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ADULT COELIAC DISEASE AND OTHER DISORDERS ASSOCIATED WITH STEATORRHOEA*

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A disturbance of function of the small intestine which is readily demonstrable is the presence of excess fat in the faeces (steatorrhoea), and the abnormality is common to a number of disorders. To these a blanket term, such as "malabsorption syndrome" (Cross *et al.*, 1953), "sprue syndrome," "steatorrhoea syndrome," "jejuno-ileal insufficiency" (Bennett and Hardwick, 1940), or "sprue" has been applied. This nomenclature has achieved much popularity in clinical usage, but, like many such terms in medicine for conditions of unknown aetiology, is too often regarded as a complete diagnosis. They are misleading and are apt to cause significant aetiological differences to be overlooked. For example, "malabsorption syndrome" is not usually applied to pernicious anaemia, but is to idiopathic steatorrhoea (adult coeliac disease), which is generally regarded as being due to malabsorption, though future research may implicate malutilization also.

Classification

The clinical disorders that have steatorrhoea as part of their presentation fall into three main groups. The first group is associated with disturbances of conditions or processes of digestion within the lumen of the bowel following upon upsets of gastric, pancreatic, biliary, or intestinal function, such as post-gastrectomy states, obstructive jaundice, intestinal resection, or entero-anastomoses. The second group is associated with the presence of pathological changes in the wall of the bowel, regional ileitis, non-specific or infective enteritis, intestinal lipodystrophy, tuberculosis, lymphoma, scleroderma, neoplasm, or amyloid disease. Disorders of the mesenteric lymph nodes or retroperitoneal tissues—for example, tabes mesenterica or lymphoma—have sometimes been placed in a separate group (disturbances of the distributive tissues), but there is no evidence to show that such disorders are associated with steatorrhoea unless the intestinal wall itself is involved.

There remains the third group of disorders, in which there is no obvious contributing factor: tropical sprue, coeliac disease, and non-tropical sprue, or idiopathic steatorrhoea. Clinical evidence is strong that coeliac disease and idiopathic steatorrhoea are basically the same disorder, partly on account of the similar reactions to gluten-free diets (van de Kamer *et al.*, 1953; French *et al.*, 1957) and partly on account of the high incidence of previous coeliac disturbance in adult patients presenting with idiopathic steatorrhoea (Cooke, Peeney, and Hawkins, 1953).

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Many consider that tropical sprue and non-tropical sprue are as closely connected. For example, Thaysen (1932) writes that the symptoms and signs of both disorders were so similar that they must be considered the same disease, whilst Bossak *et al.* (1957) thought that they were clinical manifestations of the same underlying metabolic disorder. Not infrequently observations are recorded from both conditions and discussed as though the patients were all suffering from the same disorder (Bossak *et al.*, 1957; Butterworth *et al.*, 1957; Butterworth and Perez-Santiago, 1958). However, as is pointed out below, in the absence of any known aetiology for either, there are observations which suggest that they might be more profitably regarded as separate entities. Therefore it would be wise to reserve "tropical sprue" for the disorder arising in tropical or semi-tropical countries and to use a distinctive term for the disorder encountered in temperate climates.

Adult coeliac disease is such a term, discarding both the title most favoured in the United States—"non-tropical sprue"—with its implied aetiological association with tropical sprue, and that most favoured in England—"idiopathic steatorrhoea"—with the implication that steatorrhoea is of primary importance and always present. It is therefore the purpose of this paper to consider critically the non-specific character of many clinical and laboratory findings in patients with steatorrhoea whilst emphasizing features which suggest that adult coeliac disease is a distinct clinical entity.

In any individual patient it is unfortunate that symptomatology or even physical examination gives little lead to differentiation, though the presence of an abdominal scar suggests a possible surgical cause for the steatorrhoea. Nevertheless, adult coeliac disease does possess a clinical picture which will often allow a diagnosis to be reached, albeit in many instances by a process of exclusion. Characteristic features are chronic ill-health, recurrent glossitis, disorders of haemopoiesis, and certain radiological findings, in addition to steatorrhoea (Cooke, Peeney, and Hawkins, 1953). It is on these three investigations that the main points in differential diagnosis have been based in the past.

Steatorrhoea

Other functions of the small intestine may be disturbed, but steatorrhoea remains the only satisfactory finding upon which to base a diagnosis, even though it may not necessarily be present always in adult coeliac disease. The mere determination of the percentage fat in a single specimen of dried faeces is now recognized to be of little use. The

introduction of balance techniques in which the amount of fat ingested was compared with that excreted, and the results expressed in terms of percentage absorption, led to an appreciation of the frequency of steatorrhoea (Cooke *et al.*, 1946). The use of measured intakes created difficulties, and with increasing experience it became evident that normal subjects on diets containing between 50 and 150 g. of fat rarely excreted more than 6 g. a day; indeed, the mean was usually between 3 and 4 g. (Wollaeger *et al.*, 1947; Crowe and Blackburn, 1956). It has thus become possible to dispense with rigid dietary measurements and use normal mixed diets either in hospital or at home. For diagnostic purposes it is adequate to collect the stools for 3 to 6 days without markers, using the method of fat analysis introduced by van de Kamer *et al.* (1949).

It was for long traditional that increase in the ratio of neutral fat to split fat was diagnostic of pancreatic disorders, but this determination is rarely done now, since such interpretations have been demonstrated as incorrect (Cooke *et al.*, 1946). Similarly, increase in faecal nitrogen is a reflection more of the degree of steatorrhoea or inflammation of the alimentary tract than of the presence of pancreatic dysfunction (Comfort *et al.*, 1953; Cooke, Thomas, *et al.*, 1953). According to Dreiling (1953), only about 20% of patients with pancreatitis have steatorrhoea, and certainly if there is gross steatorrhoea in such patients virtual absence of pancreatic function can be predicted.

Much has been made of tagged iodinated fats for detecting steatorrhoea (Chinn *et al.*, 1952; Beres *et al.*, 1957). For those with suitable counting apparatus these methods are convenient and simple. Unfortunately the reports indicate that the results do not give a satisfactory correlation with chemical balances in a significant number of patients (McKenna *et al.*, 1957). The source of the excess fat in the faeces has been much debated, and it is evident that fats are excreted into the intestinal tract (Sperry and Angevine, 1932; Kim *et al.*, 1956), but, except in occasional patients (Comfort *et al.*, 1953; Cooke, Thomas *et al.*, 1953; Weijers and van de Kamer, 1953), steatorrhoea is due principally to unabsorbed dietary fat. As an additional possibility, Frazer and Sammons (1956) claim to have isolated fat-forming bacteria from the stools of patients with tropical sprue, but as yet their observations have not been confirmed or repeated.

Radiology

No patient with steatorrhoea can be adequately investigated without a careful radiological examination of the small intestine. Such investigations are time-consuming and expensive, demanding the fullest co-operation between the radiologist and his clinical colleagues. The type of barium suspension used is a matter of preference, but, on balance, the poorly flocculating type of barium seems preferable at the first examination, since mucosal pattern, areas of dilatation, or strictures are more easily delineated. Jejunitis, jejuno-ileitis, scleroderma, intestinal diverticulae, blind loops, entero-anastomoses, and adult coeliac disease may often be differentiated even though the clinical picture in each condition may be somewhat similar (Adlersberg *et al.*, 1954). As Ardran *et al.* (1950) demonstrated, excess mucus is the cause of flocculation of a barium-and-water suspension. Though this is seen frequently in adult coeliac disease, flocculation of barium does occur in other conditions in which there is no steatorrhoea, as, for example, in some patients with pernicious anaemia, nephrosis, or hypoproteinaemia. It has been suggested that there are few if any disturbances of radiological pattern in pancreatic steatorrhoea and that this was of diagnostic significance (Bjerkelund and Husebye, 1950; Salvesen and Böe, 1953; Marshak and Eliasoph, 1957). However, while there are usually no significant abnormalities to be seen radiologically, except in those patients with pancreatic lithiasis, flocculation and dilatation are encountered often enough to make radiological diagnosis of pancreatitis unreliable.

Haematology

Patients with steatorrhoea may develop anaemia due to any or all of three main causes: deficiency of iron, cyanocobalamin (vitamin B_{12}), or folic acid. It is likely that anaemias due to copper (Cartwright, 1955) or pyridoxine (Harris *et al.*, 1956) deficiency occur also, but as yet none have been reported. The characteristic peripheral blood picture is that of macrocytosis with poorly staining haemoglobin and often many small cells, though not so small as noted in true iron-deficiency anaemia (Cooke *et al.*, 1948). A patient with steatorrhoea who persistently maintains a normal blood picture is unlikely to be suffering from adult coeliac disease. A more probable explanation is pancreatic atrophy, in which, except in states of marked malnutrition, anaemia is rare.

In adult coeliac disease, Badenoch and Callender (1954) demonstrated that radioactive iron was poorly absorbed. Despite this, patients will be encountered in whom the iron deficiency will readily respond to oral iron administration. More often, however, parenteral administration will be necessary to restore the blood picture, and the finding of macrocytosis following such therapy can be regarded as suggestive evidence of adult coeliac disease (Hawkins *et al.*, 1950). Though iron seems to be poorly absorbed, in some patients at least there seems to be an additional factor of poor utilization. Also patients with regional ileitis are particularly prone to iron-deficiency anaemia, which is often difficult to correct by oral iron administration. In some instances this can be demonstrated as being due to long-continued loss of blood from the intestine (Ensrud *et al.*, 1957).

It has often been suggested that intestinal lipodystrophy is associated with hypochromic anaemia (Plummer *et al.*, 1950), due in some degree to the persistent loss of blood into the intestinal tract. However, hypochromic anaemia alone is by no means invariable, as perusal of the literature will reveal a number of patients with macrocytic anaemia, observations supported by experience in Birmingham.

Vitamin B_{12} is absorbed principally from the lower end of the small intestine, and four main causes give rise to low serum vitamin B_{12} levels. The first is that due to loss of intrinsic factor and is seen in the post-gastrectomy group of steatorrhoeas. The second is thought to be due to utilization of vitamin B_{12} by the intestinal bacteria, and is seen in the macrocytic anaemias of the intestinal diverticula (Callender and Evans, 1955; Halsted *et al.*, 1956). Whether this is the correct explanation of the condition is perhaps debatable; in practice, the administration of antibiotics, in particular chlortetracycline, leads to correction of the anaemia (Dick, 1955). It is noteworthy that the antibiotic which has its major effect within the intestinal lumen—neomycin—has no effect (Doscherholmen and Hagen, 1954; Halsted *et al.*, 1956). The third cause appears to be an intracellular defect righted by steroid therapy, and is encountered in both adult coeliac disease and regional ileitis (Callender and Evans, 1955; Meynell *et al.*, 1957). Oxenhorn *et al.* (1957) found that 20 out of 25 patients with adult coeliac disease had diminished absorption of radioactive vitamin B_{12}, which was unaffected by either intrinsic factor or administration of antibiotics. In practice approximately 50% of patients with adult coeliac disease will have low serum vitamin B_{12} levels (Meynell *et al.*, 1957). In regional ileitis 60% of patients have been found to have low levels (Meynell *et al.*, 1957) due to failure of absorption of vitamin B_{12}, which is improved by steroid therapy. It is evident, therefore, that some patients with regional ileitis may simulate those with adult coeliac disease with steatorrhoea, megaloblastic anaemia, and nutritional changes, but differentiation is possible by radiological examination of the intestine. The last cause is resection of the ileum, as, for example, in the treatment of regional ileitis (Oxenhorn *et al.*, 1957).

In adult coeliac disease abnormalities in folic acid excretion following oral administration have been demonstrated as an almost invariable finding (Girdwood, 1953

1956; Cox *et al.*, 1958a). It is not surprising that many patients have a macrocytic anaemia due to both folic acid and vitamin-B_{12} deficiency. Folic acid is, however, absorbed in the jejunum (Cox *et al.*, 1958a). Consequently, the clinical picture and laboratory findings of adult coeliac disease may be simulated by some patients with jejunitis or jejunoileitis. Such patients may easily remain undiagnosed owing to the significance of the radiological pattern being overlooked. Furthermore, this condition may undergo complete resolution. Indeed, it may be questioned whether these patients are not the real non-tropical counterpart of patients with tropical sprue in which the folic acid defect is often considered the earliest manifestation.

In an endeavour to discover a specific diagnostic test for adult coeliac disease, a number of procedures have been introduced, but few have stood the test of time or proved to be more than a screening test. Glucose-tolerance tests have been a traditional diagnostic aid, but flat curves are now considered to have no great diagnostic significance, since 13 to 30% of the normal population may have such curves (Gardner, 1956; Test *et al.*, 1956). Furthermore, patients who by all other criteria have adult coeliac disease may have completely normal glucose-tolerance tests (Cooke, Peeney, and Hawkins, 1953). On the other hand, a grossly lowered tolerance test may well be evidence of pancreatitis. King (1949), from a review of the literature, concluded that 35 to 50% of patients with chronic relapsing pancreatitis had diabetic blood-sugar curves.

Should diabetes mellitus supervene in adult coeliac disease as has been reported (Bossak *et al.*, 1957), other tests, such as the folic-acid or xylose-excretion test, must be used. However, it is only too evident that as a diagnostic test there are so many different factors to be considered in the interpretation of the curves that other tests of carbohydrate absorption have been developed. A test of promise is the *d*-xylose-excretion test (Fourman, 1948; Gardner and Santiago, 1956; Benson *et al.*, 1957) in which the amount excreted in the urine in five hours after the administration of 25 g. of xylose is measured. The test is readily repeatable and the estimation is useful in differentiating between those patients with adult coeliac disease, or the active phase of tropical sprue, and those with pancreatic steatorrhoea, though a wide range of results may be encountered in other disorders with steatorrhoea.

As part of routine investigation serum calcium and phosphorus are usually estimated. Low values for both are often encountered in adult coeliac disease, but essentially similar findings are found in some patients with chronic recurrent pancreatitis (Sterkel and Kirsner, 1958), enteroanastomoses, gastro-colic fistulae, or severe post-gastrectomy steatorrhoeas. The values may also be suggestive, if not diagnostic, of certain rare clinical conditions associated with steatorrhoea: a high calcium and low phosphorus serum values may indicate the association of hyperparathyroidism and chronic pancreatitis (Davies *et al.*, 1956; Plough and Kyle, 1957), with or without jejunitis. Low calcium and high phosphorus levels in the serum are more uncommon, and may indicate hypoparathyroidism (Salvesen and Böe, 1953), often associated with moniliasis (Collins-Williams, 1950) or pseudohypoparathyroidism (Lowe *et al.*, 1950).

Amongst other screening tests should be mentioned the fasting carotene serum level, vitamin-A-absorption tests, and chylomicrographs (Barnes *et al.*, 1950; Adlersberg *et al.*, 1957; Wenger *et al.*, 1957). None are consistent; they bear a closer correlation to the degree of malnutrition than to the diagnosis, and will often produce abnormal results in disorders not associated with steatorrhoea. The main use of such tests is to indicate, in the event of abnormality, that steatorrhoea must be excluded, but, should they be normal, steatorrhoea may still be present. Intubation studies in patients with steatorrhoea are not particularly helpful in differential diagnosis. Whilst the concentration and amounts of pancreatic enzymes are usually normal in adult coeliac disease (Cooke, Peeney, and Hawkins, 1953; Bossak *et al.*, 1957) the presence of deficient pancreatic secretion may only indicate chronic malnutrition (Jackson and Linder, 1953). For differentiation between adult coeliac disease and pancreatogenous diarrhoea, either the xylose- or the folic-acid-excretion test is more simple. However, in the majority of patients it should be possible to make a fairly accurate diagnosis with haematological and careful radiological investigation only.

There are, however, three further procedures which add greater accuracy to the diagnosis and suggest that adult coeliac disease has certain distinctive features.

Intestinal Biopsy

The development by Margot Shiner (1956, 1957) of a satisfactory technique for biopsy of the jejunal mucosa has added further refinement to diagnosis. Though much more data still remain to be collected and critically assessed, it is clear that histological changes are to be found in the intestine and that previous reports of abnormalities based on post-mortem evidence (Adlersberg and Schein, 1947; Oehler, 1953) cannot be completely dismissed. Mucosal, mainly villous atrophy affecting the jejunum and ileum is the characteristic feature of adult coeliac disease, and no patient in whom this diagnosis seemed probable on other grounds has been found to have a normal jejunal mucosa. Whether such atrophy is diagnostic of adult coeliac disease is not so certain; indeed, occasional patients following gastrectomy may have a somewhat similar though less marked atrophy (Baird and Dodge, 1957). Butterworth and Perez-Santiago (1958) describe jejunal biopsies of "sprue" as showing enlarged oedematous coalescent villi, the epithelium having increased numbers of globular cells and some fibrosis and inflammation in the subepithelial layers. Another entity is emerging in which histological changes of inflammation and atrophy suggest the diagnosis of jejunitis, whilst at operation the gut may seem to be thickened and oedematous though not to the same degree that is usually seen in regional ileitis.

Clinically, steatorrhoea need not necessarily be present, since this will depend upon the extent to which the jejunum is involved. Folic-acid-excretion tests are, however, abnormal and a macrocytic anaemia responding to folic acid may develop. There is clinical evidence that some of these patients at least undergo complete cure. Whether any develop jejunal mucosal atrophy is not known, but clearly this is a possibility. Since these patients do not respond to a gluten-free diet, it is unlikely that the group have any direct relationship to adult coeliac disease. Intestinal biopsy therefore does provide some evidence that adult coeliac disease differs from tropical sprue, and tropical sprue may well prove to be analogous to the "jejunitis" encountered in non-tropical countries.

Folic-acid-excretion Test

Girdwood (1953) suggested that comparison of the amount excreted in the urine following the intramuscular injection of folic acid and that following oral administration could provide a relatively simple method for diagnosing steatorrhoea, since the amount excreted in patients following the oral dose was significantly less than that following the intramuscular. It is evident from both his original paper and his later observations (Girdwood, 1956) that he referred to adult coeliac disease rather than all the other disorders associated with steatorrhoea. His observations have been confirmed and extended, the folic-acid-excretion test being shown abnormal in adult coeliac disease, active tropical sprue (Butterworth *et al.*, 1957), and jejunitis, whilst being completely normal in pernicious anaemia, post-gastrectomy and pancreatic steatorrhoea, or any disorder in which the jejunum is not pathologically involved (Cox *et al.*, 1958a). With remission of symptoms in tropical sprue the folic-acid test returns to normal (Butterworth *et al.*, 1957). On the other hand, the attainment of "clinical cure" with a gluten-free diet and the disappearance of steatorrhoea are not necessarily associated with a return to normality of the folic-

acid-excretion test, for nine of the tests carried out in ten such patients remained abnormal (Cox *et al.*, 1958a).

The inference that has been drawn from an abnormal absorption test is that there is poor absorption from the intestinal tract. It can, however, be demonstrated that the excretion of folinic acid following both the intramuscular and the oral administration of folic acid is essentially the same (Cox *et al.*, 1958b). Since the excretion of folinic acid is known to be increased after the administration of folic acid, either the folic acid is absorbed so slowly and completely that the renal threshold of excretion is not exceeded, or there is some degree of malutilization of folic acid comparable to that postulated to occur with ascorbic acid in adult coeliac disease (Boscott and Cooke, 1954). This test, which has many important theoretical implications, is unlikely to be widely used, since it necessitates microbiological assay, and though the assay is relatively simple the number of occasions that it is likely to be required is few except in certain special centres. It is to be hoped that the xylose-excretion test can be made to provide equally useful data in differential diagnosis.

Gluten-free Diet

The third test is the therapeutic test with a gluten-free diet. Following its introduction by Dicke *et al.* (1953) and confirmation of its efficacy in coeliac disease in children (Anderson *et al.*, 1952) reports soon followed on its value in adult coeliac disease. In the largest and most recent study French *et al.* (1957) had clinical cures in 15 out of 22 patients who appeared to fulfil the criteria of adult coeliac disease. Most significant was their demonstration, in some patients, of a rapid haematological remission produced by the removal of gluten from the diet. The offending substance appears to be in the gliadin fraction of the gluten occurring in wheat or rye, and further analysis shows it to be polypeptide (Frazer, 1956).

From reports in the literature and from personal experience, it does seem justifiable to assume, should clinical cure result, that the patient was suffering from adult coeliac disease. The contrary assumption is not necessarily true. The effect of gluten appears to be quantitative, and even in patients in whom fat absorption has returned to normal the folic-acid-excretion test remains abnormal. The possibility therefore remains that there is a "constitutional enzymatic defect" which is rendered evident by gluten administration but which in some patients may be so gross that it cannot be corrected even by a gluten-free diet. From haematological effects and the persistently abnormal folic-acid excretions, gluten might be postulated as acting as a "blocking" agent of an underlying metabolic disorder, possibly of the pteroylglutamate complex. There may well be other substances, probably of protein nature, which act in a similar way. The effect of a gluten-free diet has been assessed in a number of conditions. The diet itself has a mildly constipating effect on normal subjects, and experimentally has been shown to decrease fat excretion in rats (Ribeiro *et al.*, 1957). However, no significant effect has yet been demonstrated in patients with tropical sprue (French *et al.*, 1957), regional ileitis, or pancreatogenous diarrhoea.

Conclusion

It is now apparent that tropical sprue, on the basis of the intestinal biopsy findings, the lack of response to a gluten-free diet, and the probability of the folic-acid test returning to normal, must be regarded as significantly different from adult coeliac disease. Jejunitis, which could on occasion simulate adult coeliac disease, can be shown to differ by the findings on intestinal biopsy and the invariable lack of response to a gluten-free diet, and may well prove to be the non-tropical counterpart of tropical sprue.

The condition that is known in this country as idiopathic steatorrhoea and in the United States as non-tropical sprue is now taking on more defined characteristics and deserves a distinctive name—adult coeliac disease—to replace the two previous unsatisfactory titles. In brief, it appears to be a familial constitutional disorder (Thompson, 1951; Cooke, Peeney, and Hawkins, 1953). Four observations suggest that this is an enzymatic defect and probably associated with folic acid metabolism. These are as follows: the rapid haematological remission in some patients on a gluten-free diet (French *et al.*, 1957); the abnormal folic-acid-excretion test (Girdwood, 1956; Cox *et al.*, 1958a); the rise of blood glutamine following gluten administration in some patients (Weijers and van de Kamer, 1953); and the abnormality in which pteroylglutamates may be involved and which lead to the persistent excretion of *p*-hydroxyphenylacetic acid, not easily eliminated by administration of ascorbic acid (Boscott and Cooke, 1954). As to where this enzymatic defect is sited—whether in the intestinal cell or liver—future research must show. It cannot, however, be too strongly emphasized that the actual absorptive functions of the intestinal cell are relatively minor compared with the major metabolic functions that it performs.

REFERENCES

Adlersberg, D., Marshak, R. H., Colcher, H., Drachman, S. R., Friedman, A. I., and Wang, C. I. (1954). *Gastroenterology*, **26**, 548.
—— and Schein, J. (1947). *J. Amer. med. Ass.*, **134**, 1459.
—— Wang, C. I., and Bossak, E. T. (1957). *J. Mt Sinai Hosp.*, **24**, 206.
Anderson, C. M., Frazer, A. C., French, J. M., Gerrard, J. W., Sammons, H. G., and Smellie, J. M. (1952). *Lancet*, **1**, 836.
Ardran, G. M., French, J. M., and Mucklow, E. H. (1950). *Brit. J. Radiol.*, **23**, 697.
Badenoch, J., and Callender, S. T. (1954). *Blood*, **9**, 123.
Baird, I. M., and Dodge, O. G. (1957). *Quart. J. Med.*, **26**, 393.
Barnes, B. C., Wollaeger, E. E., and Mason, H. L. (1950). *J. clin. Invest.*, **29**, 982.
Bennett, T. I., and Hardwick, C. (1940). *Lancet*, **2**, 381.
Benson, J. A., Culver, P. J., Ragland, S., Jones, C. M., Drummey, G. D., and Bougas, E. (1957). *New Engl. J. Med.*, **256**, 335.
Beres, P., Wenger, J., and Kirsner, J. B. (1957). *Gastroenterology*, **32**, 1.
Bjerkelund, J., and Husebye, O. W. (1950). *Amer. J. dig. Dis.*, **17**, 139.
Boscott, R. J., and Cooke, W. T. (1954). *Quart. J. Med.*, **23**, 307.
Bossak, E. T., Wang, C. I., and Adlersberg, D. (1957). *J. Mt Sinai Hosp.*, **24**, 286.
Butterworth, C. E., Nadel, H., Perez-Santiago, E., Santini, R., and Gardner, F. H. (1957). *J. Lab. clin. Med.*, **50**, 673.
—— and Perez-Santiago, E. (1958). *Ann. intern. Med.*, **48**, 8.
Callender, S. T., and Evans, J. R. (1955). *Clin. Sci.*, **14**, 387.
Cartwright, G. E. (1955). *Amer. J. clin. Nutr.*, **3**, 11.
Chinn, A. B., Lavik, P. S., Stitt, R. M., and Buckaloo, G. W. (1952). *New Engl. J. Med.*, **247**, 877.
Collins-Williams, C. (1950). *Pediatrics*, **5**, 998.
Comfort, M. W., Wollaeger, E. E., Taylor, A. B., and Power, M. H. (1953). *Gastroenterology*, **23**, 155.
Cooke, W. T., Elkes, J. J., Frazer, A. C., Parkes, J., Penney, A. L. P., Sammons, H. G., and Thomas, G. (1946). *Quart. J. Med.*, **15**, 141.
—— Frazer, A. C., Peeney, A. L. P., Sammons, H. G., and Thompson, M. D. (1948). Ibid., **17**, 9.
—— Peeney, A. L. P., and Hawkins, C. F. (1953). Ibid., **22**, 59.
—— Thomas, G., Mangall, D., and Cross, H. (1953). *Clin. Sci.*, **12**, 223.
Cox, E. V., Meynell, M. J., Cooke, W. T., and Gaddie, R. (1958a). *Gastroenterology*. In press.
—— —— Gaddie, R., and Cooke, W. T. (1958b). Unpublished observations.
Cross, R. J., Sant'Agnese, P., Lepore, M. J., Plimpton, C. H., and Stetten, D. (1953). *Amer. J. Med.*, **15**, 790.
Crowe, P. J., and Blackburn, C. R. B. (1956). *Aust. Ann. Med.*, **5**, 32.
Davies, D. R., Dent, C. E., and Willcox, A. (1956). *Brit. med. J.*, **2**, 1133.
Dick, A. P. (1955). Ibid., **1**, 145.
Dicke, W. K., Weijers, H. A., and Kamer, J. H. van de (1953). *Acta pediat. (Uppsala)*, **42**, 34.
Doscherholmen, A., and Hagen, P. S. (1954). *J. Lab. clin. Med.*, **44**, 790.
Dreiling, D. A. (1953). *Gastroenterology*, **24**, 540.
Ensrud, E. R., Owen, C. A., Dearing, W. H., and Waugh, J. M. (1957). Ibid., **33**, 837.
Fourman, L. P. R. (1948). *Clin. Sci.*, **6**, 289.
Frazer, A. C. (1956). *Proc. roy. Soc. Med.*, **49**, 1009.
—— and Sammons, H. G. (1956). *Clin. Chem.*, **2**, 272.
French, J. M., Hawkins, C. F., and Smith, N. (1957). *Quart. J. Med.*, **26**, 481.
Gardner, F. H. (1956). *A.M.A. Arch. intern. Med.*, **98**, 44.
—— and Santiago, E. P. (1956). Ibid., **98**, 467.
Girdwood, R. H. (1953). *Lancet*, **2**, 53.
—— (1956). *Quart. J. Med.*, **25**, 87.
Halsted, J. A., Lewis, P. M., and Gasster, M. (1956). *Amer. J. Med.*, **20**, 42.
Harris, J. W., Whittington, R. M., Weisman, R., and Horrigan, D. L. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **91**, 427.
Hawkins, C. F., Peeney, A. L. P., and Cooke, W. T. (1950). *Lancet*, **2**, 387.
Jackson, W. P. U., and Linder, G. C. (1953). *Metabolism*, **2**, 562.
Kamer, J. H. van de, Huinink, H. ten B., and Weijers, H. A. (1949). *J. biol. Chem.*, **177**, 347.
—— Weijers, H. A., and Dicke, W. K. (1953). *Acta paediat. (Uppsala)*, **42**, 223.

Kim, K. S., Bollman, J. L., and Grindlay, J. H. (1956). *Amer. J. Physiol.*, 184, 445.
King, S. E. (1949). *Med. Clin. N. Amer.*, 33, 883.
Lowe, C. U., Ellinger, A. J., Wright, W. S., and Stauffer, H. M. (1950). *J. Pediat.*, 36, 1.
McKenna, R. D., Bourne, R. H., and Matzko, A. (1957). *Gastroenterology*, 32, 17.
Marshak, R. H., and Eliasoph, J. (1957). *Med. Clin. N. Amer.*, 41, 1565.
Meynell, M. J., Cooke, W. T., Cox, E. V., and Gaddie, R. (1957). *Lancet*, 1, 901.
Oehler, V. (1953). *Gastroenterologia (Basel)*, 79, 257.
Oxenhorn, S., Estren, S., and Adlersberg, D. (1957). *J. Mt Sinai Hosp.*, 24, 232.
Plough, I. C., and Kyle, L. H. (1957). *Ann. intern. Med.*, 47, 590.
Plummer, K., Russi, S., Harris, W. H., and Caravati, C. M. (1950). *A.M.A. Arch. intern. Med.*, 86, 280.
Ribeiro, E., Sobrinho-Simoes, M., and Mesquita, A. (1957). *Metabolism*, 6, 378.
Salvesen, H. A., and Böe, J. (1953). *Acta med. scand.*, 146, 290.
Shiner, M. (1956). *Lancet*, 1, 17.
—— (1957). *J. Mt Sinai Hosp.*, 24, 273.
Sperry, W. M., and Angevine, R. W. (1932). *J. biol. Chem.*, 96, 769.
Sterkel, R. L., and Kirsner, J. B. (1958). *A.M.A. Arch. intern. Med.*, 101, 114.
Test, C. E., Nichols, R. L., Landau, R. L., Ricketts, H. T., and Loughhead, R. (1956). *Amer. J. med. Sci.*, 231, 69.
Thaysen, T. E. H. (1932). *Non-tropical Sprue*. Humphrey Milford, London.
Thompson, M. W. (1951). *Amer. J. hum. Genet.*, 3, 159.
Weijers, H. A., and Kamer, J. H. van de (1953). *Acta paediat. (Uppsala)*, 42, 97.
Wenger, J., Kirsner, J. B., and Palmer, W. L. (1957). *Amer. J. Med.*, 22, 373.
Wollaeger, E. E., Comfort, M. W., and Osterberg, A. E. (1947). *Gastroenterology*, 9, 272.

GIANT-CELL GRANULOMA OF THE RESPIRATORY TRACT (WEGENER'S GRANULOMATOSIS)

BY

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This paper is based on a retrospective study of data from 10 patients who had in common an illness characterized by symptoms of progressive ulceration in the respiratory tract together with signs of widespread inflammatory disease. Histological examination of material from each case shows disseminated granulomata, most common in the respiratory tract and kidneys, and widespread vascular lesions similar to polyarteritis nodosa. The name Wegener's granulomatosis has been applied to this syndrome (Ringertz, 1947; Johnsson, 1948; Fahey *et al.*, 1954). The purpose of this paper is to describe in brief the clinical and pathological features, to give a concept of the pathogenesis, and to suggest a method of treatment. The cases, which were selected according to the pathological criteria of Godman and Churg (1954), have been described in detail elsewhere (Leggat and Walton, 1956; Walton, 1957).

Clinical Features

The main data from each case, and from 46 others selected from the literature, are summarized in Table I. An analysis of symptoms and signs is given in Table II. Typically, the disease occurs in previously healthy young or middle-aged adults of either sex. The onset is insidious, with non-specific symptoms of infection in some part of the respiratory tract. Two patterns can be distinguished. In about two-thirds of the cases persistent purulent rhinorrhoea is accompanied by nasal obstruction and crusting, antral pain, and epistaxis. Otorrhoea, deafness, or ulceration of the gums was the initial symptom in a few of these: each later developed rhinorrhoea. In the second, smaller group, attention is drawn to the lungs because of chronic cough, haemoptysis, or pleurisy. Often the constitutional upset is out of proportion to the apparent intensity of the local lesion, and the patient seeks advice because of persisting malaise, fever, or weakness.

The course is usually rapid and full of incident, progressing to death in, on average, five months, occasionally in as little as four weeks. A few patients (Cases 9, 19, 43, 45, and 47, Table I) have had a more chronic illness with periods of remission, and survival for up to four years. Though temporary improvement sometimes follows antibiotic treatment, the local lesion always persists. Spread of the inflammatory process leads to extensive mucosal ulceration and cartilaginous or osseous destruction in the nose and palate on the one hand, and to widespread pulmonary consolidation on the other. Spread through the upper air passages is often followed by conjunctivitis, dimness of vision, increased lacrimation, and exophthalmos, deafness, earache, and otorrhoea. The development of a sore mouth, hoarseness, or dysphagia has resulted in the discovery of ulceration in the fauces, pharynx, or larynx. Only twice (Cases 1 and 53) has the mucosal ulceration spread to involve the skin of the face.

Sooner or later signs of widespread inflammatory disease appear in every case: fleeting arthralgia, numbness and tingling in the limbs, sensory loss, muscle weakness or paralysis, and a haemorrhagic vesicular rash most frequent on the skin of the face, wrists, and elbows and the oral mucosa are all common. A pericardial friction rub or electrocardiographic changes occasionally indicate involvement of the heart; parotitis, orchitis, and prostatitis also occur. In the late stages fever, usually of septic type, is almost constant, and albuminuria, haematuria, cylinduria, and/or pyuria have indicated renal involvement in nearly every case.

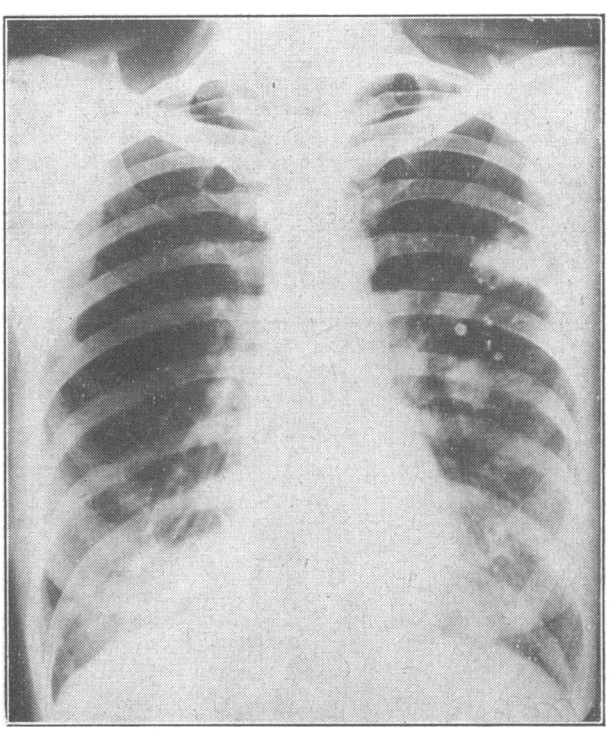

FIG. 1.—Case 10. Multiple rounded opacities are present in the left upper zone and both lower zones. Spicules of calcification are seen in the left upper zone.

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