greater than before the transfusion. It is interesting to note that these 2 instances were of transfusions resulting in satisfactory diuresis. In the other transfusion resulting in good diuresis (third transfusion, Case 4) serum protein estimations are unfortunately not available.

The rapid fall in serum protein concentration after an initial rise indicates that the injected protein does not remain long in the circulation. It might be thought that this fall is due to dilution of the serum proteins by the drawing in of water from the tissues. Haemoglobin or haematocrit estimations at intervals after transfusion show, however, that the lowest figures are found immediately after transfusion and that there is then a gradual return to the pre-transfusion level, which is usually reached at 24 to 48 hours. The evidence suggests, therefore, that no further increase in plasma volume occurs after the end of transfusion, and that any subsequent fall in serum protein concentration must be due to loss of protein from the blood stream.

In cases in which haemoglobin or haematocrit readings were determined both immediately before and after transfusion, the approximate increase in blood volume can be calculated. Changes in haematocrit readings are probably less reliable than changes in haemoglobin, because alterations in the osmotic pressure of the plasma may cause swelling or shrinking of the recipient's erythrocytes, and thus produce alterations in the red cell volume which make it difficult to interpret the significance of haematocrit changes. If a figure for the initial blood volume is assumed, the approximate increase in the blood volume represented by the fall in haemoglobin can be calculated. In cases in which calculations could be made, it was found that the increase in blood volume was greater than the amount of concentrated serum injected, and this suggests that fluid is drawn into the circulation during transfusion.

[Since writing this article, we observe that Beattie (1942) has recently drawn attention to the fact that after a plasma transfusion some of the transfused plasma may leave the circulation within an hour, and, furthermore, that only about 80% of the volume transfused is available to "dilute" the circulating blood. For both these reasons the observed decrease in haemoglobin concentration may be less than the "expected" figure. Since in the present cases the observed fall in haemoglobin was often much greater than that expected from the volume of concentrated serum transfused, there is further reason to think that fluid is drawn into the circulation during these transfusions.]

Although the available figures are not conclusive, the impression is that the amount of protein lost in the urine is not sufficient to account for the lack of increase in serum protein concentration in many of the cases, and it therefore seems likely that part of the protein is taken up from the blood stream, possibly to fill depleted tissue reserves. Cases 11 and 12 provide the best evidence for this supposition.

Harper, Osterberg, Priestley, and Seldon (1941) also concluded that protein was lost from the circulation following serum transfusions, and in almost all their cases loss in the urine could be excluded. Weech, Goettsch, and Lyttle (1940) have put forward the theory that diuresis, when it occurs, is due to the mechanical effect of a raised blood volume. Our observations, so far as they go, do not support this view, since a considerable fall in haemoglobin or in the haematocrit reading was often found in cases in which no diuresis occurred.

It may be well to point out that concentrated serum is concentrated with regard to salts as well as to protein, and that therefore a considerable amount of salts is administered when a transfusion of concentrated serum is given. This may be an important factor in the prevention of diuresis. If it were possible to obtain by sterile dialysis a protein solution free of salts the resulting fluid might prove of greater value.

Summary

Twelve patients exhibiting hypoproteinaemia have been treated with transfusions; in almost all cases concentrated human serum was used. Dosage ranged from 10 to 15 g. of protein in children and from 20 to 100 g. in adults, and more than one transfusion of these amounts was given in most cases.

Immediately after transfusion the serum protein level was generally found to have risen and the haemoglobin to have fallen; 24 to 48 hours after transfusion, however, the serum protein concentration was usually scarcely greater than before

transfusion, and the haemoglobin had usually returned to the pre-transfusion level. This failure to produce an increase in serum protein cannot have been due to loss of protein in the urine in either Case 12 or, in all probability, in Case 11. In several other cases also it appeared that the amount of albumin passed in the urine was not sufficient to account for the failure of the serum proteins to increase.

Of the 12 patients 11 were suffering from some degree of oedema at the time of the transfusions. In only 2 was a good diuresis produced by administration of serum, and in one of these the oedema returned within 10 days and failed to respond to a further transfusion.

It appears that in the nephrotic stage of glomerulonephritis a transfusion of concentrated serum is as likely to be followed by an adverse as by a favourable effect.

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CANCER OF THE STOMACH A STRIKING CONTRAST IN CLINICAL FEATURES

BY

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The symptoms presented by the patient afflicted with carcinoma of the stomach have been fully described by many writers in recent years, and that they may vary greatly in any considerable group of patients is well recognized. Little attention, however, has been devoted to the factors which influence and determine these variations in the clinical picture, and it is my purpose, by contrasting two very different types of illness produced by primary carcinoma of the stomach, to present at least one factor the importance of which is not sufficiently appreciated.

The Symptomless Type

First we may take the case in which the disease produces no symptoms or appreciable decline in health until a late stage has been reached—so late indeed that a large proportion of such patients are beyond surgical help at the time they first consult their doctor. One example will suffice, though in a series of 145 patients operated upon or observed by me some 13 others would serve just as well.

The patient, an intelligent and industrious man aged 57, complained of epigastric pain of one month's duration. The pain was persistent, but became worse after food. Prior to the onset of pain a month before the examination, he was emphatic in his statement that he had noticed nothing amiss with his digestion, which had always been good, or with his health; but since then he had lost appetite and vigour though he had remained at full work until a fortnight before he visited me.

Examination revealed a large ovoid mass lying across the epigastrium and a gross enlargement of the liver, which presented palpable bosses on its surface. A radiograph showed "an extensive filling defect in the distal half of the stomach." The red cell count was 4,800,000 per c.mm.; the haemoglobin, 98%; and white cells, 7,000. Gastric analysis revealed a lasting achlorhydria. Clearly operation was out of the question, and the man died some four months later, jaundiced and with ascites.

Several British surgeons have recently alluded to this type. Thus Walton (1939), commenting on the advanced stage of the disease in many of his patients, says: "I wish I could say that this was due to the fact that errors of diagnosis had been made in the earlier period, for then one could hope that with a wider recognition of the symptoms more cases would be cured; but unfortunately in many the symptoms may have been present for only two or three weeks, but the condition is already inoperable when advice is first sought"; and Ogilvie (1938) writes: "Early diagnosis, however greatly it might improve the prospects in this disturbing condition, is rarely possible owing to its remarkable silence. Many have no symptoms of the slightest kind till the tumour has replaced nearly the whole stomach." These observations by surgeons of great experience in gastric surgery suffice to show that my own experience of the silent or symptomless type is not exceptional.

The Type associated with Infection

The other kind of illness to which attention is sought forms a striking contrast; for its features are the early appearance of anaemia, which soon becomes profound, and with it breathlessness, dizziness, great muscular weakness, and loss of flesh. Indigestion, variable in degree, may not occur till many months later, and until that clue appears the disease has been regarded as pernicious anaemia, though examination of the blood, and if need be of the sternal marrow, will put that diagnosis out of court. Only three well-marked examples occur in this series of 145 cases, but as these come out of the last 40 of the series it is very possible that similar early cases were overlooked before my interest was aroused sufficiently for the relevant observations to be recorded in my notes. It is noteworthy that each of these three patients was referred directly by his own doctor to the haematologist, who, finding the anaemia to be of a secondary type, searched for a primary disease and found this, with the help of radiology, in the stomach. The record of one of these patients is as follows:

A man aged 65 some eight months before examination developed shortness of breath on slight exertion, followed a little later by an increasing pallor of the face, which attracted the notice of his friends, by progressive loss of strength, and by moderate loss of weight. He had not had any gastric discomfort or eructations, and had taken his food well throughout the illness; nor had he ever been troubled with indigestion of any kind. He was sent by his doctor to Dr. J. F. Wilkinson with a tentative diagnosis of pernicious anaemia. A blood count showed 3,100,000 red cells, 56% haemoglobin, and 14,000 white cells; and gastric analysis a lasting achlorhydria. No tumour could be felt in the abdomen, but a radiograph of the stomach, made at Dr. Wilkinson's request, revealed "a gross filling defect in the pyloric antrum." A partial gastrectomy was carried out, and the specimen showed an ulcerating carcinoma (microscopically confirmed) extending over the greater part of the lower third of the stomach, but not at any point annular; several of the grossly enlarged lymph glands along the lesser curve were examined histologically and were reported to show only inflammatory changes. The patient made a good recovery apart from wound suppuration, and within two weeks of the operation—before iron had been given—his facial colour had notably improved. Three months after operation his colour was normal, he felt quite well, and his dyspnoea had gone. When seen two years after the operation he looked in good health and expressed himself as being very well.

Discussion

These two patients suffered, then, from the same disease, yet how different was the illness produced: in one an advanced and hopeless stage was reached before the appearance of any symptoms or impairment of health; in the

other a serious breakdown in health while the disease was still within the limits of operability. What is the explanation? The histological type of the growth is very unlikely to be a factor, for the few specimens available from each group (5 in one and 3 in the other) have been described by the pathologist in very much the same terms. The extent of the growth—i.e., the amount of stomach functionally destroyed—can hardly be a factor, for all three of the anaemic group were suitable for a radical operation whilst only 5 of the 14 in the silent group were eligible for such an operation. Haemorrhage, its time of onset in the development of the disease and its amount, might be suggested as responsible, but it alone cannot account for all the factors which distinguish the two groups, and if it did we should still have to explain the early onset and persistence in the one and the presumed very late onset in the other.

It is submitted that the difference between the illnesses of these two patients (and of the groups they represent, only one of which is numerically important) is the difference between carcinoma uninfected and carcinoma infected. The influence of infection in determining the response of the patient to cancer of other organs is a matter of everyday observation. The enclosed cancer, of which breast cancer is the most familiar example, causes no impairment of health until vital parts are invaded by direct spread or metastasis, so long as the overlying skin remains intact as a barrier against infection; while cancer open to infection from the beginning—e.g., cancer of the caecum—sets up a disturbance of the general health and nutrition often a considerable time before symptoms due to purely local effects appear. Infection of the cancerous stomach very soon leads to ulceration of the growth—which in the absence of infection may remain submucous for a considerable period—and so to haemorrhage, usually slight but persistent, to bacterial toxæmia and hence the irregular rises of temperature and the leucocytosis, features present in each of the three patients in the anaemic group; hence also the loss of weight and vigour, to which interference with gastric digestion from the perpetual presence of septic contents may be a contributory factor. Other features which support the view that infection or its absence was the factor responsible for the nature of the illness in these groups must be mentioned. Two of the specimens from the five patients of the silent group who underwent partial gastrectomy showed a very extensive involvement of the stomach wall from submucosa to peritoneum; but the overlying mucosa was still intact, and was raised up and stretched over the growth like a cloth covering a table. The other three specimens showed ulceration of varying extent; but in all of them the ulcer floor was clean, fairly smooth, and had the appearance of a large granulating wound. In the specimens obtained from the three patients of the anaemic group ulceration was the striking feature, for this corresponded closely in its extent to the spread of the underlying growth; the ulcer floor in its central (and older) areas showed deep excavations covered over with sloughs and slime, and in its marginal areas large protuberant masses of growth. It is noteworthy that in the course of the operations on these three patients, after section of the stomach, a foul odour—a veritable stench—pervaded the theatre, and that during recovery the operation wounds of two of them suppurred badly—an incident which did not occur after any of the operations on the patients of the silent group.

There are good grounds, then, for claiming that the great difference in the symptoms manifested by these two groups is entirely accounted for by the absence of infection (of the growth) in one group and its early occurrence and

intensity in the other. If this claim be allowed, the next step is to explain or account for the absence of infection in one group and its dominant influence in the other. Clearly the most likely sources of infection must be sought in the mouth, the nose and accessory cavities, and the pharynx; and it can be stated at once that in the matter of cleanliness of the mouth there was an obvious difference between the two groups. All 14 members of the silent group were edentulous and had been so for several years before the presumed onset of the disease, whilst of the 3 members of the anaemic group not one was edentulous, for all possessed natural but bad teeth: in two the teeth were carious, broken, and blackened, and there was severe gingivitis; in the third patient, aged 43, the teeth were not so manifestly diseased, but actually several were found to be dead and to show x-ray evidence of root infection. Dr. J. F. Wilkinson, to whom first this patient was sent because of the strong suspicion of haemolytic anaemia, recorded: "Very pale, with suspicion of yellow in skin. Teeth almost normal in number but dark in colour and free from gross caries. Red cell count 3,500,000, Hb 37%, colour index 0.52, white cell count 16,000." Within two weeks of an exceptionally severe operation—for this involved *en bloc* resection of three-quarters of the stomach, and the transverse colon with omental and mesenteric attachments—this patient's facial appearance had improved remarkably, though none of the teeth had been removed. The improvement continued steadily, and was no doubt later accelerated by the administration of iron. It is probable that infection of dental origin so severe as to cause the kind of illness described will only be met with in patients whose teeth and gums are badly infected; but the patient of cancer age rarely has perfectly sound teeth, and it is likely that lesser degrees of infection may be found in patients who have retained their teeth in apparently fair condition, and may well account for the varying degrees of anaemia and asthenia so noticeable in any large series of patients with gastric cancer. Indeed, the patient whose disease runs a silent or symptomless course and whose blood picture remains almost normal in an advanced stage will, I suspect, almost invariably be found to be edentulous and to have been so for several years before the approximate time of onset of the disease. It is hardly necessary to point out that this suspicion does not imply that cancer of the stomach in a patient already edentulous will always run a silent course. Clearly there are other important factors which influence the symptoms, such as the position of the growth: cancer beginning at the inlet or outlet of the stomach will produce obstructive troubles before infection has had time to play a part; cancer developing in a chronic ulcer is very unlikely to be symptomless; and the primary cancer which imitates closely in its earlier stages the clinical and even radiographic features of a gastric ulcer is almost a clinical entity which is probably quite independent of infection. Furthermore, as already suggested, there are other possible sources of infection, though I have not observed these in actual practice.

Conclusion

An attempt, then, has been made to show the influence of infection, and a common source of this, on the clinical expression of gastric cancer, and, by taking two groups, each of extreme and unmixed examples, it has been possible to exhibit two pictures, the contrast between which is so arresting—for the disease is the same in each group—that it challenges the clinician to seek an explanation.

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THE TREATMENT OF DEPRESSION IN LATER LIFE

BY

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In Great Britain severe mental depression occurs every year in thousands of patients between the ages of 40 and 65. Obsessional, hypochondriacal, and paranoid symptoms may complicate the picture, which must nevertheless be distinguished from an organic dementia such as general paralysis or the late onset of a schizophrenic illness. The fate of patients with a late depressive illness is more serious than is generally realized. According to reliable English and American estimates, only a little over a third of those who enter mental hospitals recover, excluding those with manic-depressive syndromes. Very many more patients remain at home as total invalids, not bad enough to be treated in hospital; some carry on at work with greatly reduced efficiency: these contribute to the heavy yearly quota of suicides. Spontaneous remission, if it should occur, generally takes months or years. Particularly at present, such patients, if well, would be replacing younger men and women in industry and holding responsible positions, instead of being a total loss to the community.

In the past, specific treatment of this condition has seemed hopeless, and the long-drawn-out suffering of patients has been more pitiable than in most other forms of mental illness. Suggested treatments have, in the hands of independent workers, failed to show a recovery rate greater than that for spontaneous remission. Convulsion therapy should by now have altered this picture completely. For the past 6 years a continuous stream of favourable reports have been coming in, particularly from America, as to its benefit in depressive illness and, for the last 4 years, even in depressions of later life. 60 to 90% of social remissions or cases greatly improved are continually being reported. Osgood (1942), for instance, wrote a paper solely to analyse why 5 patients out of a group of 72 cases of depression adequately treated with cardiazol failed to respond.

Convulsion therapy appears, in fact, to be far more certain in its effects in depression than it is in schizophrenia, but in the English literature we can find few references to its specific value in those depressions of later life; even in the psychiatric journals only one reasonably but briefly reported series of cases treated among other mixed psychiatric conditions has been found (Wyllie, 1940). Consequently, treatment of these cases is still often neglected. Patients are allowed to drag on for years in mental hospitals in a state of avoidable misery, and business men and civil servants, indispensable at the present time, are being unnecessarily retired from their jobs.

A Series of Cases treated by Convulsion Therapy

For these reasons we wish to report a series of 39 cases of depression, most of them typical "involutional" states, which have been treated by convulsion therapy. This series comprised 21 men and 18 women between the ages of 40 and 62, 35 being treated by electrically induced convulsions, 1 with cardiazol alone, and 3 by combined cardiazol and electrical methods. Of the cases 14 were dealt with in two separate mental hospitals, one group being specially selected because of their desperate mental state and reasonably good previous personality; 21 were treated in an E.M.S. neurological unit, and 4 patients of this type were treated among others as out-patients at a London teaching hospital. Every degree of severity was therefore investigated. The only selection attempted was that in most cases the patients had had a reasonably good previous personality and work record. The duration of the attack varied from 3 years to 2 months in different patients. At the time of writing no fewer than 32 (82%) have either made social remissions or been very greatly improved. All except 3 of these