the gastrostomy opening and utilized as a guide for introducing a rubber tube and eventually a series of bougies of increasing size. By one or other of these methods dilatation has been successfully carried out in every case.

It is noteworthy that one patient, who had been burnt with nitric acid, had a fistula into the trachea and false passages in his oesophagus, the results of attempts at oesophagoscopy dilatation. Another patient, who had swallowed hydrochloric acid, had burnt the lower end of the oesophagus and also the pylorus, producing a stricture at each site. Yet another patient had had what appeared to be complete obliteration of his oesophagus for a period of 19 years. Patience is required in treating strictures of this nature by autodilatation, and the treatment must be continued for several years, but the final result should be a complete return to normal. Ten patients have been treated in this way in the past 20 years.

Congenital Atresia of the Oesophagus

It is very pleasant to finish my address by mentioning the great progress which has been made in the treatment of this anomaly. The condition was described by Gibson in 1697 and again by Sir Arthur Keith (1910) and others, but no patient was successfully operated upon until 1939, when a staged operation was carried out by Ladd (1944). The first completely successful operation of direct anastomosis was carried out in 1941 and reported by Haight and Towsley in 1943.

The commonest type of deformity is an atresia of the oesophagus at the level of the vena azygos arch, with the lower segment of the oesophagus arising from the trachea. This type of deformity accounts for 80% of the patients,

and in most of the others there is an upper and lower blind segment without any communication with the trachea. It is difficult to estimate the frequency of this anomaly because even now many infants die from what is attributed to pulmonary or cerebral conditions and the true diagnosis is not suspected. Similarly death may be attributed to an imperforate anus when the real cause is an oesophageal anomaly.

Cyanosis and attacks of choking in the newborn infant should at

FIG. 4.—Radiological appearance of congenital atresia of the oesophagus with fistula. The blind upper segment can be seen, and the fact that air is present in the stomach and intestines shows that there is a fistula between the lower segment and the trachea.

once suggest the possibility of an atresia of the oesophagus, and if a well-lubricated catheter, passed down the oesophagus via the mouth, is arrested at a point 10 cm. from the alveolar margin it is almost certain that the condition exists. The infant should then be transferred to a centre where x-ray confirmation and operation can be carried out (Fig. 4).

Both the operation and the anaesthesia require special experience and must be carried out very delicately. The subsequent nursing is of equal importance, and unless experienced and conscientious nursing is available it is useless to attempt the surgical treatment of these patients.

In my own first successful case the patient is now 7 years old, and altogether I have 17 patients who have recovered from the operation.

Conclusion

Many of the procedures in oesophageal surgery have now passed the pioneer stage and taken their place amongst the accepted operations. Some of them will always carry a very great risk, and for this reason it is essential that diagnosis should be accurate and that due consideration is given to the problem before embarking on this form of surgery. The treatment of cancer is still largely palliative but is none the less well worth while carrying out. Reflux oesophagitis presents a complex problem affecting patients of all ages. The symptoms may vary from a minor disturbance to a crippling or killing disease, and much work is needed to elucidate the underlying causes. The gastric secretion in infants requires further investigation and in adults there is scope for the simultaneous estimation of gastric and oesophageal pressures. The association of duodenal ulcer with reflux oesophagitis demands close study, always bearing in mind the possibility that in some patients at least the reflux oesophagitis appears to precede the formation of the hernia.

The problems connected with the diagnosis and treatment of oesophageal conditions require special methods and technique. This does not imply still narrower specialization, and in fact a broad approach is needed, because to understand and appreciate the various conditions affecting the oesophagus it is essential to have a knowledge of abdominal conditions in general and peptic ulceration and its complications in particular. Familiarity with the oesophagoscope and experience in paediatric surgery are also required. In fact the narrower the field the more general must be the approach.

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AMYLOIDOSIS IN RHEUMATOID ARTHRITIS, AND SIGNIFICANCE OF "UNEXPLAINED" ALBUMINURIA

A REPORT OF EIGHT CASES

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The complication of rheumatoid arthritis by amyloidosis is more often diagnosed by the pathologist than by the clinician. Fingerman and Andrus (1943) found amyloid deposition in 13 of 61 (21%) necropsied cases of rheumatoid arthritis. Teilum and Lindahl (1954) have reported an instance of 60%. By contrast, Hench and co-workers (1948) have stated that "the association of amyloidosis and rheumatoid arthritis rarely occurs, and then only in severe cases of long duration." On the clinical side, reports have been for the most part confined to single or at most two cases. The only clinical investigation of a population of rheumatoid arthritics for amyloidosis has been that of Unger *et al.* (1948),

who studied 52 rheumatoid patients by means of a modified Congo-red test, and found the complication to be present in six. Reece and Reynolds (1954) found five instances of amyloidosis with rheumatoid arthritis when all patients with the latter condition who attended their hospital from 1935 onwards were reviewed.

Our interest in the association of these two conditions was aroused when a patient with mild rheumatoid arthritis of about four years' duration died of renal failure. The ante-mortem diagnosis was chronic nephritis; at necropsy the cause of the renal failure was found to be amyloidosis, a possibility not entertained because the arthritis was so mild and of such short duration. We therefore decided to find out whether this complication could be recognized during life with greater certainty than previously. The initial problem was to find a clinical pointer. Splenomegaly and sometimes hepatomegaly occur not infrequently in uncomplicated rheumatoid arthritis and therefore cannot be taken to indicate the presence of amyloidosis. Since the essential morbidity of the complication is due to renal involvement, it seemed likely that the most reliable guide would be albuminuria. We therefore screened all patients with rheumatoid arthritis seen by us over a one-year period (July, 1953, to July, 1954) for albuminuria, and investigated its cause when found.

Clinical Material

A total of 183 cases, both in-patients and out-patients, were seen by us. Each of these patients had, in our opinion, unequivocal rheumatoid arthritis; patients whose diagnosis was doubtful were not included. Fig. 1 shows the age and sex distribution of the patients. Fig. 2 shows the duration of their rheumatoid arthritis. It can be seen that there was a fairly high proportion of patients whose disease was of short duration.

FIG. 1.—Age distribution of 183 patients with rheumatoid arthritis.

FIG. 2.—Duration of disease in 183 patients with rheumatoid arthritis.

a week. The number of tests per patient varied from 1 to 25, depending on the number of out-patient attendances or the duration of stay in hospital, or a combination of both. A trace of albumin on only one occasion was disregarded. Those patients who showed a more persistent albuminuria were further investigated; a catheter or mid-stream specimen was taken and, where necessary, the appropriate urological investigation made. Of the 183 patients, 24 were found to have significant albuminuria: 5 of the 24 had urinary infection, 2 G.U. tuberculosis, 3 congestive heart failure, 1 chronic nephritis, 1 drug reaction, and 12 cases were unexplained. Of the latter 12 patients, one (F.P.) died of an acute surgical emergency before she could be further investigated, and at necropsy extensive amyloidosis with renal involvement was found. For various reasons it was not possible to investigate a further four of these patients. The seven remaining cases were investigated by the modified Congo-red test of Unger *et al.* (1948) or by liver biopsy, or by both methods.

Modified Congo-Red Test of Unger

Unger *et al.* have introduced a modification of the Congo-red absorption test, which we believe to be greatly superior to the test as usually performed. In brief, their modification consists in obtaining frequent samples during the first ten minutes after the injection of the dye, so that a zero time concentration can be obtained by extrapolation. The advantages over the standard Congo-red test in which a two- or four-minute sample is taken and the absorption calculated at one hour are as follows: errors due to incomplete mixing, which may take up to ten minutes or longer, are avoided; false-negative results due to very rapid fixation of the dye by massive amyloid deposits are also avoided. With the standard Congo-red test at least 90% absorption at one hour is required to constitute a positive result. Unger *et al.* believe that 35% or greater absorption at 30 minutes is good evidence of amyloidosis when their method is used: we have no reason to differ from their conclusion.

We modified the method slightly in that we set up a slow saline drip (10 drops a minute) which could be discontinued for the obtaining of blood samples, thus avoiding the discomfort to the patient of frequent venepunctures. Before each sample was obtained about 5 ml. of blood was aspirated and discarded in order to avoid error from saline dilution. Where necessary the volume of blood removed during the test was replaced by cross-matched bank blood.

Results

Fig. 3 shows the data obtained when the Congo-red test, as described above, was performed on three patients. The logarithm of Congo-red concentration is plotted against time, and then the theoretical zero time concentration is obtained by extrapolation from the readings made during the first 10 minutes after injection.

Patient A.H.—Rheumatoid arthritis with splenomegaly

FIG. 3.—Congo-red absorption curves in three patients.

and hepatomegaly, but without albuminuria. The test was negative, there being only 19% absorption at 0-30 minutes. The test was also negative when the absorption at 60 minutes was calculated from the two-minute or four-minute sample (36% and 31% respectively), as is done with the standard Congo-red absorption test.

Patient A.C.—Rheumatoid arthritis with albuminuria. The test was positive, there being 55.7% absorption at 0-30 minutes. Note that when the absorption at 60 minutes was calculated from the two-minute or the four-minute sample, as in the standard test, the result was negative.

Patient H.S.—Rheumatoid arthritis, splenomegaly, hepatomegaly, and albuminuria. The test at 0-30 minutes was strongly positive (92%), as was also the absorption at 60 minutes calculated from either the two-minute or four-minute sample (97% and 95% respectively).

The table shows the data of the seven patients investigated and of the patient who showed amyloidosis at necropsy. Albuminuria was constant in every case except the latter, who showed only two positive tests out of five. The diagnosis was confirmed by liver biopsy in the first four patients

Case	Sex and Age	Duration	Liver	Spleen	No. of Urine Tests	Positive Albumin Tests	Congo Rcd 0-30 min. Absorption	Liver Biopsy
H. S.	M 30	1 yr.	+	+	25	25	92%	+
J. L.	M 74	8 "	+	0	10	10	90.9%	+
W. R.	F 38	16 "	+	0	12	12	77.9%	+
A. S.	F 61	11 "	+	0	13	13	53.5%	+
F. L.	F 67	18 "	0	+	13	12	Not done	+
A. C.	M 39	12 "	0	+	15	15	28.5% 55.7% 77%	Not done
N. B.	M 55	15 "	0	+	3	3	P.m. confirmation extensive amyloidosis,	"
F. P.	F 69	18 "	+	0	5	2		

of the table. In Case F.L. severe flexion contractions of the elbows made it impracticable to perform the Congo-red test, and the diagnosis was made by liver biopsy alone. A liver biopsy was considered to be unnecessary for the next two patients. In Case A.C. the Congo-red test two months after the onset of albuminuria was negative. The albuminuria persisted, and when the test was repeated ten months later it had become positive with 55.7% absorption from

FIG. 4.—Data of Case A.C.

0-30 minutes (see Fig. 4). In Case N.B., 77% absorption from 0-30 minutes was considered to be sufficiently good evidence of amyloidosis.

The duration of rheumatoid arthritis in these patients at the time the diagnosis of amyloidosis was made ranged from one to eighteen years, and six of the eight patients had had their disease for more than ten years. Both liver and spleen were palpably enlarged in only one patient, H.S. Hepatomegaly alone was present in four patients, and splenomegaly alone in three. This confirms that amyloidosis may be present without enlargement of both the liver and spleen,

and, conversely, both these organs may be palpable when the quantitative Congo-red test is strictly negative (Case A.H., Fig. 3).

In two patients, H.S. and W.R., there was a past history of tuberculosis. Patient W.R. had had pulmonary tuberculosis some twenty years previously, complicated by tuberculous involvement of one knee-joint, for which arthrodesis had been performed. Her rheumatoid arthritis is relatively mild, and there is no evidence of active tuberculosis. Case H.S. is described briefly below.

This patient was aged 28 on his first admission to Hammersmith Hospital in July, 1952. In 1948 bilateral pulmonary tuberculosis had been diagnosed. Chemotherapy and a right pneumothorax failed to control the disease in the right lung, although the lesions in the left lung became inactive. In May, 1950, a right thoracoplasty was done, since when to the time of writing there has been no evidence of active tuberculosis. In July, 1952, he was admitted to Hammersmith Hospital with fever, tachycardia, and flitting polyarthritis, the onset of which was preceded by a sore throat three weeks before. A diagnosis of rheumatic fever was made, and sodium salicylate, 120 gr. (8 g.) a day, was given. At first his fever and joint symptoms responded, but, in spite of continued salicylate therapy, both fever and joint involvement reappeared a fortnight later. Gradually over the next three months the picture of rheumatoid arthritis appeared, with symmetrical involvement of hands, elbows, knees, and feet. Until May, 1953, the urine was free from albumin, and in that month albuminuria first appeared. Albuminuria (4-6 g. a day) then became persistent. In July, 1953, he was readmitted for further investigation. At that time the spleen but not the liver was palpably enlarged. Congo-red absorption and liver biopsy were as shown in the table. Subsequently the liver enlarged 6 in. (15 cm.) below the costal margin.

It should be noted that this patient had a past history of extensive tuberculosis, and it is entirely probable that this may have contributed to the development of amyloidosis. That the rheumatoid arthritis played a part, however, is indicated by the absence of the albuminuria until the arthritis had been present for a year, and by the subsequent rapid enlargement of the liver—all in the absence of any evidence of tuberculous reactivation.

Comment

Amyloidosis is one of the few potentially fatal complications of rheumatoid arthritis. Its recognition is therefore of some importance for prognosis. The finding of eight patients with this complication out of 183 patients with rheumatoid arthritis seen throughout a year suggests that amyloidosis in this disease is by no means rare. Since rheumatoid arthritis is extremely common, and since conditions which in the past produced amyloid deposition are now largely controlled by chemotherapy, it seems probable that rheumatoid arthritis may come to be the principal cause of amyloidosis. Missen and Taylor (1955), in a survey of necropsy material at the Postgraduate Medical School, found amyloidosis to be present in 8 of 48 patients with rheumatoid arthritis; each of these cases had shown proteinuria during life. We believe that attention to the presence of albumin in the urine of patients with rheumatoid arthritis would bring to light more of these cases.

Summary

Out of 183 patients with rheumatoid arthritis seen throughout a one-year period, eight were found to be suffering from amyloidosis.

The clinical pointer to the complication was albuminuria, unexplained by routine investigations.

The modified Congo-red test of Unger *et al.* was found to be more reliable than the standard Congo-red test in making the diagnosis.

In all patients the rheumatoid arthritis could be held responsible for the complication; in one, pre-existing tuberculosis may have played a part.

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MALARIAL THERAPY IN THE NEPHROTIC SYNDROME

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The effect of infection on the nephrotic syndrome has long been known, and massive diuresis with disappearance of oedema and great diminution in proteinuria has been observed to follow a variety of agents, including measles, chicken-pox, pneumonia, infusions of plasma or dextran, large doses of urea, or corticotrophin. The occasional dramatic response elicited by one or other of these agents has led several physicians to the use of malaria, as this was an acute fever that could be easily induced and readily controlled. The reasons for using malaria as a therapeutic agent have varied from that of Gairdner (1952), who considered that there was sufficient clinical evidence for the empirical use of acute febrile infections, to that of Byrne (1952), who holds that the response shown is due to stimulation of the acute defence phase of the adaptation syndrome of Selye. In conditions such as the nephrotic syndrome, where treatment after treatment may follow with no sign of symptomatic relief, "it behoves the physician to attempt in turn those agents which are known to have initiated remissions, as, in the earliest stages at least, this condition may be reversible" (Gairdner, 1952).

There is still much discussion and dispute regarding the nomenclature and classification of renal disease, and for the purpose of this report the term "nephrotic syndrome" is used. This term (Squire, 1953) is applied to those cases with oedema, proteinuria, and hypoalbuminaemia, but without hypertension, nitrogen retention, or electrolyte disorder, and without an appreciable excess of red blood cells in the urine. The majority of cases in this series can be regarded as Ellis Type II nephritis, but as this description implies the presence of particular pathological changes, and as in so many patients with renal disease the essential pathology is not known, it is justifiable to use a wider descriptive term.

Malarial therapy has been used over a period of several years in the Tropical Diseases Centre, using strains of benign tertian malaria, and occasionally *Plasmodium ovale*, in patients with the nephrotic syndrome. In some it was used as a primary procedure, in others as a last resort after many varied and unsuccessful forms of therapy. Brief clinical reports are given of seven patients in whom the infection had been sufficiently severe and long-continued to regard them as having undergone "malarial therapy." The methods of infection and the management of induced malaria are dealt with by Shute (1952).

Method

Selection of Cases.—There are no precise indications for the use of malarial therapy. It is usually reserved for patients with a nephrotic syndrome which has failed to respond to more conservative forms of treatment.

Duration of Treatment.—The patient should be allowed to have as many rigors as he is capable of withstanding. The indications for cutting short the treatment are a marked deterioration in general condition, sustained fever, or severe oliguria.

Interruption of Quotidian Fever.—In most cases the fever initially assumes a quotidian periodicity but then settles down to a tertian periodicity. In some the quotidian fever persists, and in order to procure relief from the daily paroxysm a single dose of bismuth sodium thioglycollate ("thio-bismol"), 0.2 g. intramuscularly, may be given. This will usually cause the fever to become tertian in periodicity. Alternatively, small doses of quinine may be given for one day. This may stop the fever, but it will relapse in a week or two.

Method of Eradication of Malarial Infection.—In all patients the fever can rapidly be terminated by giving full doses of chloroquine, mepacrine, or quinine for a few days. In those infected by blood inoculation from other patients suffering from malaria this will eradicate the infection. In patients infected by parenteral injection of sporozoites, or by feeding infected anopheline mosquitoes, the treatment must be continued with a ten-day course of pamaquin, 10 mg. three times a day (Adams and Macgrath, 1953), to sterilize the exo-erythrocytic cycle of parasite development which results from this mode of infection, or a relapse will occur.

Case 1

The patient, a man aged 29, had a history of oedema of the lower limbs and puffiness of the face, associated with some lumbar backache over a period of six weeks. On admission there was pitting oedema of the lower limbs of moderate severity and the urine contained a moderate amount of protein, granular casts, and a few red blood cells. The blood pressure was 130/80 mm. Hg; the retinal vessels were normal. Other findings were: haemoglobin, 100%; serum proteins, 2.45 g.%, with reversal of the albumin/globulin ratio; blood urea, 28 mg. per 100 ml. and serum cholesterol, 262 mg. per 100 ml. The patient was observed for three months, during which time he was treated with a high-protein salt-free diet; although the serum protein level rose to 5.67 g.% the oedema gradually increased in severity until it was generalized and extreme.

Malarial Therapy.—He was infected with a strain of *P. vivax*, using infected anopheline mosquitoes. After a short initial period of irregular fever the temperature assumed the usual tertian periodicity. After four pyrexial episodes associated with severe rigors, his oedema had further increased, so that even in the sitting position it extended to his cervical region. There was a marked reduction in urinary output, accompanied by gross haematuria. The fever was stopped with chloroquine.

Four days after the subsidence of fever his urinary output increased to 80–100 fl. oz. (2,270–2,840 ml.) daily, on an intake of 40–50 fl. oz. (1,140–1,420 ml.). This diuresis continued for four weeks, leaving only minor residual oedema of the legs and sacrum. The diuresis then ceased, and over the next two weeks there was a slight increase in the oedema. As a relapse had not occurred the patient was reinfected with benign tertian malaria, and developed a gross haematuria, followed after 24 hours by a temperature rise and a rigor. After four pyrexial episodes, the haematuria was still present and the oedema was more marked. The fever was interrupted for one week with bismuth sodium thioglycollate, and its reappearance was again preceded by gross haematuria, followed by increasing oedema. After a further five pyrexial episodes the fever was arrested with chloroquine. During the next eleven days