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Enzymes and Emphysema

Since the original report by C-B. Laurell and S. Eriksson in 1963[1] the relationship between alpha$_1$ antitrypsin deficiency and emphysema has become well established. It is known that the enzyme deficiency is inherited as an autosomal recessive gene, that the emphysema occurs at an earlier age than in ordinary forms of the disease, that the physiological characteristics are usually those of severe primary emphysema, and that the lung bases are predominantly affected.

But many aspects of this important relationship are still to be resolved. They include the frequency of the enzyme deficiency as a cause of emphysema, whether heterozygotes (with intermediate levels of antitrypsin) are also susceptible to lung disease, and the part played by smoking, bronchitis, proteolytic enzymes, or other agents in the actual development of the pulmonary lesion.

The true frequency of homozygotes with enzyme deficiency among patients with "obstructive lung disease" is not known because of varying criteria for the diagnosis—and differentiation—of chronic bronchitis and emphysema, and also because no adequately controlled epidemiological survey has been undertaken. The rising incidence in successive reported series probably reflects an increasing awareness of the type of case in which the deficiency is to be expected: 1% in 1964,[2] 10% in 1969,[3] 18% in 1971,[4] and now in 1972 D. C. S. Hutchison and others[5] have discovered eight cases (29%) among 28 patients with severe emphysema. However, this last series was drawn from a clinic well known for the investigation and treatment of localized emphysema, and in fact only 2 of their 28 patients had diffuse disease.

Heterozygotes tend to have alpha$_1$ antitrypsin levels intermediate between homozygote and normal levels, and there is even greater disagreement about the incidence of the heterozygote state among patients with "obstructive lung disease." Some workers[6 7] have found an increased frequency and others[8 9] have not. The same divergence of opinion occurs when groups of heterozygotes are examined for evidence of increased frequency of obstructive lung disease. Some workers[10 11] have found such an increase and others[9 12] have not. The principal cause for these conflicting findings almost certainly arises from the methods used for identifying the heterozygotes and for diagnosing emphysema. In most series of cases heterozygotes were defined as those with intermediate values for trypsin inhibitory capacity (T.I.C.), but since the T.I.C. levels of true heterozygotes can fall within the normal range and can also be increased by non-specific causes such as inflammation, the method is clearly unreliable for this purpose. Criteria for the diagnosis of emphysema have also been unsatisfactory in most of the reported series and have usually been based on clinical or radiographic evidence without adequate physiological studies. A solution to this problem may not be found until a sufficient number of obligatory heterozygotes (children of those with unequivocal deficiency) have been studied with a full range of physiological techniques and compared with a group of matched controls.

Hutchison and others found that all their 28 patients had been cigarette smokers. This is in keeping with previous reports of a link between smoking and emphysema,[13 14] and with the fact that some enzyme-deficient non-smokers escape emphysema.[4 15 16] Cigarette consumption per annum was the same in their group of eight enzyme-deficient patients as in the 20 non-deficient patients, but since the former were an average ten years younger their total consumption was less. The incidence of chronic bronchitis was also similar in the two groups, but in only two of the enzyme-deficient patients had bronchitis preceded the onset of dyspnoea, while three had never had bronchitis at all. However, the seven non-deficient patients who (like the enzyme-deficient group) had basal emphysema gave a history of bronchitis starting on average ten years earlier than it it did in the 11 with apical emphysema. These observations thus confirm previous reports that chronic bronchitis is associated with basal rather than apical lung disease,[17 18] but they also suggest that the basal distribution of emphysema in antitrypsin deficiency cannot be attributed to bronchitis alone. The exact mechanism whereby enzyme deficiency causes basal emphysema is still not known, but smoking and chronic bronchitis are probably no more essential to its development than in other forms of emphysema.

The possibility arises that a noxious agent, presumably a proteolytic enzyme normally inhibited by alpha$_1$ antitrypsin, could reach the lung by the pulmonary blood stream (which, in the upright posture, is preferentially distributed to the lung bases) rather than by the airways. It is known that proteolytic enzymes are released by the disruption of bacteria and leucocytes, so that, in theory at least, any systemic infection could initiate basal lung damage in the absence of antitrypsin or even in its presence if the enzyme release were intense enough. A direct correlation has also been noted be-

tween levels of pancreatic elastolytic enzymes and emphysema at necropsy.[19]

Some forms of apical emphysema have recently been attributed to mechanical and gravitational causes operative in the upright posture and possibly related to tall stature.[20] But it is worth remembering that in the supine posture the apices of the lung are slightly better perfused than the bases,[18] and they should therefore be at least as available to blood-borne pathogens during any illness confining the patient to bed. In this connexion it is of interest that, in Hutchison and his colleagues' series, patients with upper zone emphysema had higher values for antitrypsin (as T.I.C.) than the healthy control subjects. No explanation for this was offered, but it does suggest the possibility of an inflammatory or other process involving the release of tissue enzymes—and therefore that pathogenic forces other than purely mechanical ones may be active in patients with apical emphysema. Small clues such as these are worth pursuing if they offer the smallest chance of disclosing causes of emphysema more remediable than tall stature and the force of gravity.

[1] Laurell, C-B., and Eriksson, S., *Scandinavian Journal of Clinical and Laboratory Investigation*, 1963, **15**, 132.
[2] Kueppers, F., Briscoe, W. A., and Bearn, A. G., *Science*, 1964, **146**, 1678.
[3] Lieberman, J., *New England Journal of Medicine*, 1969, **281**, 279.
[4] Jones, M. C., and Thomas, G. O., *Thorax*, 1971, **26**, 652.
[5] Hutchison, D. C. S., *et al.*, *Quarterly Journal of Medicine*, 1972, **41**, 301.
[6] Lieberman, J., Mittman, C., and Schneider, A. S., *Journal of the American Medical Association*, 1969, **210**, 2055.
[7] Kueppers, F., Fallat, R., and Larson, R. K., *Science*, 1969, **165**, 899.
[8] Talamo, R. C., Allen, J. D., Kahan, M. G., and Austen, K. F., *New England Journal of Medicine*, 1968, **278**, 345.
[9] Welch, M. H., Reinecke, M. E., Hammarsten, J. F., and Guenter, C. A., *Annals of Internal Medicine*, 1969, **71**, 533.
[10] Stevens, P. M., Hnilica, V. S., Johnson, P. C., and Bell, R. L., *Annals of Internal Medicine*, 1971, **74**, 672.
[11] Ostrow, D. N., and Cherniak, R. M., *American Review of Respiratory Diseases*, 1972, **106**, 377.
[12] Richardson, R. H., Guenter, C. A., Welch, M. H., Hyde, R. M., and Hammarsten, J. F., *American Review of Respiratory Diseases*, 1969, **100**, 619.
[13] Fletcher, C. M., Jones, N. L., Burrows, B., and Niden, A. H., *American Review of Respiratory Diseases*, 1964, **90**, 1.
[14] Auerbach, O., Stout, A. P., Hammond, E. C., and Garfinkel, L., *New England Journal of Medicine*, 1963, **269**, 1045.
[15] Guenter, C. A., Welch, M. H., Russell, T. R., Hyde, R. M., and Hammarsten, J. F., *Archives of Internal Medicine*, 1968, **122**, 254.
[16] Townley, R. G., Ryning, F., Lynch, H., and Brody, A. F., *Journal of the American Medical Association*, 1970, **214**, 325.
[17] Anthonisen, N. R., Bass, H., Oriel, A., Place, R. E. G., and Bates, D. V., *Clinical Science*, 1968, **35**, 495.
[18] Gaziano, D., Seaton, A., and Ogilvie, C., *British Medical Journal*, 1970, **2**, 330.
[19] Loeven, W. A., *Journal of Atherosclerosis Research*, 1969, **10**, 379.
[20] *British Medical Journal*, 1971, **4**, 573.

Zollinger-Ellison Syndrome Revisited

In 1955 R. M. Zollinger and S. H. Ellison described a new syndrome with three cardinal features: fulminating peptic ulcer, massive secretion of acid by the stomach, and islet cell tumours of the pancreas which did not arise in the β-cells and did not secrete insulin. Attempts to attribute the syndrome to the overproduction of a humoral agent were eventually rewarded when the hormone gastrin[1] was isolated from tumour tissue[2] and serum.[3]

Patients present with the symptoms and signs of peptic ulcer. The syndrome usually develops during the third to fifth decades of life but may occur at any age. Males are affected only slightly more frequently than females. Early reports stressed the severity of the ulcer disease and its complications such as haemorrhage, perforation, and obstruction; patients being described as "recurrent ulcerators, persistent perforators and bleeders unto death."[4] But the course of the disease may be less virulent and more like that of severe duodenal ulcer, though the symptoms rarely remit and so lack their usual cyclical variation. The ulcers may be multiple or occur in unusual locations such as the distal duodenum, jejunum, or oesophagus, but two-thirds are found in the duodenal cap. The symptoms are unusually resistant to all forms of medical and surgical treatment except total gastrectomy. Stomal ulcers are frequent after conventional operations, so that recurrent stomal ulceration after each of several operations should suggest the diagnosis. Patients may also harbour other endocrine tumours, especially adenomata of the parathyroids or pituitary and carcinoid tumours.[5] The Zollinger-Ellison syndrome is therefore associated with the pluriglandular syndrome (multiple endocrine adenomatosis), and there is often a family history of either duodenal ulcer or endocrine abnormalities. Metabolic disturbances may also occur as a result of gastrointestinal dysfunction.[6] Diarrhoea is common and usually attributed to steatorrhoea. The low pH in the upper jejunum denatures lipase and so impairs the hydrolysis of fat.[7] Vitamin B_{12} absorption may be decreased. The excessive quantities of acid in the jejunum may also damage the intestinal villi,[8] but this is probably only a minor cause of absorptive defects.

Until recently the diagnosis of the Zollinger-Ellison syndrome has depended on the demonstration of massive gastric hypersecretion. Overnight (12-hour) gastric aspiration should yield more than 1,000 ml of fluid containing more than 100 mEq of acid. The basal acid secretion should be very high and approach the levels obtained after adminstering pentagastrin, so that little increase occurs on maximal stimulation. The juice should also contain a disproportionate amount of acid compared to pepsin. However, there are no reliable criteria of gastric hypersecretion,[9] and production of acid may vary from time to time in individual patients[10] or remain in the range found in simple duodenal ulcer. The linchpin of diagnosis is therefore the finding of a high fasting level of serum gastrin, provided that pernicious anaemia has been excluded. The measurement involves a radioimmunoassay and is not widely available, but it may have to be performed on all patients with severe ulcer symptoms, unexplained diarrhoea, or multiple endocrine abnormalities. Radiography may sometimes suggest the diagnosis by showing hypertrophied mucosal folds in the stomach, duodenum, and jejunum, excess fluid, atypical sites of ulceration, and rapid transit through the small bowel.[11]

Treatment is by total gastrectomy, which carries a better prognosis than operations directed at the pancreas.[12] This is due to several factors which make total excision of the tumour impracticable. The tumour may be malignant or multifocal or the pancreas may show diffuse hyperplasia of the islets.[13] The primary may be situated at an ectopic site such as the duodenum or it may never be found. Moreover, metastatic tumour deposits may disappear and serum gastrin levels return to normal after total gastrectomy alone.[14 15]

This regression of tumour after resection of the stomach and the association of the Zollinger-Ellison syndrome with other endocrine abnormalities has led to speculation about the effects of the pituitary and hypothalamus on the different gastrin-producing cells in the antrum, pancreas, tumour, and elsewhere.[16] The pathogenesis of the syndrome may therefore be both varied and complex. J. M. Polak and her colleagues[17] have now divided patients with the syndrome into two groups on the basis of immunofluorescent, cytochemical, and ultrastructural findings. In the first group (type 1) the patients