques with high-energy *x* rays. The total radiation dose is usually delivered in daily fractions over a period of three to four weeks. The treatment does more than merely incapacitate adequately oxygenated malignant cells. After each fractional dose of radiation some anoxic cells become reoxygenated and become more sensitive to subsequent attack.[4-6] In these circumstances the correct fractionation regimen required for neutron therapy remains to be established by further experiment.

Radiation is a comparatively crude instrument for tackling the complex challenge presented by cancer, but neutron therapy, used with scientific insight, may add to the basic knowledge needed for therapeutic advances.

Psychogenic Dyspnoea

The diagnosis of psychogenic dyspnoea is too often based on a failure to find organic cause for the breathlessness. A more positive approach to this problem has now been made by B. H. Burns and J. B. L. Howell, who carried out a careful psychiatric assessment of 62 patients attending a clinic for respiratory diseases. In 31 of these patients dyspnoea was regarded as disproportionate in relation to the severity of organic disease. The remaining 31 were considered to have a degree of organic disease appropriate to their complaint of breathlessness, and these served as a control group.

A comparison of the two groups showed that both a past and family history of mental illness were more frequent among the patients with "disproportionate" dyspnoea. Recent bereavement, marital dysharmony, iatrogenic influences, potential gain from illness, and absence from work were also recorded more often in this group. The patient's account of his breathlessness differed between the two groups, those with "disproportionate" dyspnoea complaining of difficulty in breathing in rather than out and of episodic dyspnoea, especially during the night or while talking. Dyspnoea was more closely related to the emotional environment than to effort and could often be relieved by sedatives or alcohol. Other features characteristic of this group included sighing and other abnormal breathing patterns, noisy respiration and hyperventilation resulting in hypocapnia, tetany, cramps, fainting attacks, tightness in the chest, angor animi, paraesthesiae, palpitations, and dryness of the mouth. These symptoms had often led to extensive hospital investigations to exclude conditions such as epilepsy, angina, and thyrotoxicosis.

Ultimately it was possible to make a definitive psychiatric diagnosis in all the patients with disproportionate dyspnoea and to classify their illness as depressive or hysterical or an anxiety reaction. Suitable psychotherapy produced symptomatic improvement in all patients except for those with hysterical reactions. This improvement was sustained over a two- to three-year period of observation, and during this time there had been no deterioration in lung function.

It should be noted that Burns and Howell used patients with severe airways obstruction as their controls. In such cases the organic nature of the disease is usually obvious to relatives and doctors, so that both sympathy and active therapy are readily available. Unfortunately, this does not apply to all forms of organic dyspnoea. For example, in the early stages of fibrosing alveolitis and of recurrent pulmonary embolism breathlessness may be "disproportionate" in relation to clinical, radiological, and spirometric evidence of disease. The suspicion of malingering may then arise and so damage the relationship between the patient, his family, and his medical adviser that a true psychiatric illness may ensue. Moreover, these patients can display some of the most characteristic symptoms of Burns and Howell's "psychogenic" group. Episodic dyspnoea at rest with tightness in the chest, sweating, palpitations, faintness, and angor animi may result from pulmonary embolism as well as from hyperventilation, while hyperventilation itself is a well-recognized feature of fibrosing alveolitis. Another difficulty arises from the fact that hypoxia can cause mental symptoms and still further confuse the psychiatric assessment.

Burns and Howell did not record the arterial oxygen tension of their patients (except in three cases) but confined their physiological measurements to the vital capacity, forced expiratory volume, and P_{CO_2}. These tests, together with clinical radiological and psychiatric assessment, proved sufficient to distinguish their patients with "psychogenic" dyspnoea from those with severe airways obstruction. The separation of patients with psychogenic and organic dyspnoea might well have been less distinct if those with dyspnoea due to causes other than airways obstruction had been studied. More comprehensive tests of lung function (to include arterial oxygen tension and the gas transfer factor) are then needed to detect organic disease, and these should invariably be done before dyspnoea is attributed to psychogenic causes.

Immunological Aspects of Addison's Disease

Most patients with Addison's disease seen at the present time have idiopathic atrophy of the adrenal glands. This form of the disease is known to have clinical associations with thyroiditis, as in Schmidt's syndrome,[1] or with other autoimmune diseases, including pernicious anaemia, thyrotoxicosis, idiopathic hypoparathyroidism with or without moniliasis,[2] and also diabetes mellitus, in which autoimmunity has not been detected. Histologically the adrenal lesions[3] bear a striking resemblance to the thyroid atrophy of myxoedema and to the atrophic gastritis of pernicious anaemia. The cortical epithelial cells undergo destruction, with attempts at regeneration, and are surrounded with lymphoid cells with occasional follicles and plasma cells, while the medulla is spared. Immunization of animals with adrenal extracts and Freund's adjuvant leads to an adrenalitis resembling the human condition.[4-6]

Adrenal antibodies were first reported in 1957 by J. R. Anderson and colleagues[7] in the serum of a patient who suffered from Hashimoto's disease and later developed adrenal

[1] Burns, B. H., and Howell, J. B. L., *Quarterly Journal of Medicine*, 1969, **38**, 277.

failure. Many workers confirmed and extended this finding,[8-11] and immunofluorescence with human adrenal has become a useful diagnostic test for Addison's disease. The antibodies react with a cytoplasmic component of the adrenal cortical cells recovered in the "microsomal" fraction on ultracentrifugation and which is probably part of a lipoprotein membrane since the antigen behaves biochemically,[12] like the parallel microsomal antigens of the thyroid and the gastric parietal cells. Adrenal fluorescence is obtained with the sera of about 50% of patients with idiopathic adrenal atrophy. In one series[11] up to 80% of female patients gave positive results, though male patients showed a much lower incidence. Other authors report a higher rate of success with recent diagnosis.[13] All agree that adrenal antibodies are rarely found in cases of tuberculous Addison's disease and in diseases not affecting the adrenal. But patients with idiopathic adrenal atrophy have a high incidence of other autoantibodies, including thyroid and gastric,[11] antinuclear, and occasionally even mitochondrial antibodies. Recent work has shown that cell-mediated immune responses play an important part in the destruction of adrenal cells, as they do also in autoallergic diseases affecting other organs. Thus, the circulating leucocytes of patients with Addison's disease are inhibited in their normal migration from capillary tubes by addition of adrenal antigen to the cell cultures,[14] and in experimental adrenalitis in the rat it has been shown[15] that passive transfer of sensitized lymph-node cells can produce lesions in the adrenal gland of intact animals.

In some cases of Cushing's syndrome the hyperactivity of the adrenal glands is associated with bilateral cortical hyperplasia in the absence of a pituitary or extra-pituitary A.C.T.H.-producing tumour, and this is reminiscent of the hypertrophy of the thyroid gland induced by the "long-acting thyroid stimulator" (L.A.T.S.) in thyrotoxicosis. L.A.T.S. is now known to be an immunoglobulin (IgG), and it is possible that a similar stimulating autoantibody might be found in future in relation to this type of adrenal hyperplasia. It is therefore of interest that adrenal antibodies were found in a patient with Cushing's syndrome[16] whose hyperactive adrenals showed focal lymphoid infiltration similar to that seen in the thyroid in Graves's disease.

One of the most interesting recent developments is the discovery by Anderson and colleagues[17] of a second antigen-antibody system in autoimmune adrenal disease which may explain some cases of associated ovarian atrophy with premature menopause.[18] The antibodies react with the cytoplasm of adrenal cells and also with steroid-producing cells in the ovary, testis, and placenta.[17] W. J. Irvine and colleagues[19] have made a detailed analysis of this new family of autoantibodies, and it seems that several components of the steroid-producing cells react with them. Most of the patients with serum antibodies to ovarian antigens suffered from premature menopause and probable ovarian atrophy. However, the few male patients whose serum reacted with testicular antigens have shown no evidence of clinical hypogonadism so far.[17]

Thus there is strong evidence to suggest that "idiopathic" adrenal atrophy is an organ-specific primary autoimmune disease belonging to the same category as Hashimoto's thyroiditis and autoimmune gastritis. Family studies have shown an increased incidence of these diseases in relatives of patients with Addison's disease,[13] though there may be a second variety of familial adrenal deficiency, possibly due to enzyme defects, in which autoimmune mechanisms are not at work.[20]

[1] Carpenter, C. C. J., *et al.*, *Medicine*, 1964, **43**, 153.
[2] Blizzard, R. M., Chee, D., and Davis, W., *Clinical and Experimental Immunology*, 1967, **2**, 19.
[3] Wells, H. G., *Archives of Pathology*, 1930, **10**, 499.
[4] Barnett, E. V., Dumonde, D. C., and Glynn, L. E., *Immunology*, 1963, **6**, 382.
[5] Steiner, J. W., Langer, B., Schatz, D. L., and Volpe, R., *Journal of Experimental Medicine*, 1960, **112**, 187.
[6] Witebsky, E., and Milgrom, F., *Immunology*, 1962, **5**, 67.
[7] Anderson, J. R., Goudie, R. B., Gray, K. G., and Timbury, G. C., *Lancet*, 1957, **1**, 1123.
[8] Blizzard, R. M., and Kyle, M., *Journal of Clinical Investigation*, 1963, **42**, 1653.
[9] Nerup, J., Søborg, M., Halberg, P., and Brøchner-Mortensen, K., *Acta Medica Scandinavica*, 1966, Suppl. No. 445, p. 383.
[10] Goudie, R. B., Anderson, J. R., Gray, K. G., and Whyte, W. G., *Lancet*, 1966, **1**, 1173.
[11] Irvine, W. J., Stewart, A. G., and Scarth, L., *Clinical and Experimental Immunology*, 1967, **2**, 31.
[12] Goudie, R. B., McDonald, E., Anderson, J. R., and Gray, K. G., *Clinical and Experimental Immunology*, 1968, **3**, 119.
[13] Wuepper, K. D., Wegienka, L. C., and Fudenberg, H. H., *American Journal of Medicine*, 1969, **46**, 206.
[14] Nerup, J., Andersen, V., and Bendixen, G., *Clinical and Experimental Immunology*, 1969, **4**, 355.
[15] Levine, S., and Wenk, E. J., *American Journal of Pathology*, 1968, **52**, 41.
[16] Wegienka, L. C., Wuepper, K. D., Komarmy, L. E., and Forsham, P. H., *Lancet*, 1966, **1**, 741.
[17] Anderson, J. R., Goudie, R. B., Gray, K. G., and Stuart-Smith, D. A., *Clinical and Experimental Immunology*, 1968, **3**, 107.
[18] Irvine, W. J., *et al.*, *Lancet*, 1968, **2**, 883.
[19] Irvine, W. J., Chan, M. M. W., and Scarth, L., *Clinical and Experimental Immunology*, 1969, **4**, 489.
[20] Spinner, M. W., Blizzard, R. M., and Childs, B., *Journal of Clinical Endocrinology and Metabolism*, 1968, **28**, 795.

Anaesthesia in the Dark

Death under anaesthesia is bad enough during an attempt to remove a massive tumour or to deal with overwhelming injuries; but it is still worse when a patient dies while undergoing a minor operation.

Cardiac arrest in a previously healthy subject during such a procedure is almost always the result of hypoxia. This may be due to airway obstruction, a fault in the anaesthetic apparatus, an empty oxygen cylinder, or a whole variety of other mishaps which can usually be avoided or anticipated by constant alertness on the part of the anaesthetist. A great deal of this vigilance depends on observation—the observation of the patient's colour and his breathing, and of the dials and flow meters on the anaesthetic monitoring equipment.

Unfortunately, some surgeons and radiologists even today make the anaesthetist's task a difficult one by asking for conditions mimicking a war-time blackout during such procedures as endoscopies, retinoscopy, and angiography. Always helpful, the anaesthetist tries to provide his colleague with an efficient anaesthetic service during these apparently necessary circumstances of darkness, and as a result he is forced to supervise his patient in considerably less than ideal surroundings. He has to rely either on such means as keeping a hand on the chest of the patient to monitor respirations, ingenious arrangements of luminous dials, or, as recently suggested[1] by S. Mehta, luminous dots and lines painted on the rebreathing bag.

J. A. Lee has pointed out[2] that very few examinations require more than dimming of the theatre lights, and notes that anaesthetists, who probably perform more "'oscopies"

[1] Mehta, S., *British Journal of Anaesthesia*, 1969, **41**, 465.
[2] Lee, J. A., *British Journal of Anaesthesia*, 1969, **41**, 641.