anatomical and patho-physiological changes in the course of parenchymal liver disease.

In mild cases of hepatitis the T.A. generally shows a rapid and abrupt increase, reaching its peak approximately at the onset of jaundice. In more severe hepatitis, the peak value is much higher, and is attained some time after the appearance of jaundice but some time before the jaundice has culminated. Like other workers (Wróblewski and LaDue, 1956a, 1956b) we observed that subjective improvement occurs simultaneously with or just before the precipitous fall in T.A. We think this may indicate that in mild hepatitis the liver-cell destruction takes place within a very limited period, coinciding approximately with the onset of jaundice, whereas in more severe hepatitis an active necrotizing process will persist for some time after the onset of jaundice.

In clinical practice, repeated T.A. determinations during the first days of the disease may to a certain extent afford an evaluation of the prognosis as regards duration.

Also in cirrhosis and in chronic hepatitis, transaminase determinations may be of help in evaluating the activity of the necrotizing process. As mentioned above, a considerable rise in T.A. followed upon alcohol intake in a patient with cirrhosis, and in most patients with cirrhosis a rapid decrease in T.A. was observed during conservative treatment. These findings are interesting because they suggest that this sensitive laboratory test may become a key to a better understanding of the effect of hepatotoxic agents and of therapeutic measures in chronic hepatic disorders.

Our epidemiological studies show that the transaminase test is a valuable aid in the diagnosis of anicteric hepatitis and a supplement to the thymol test, which—in children especially—is not quite specific. Like LaDue *et al.* (1954), we believe that the transaminase test gives us increased possibilities of diagnosing cases of hepatitis in the early prodromal stages, sometimes before the appearance of any symptoms. Furthermore, this laboratory test apparently makes the detection of subclinical asymptomatic cases possible at the moment when the liver-cell damage occurs.

Summary

A total of 151 patients suffering from disorders of the liver and biliary tract were investigated by repeated serum transaminase tests (glutamic oxalacetic transaminase). Clinically there was a good correlation between the serum level of transaminase and the severity of parenchymal liver disease. As regards diseases of the biliary tract, patients with acute cholecystitis or cholangitis showed on the average much higher transaminase values than patients without evidence of inflammation in the biliary tract.

In a study of an epidemic of hepatitis in a children's institution, the serum transaminase test proved of value in diagnosing anicteric hepatitis and in detecting asymptomatic contact cases. Rises of transaminase activity to abnormal values were encountered two to eight days before the onset of clinical symptoms.

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"THYROGENIC" INFANTILISM DISPLAYING AN UNUSUAL PATTERN OF THYROID FUNCTION

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In 1923 one of us described a form of infantilism characterized solely by a marked retardation of growth and of sexual maturation which responded promptly to thyroid therapy, although there were none of the usual signs of thyroid insufficiency (Zondek, 1923). The case of a 19-year-old youth was recorded. Because of the favourable effect of thyroid therapy, which was regarded as specific, this form of infantilism was considered to be of thyroid origin and consequently termed "thyrogenic" infantilism. Falta (1928) confirmed the beneficial effect of thyroid medication in certain cases of infantilism. So far as we are aware, no other reports on the subject have appeared. Zondek himself (1953) admitted that "it is hard to conceive that thyroid hypofunction may be restricted to processes of growth and maturation without producing at the same time well-known features of myxoedema."

Nevertheless, following the investigations of a recent case which corresponded closely to the original description of "thyrogenic" infantilism, the existence of this syndrome has been confirmed.

Case Report

A youth aged 18 was born in Morocco and had lived there until a month before his admission to hospital. The members of his maternal and paternal families are said to be in good health. An accurate medical history of the patient was unobtainable. He claims that he had been small for his age from the age of at least 8 or 9 onwards. Owing to his underdevelopment he had been neglected by his family and had almost never attended school.

With the exception of his head, which was rather large in comparison with the rest of his body, the patient was a proportionate dwarf, whose general appearance on admission corresponded to that of a 9-year-old boy. His height was 4 ft. 5 in. (1.35 m.) and weight 94 lb. (42.5 kg.) (Fig. 1). He appeared to be completely normal in intelligence: he studied hard, learning, among other subjects, to speak, read, and write the rather difficult Hebrew language. He was lively and active, both physically and mentally.

Careful palpation of the neck region did not reveal any enlargement of the thyroid. The skin was of normal texture. There was neither body nor facial hair. The voice had a high pitch. The testicles were about 2 by 1.5 cm., and the penis was 4 cm. long and very thin.

The pulse rate was 80–90 per minute, and the blood pressure 100–110/80 mm. Hg. Percussion and radiography showed that the heart was enlarged on both sides; there were no murmurs. The electrocardiogram was normal, as were the tendon reflexes.

Laboratory Investigations

Routine urinalysis, the blood count, and the erythrocyte sedimentation rate were within normal limits. The values for serum urea, glucose, calcium, phosphorus, sodium, and potassium were also normal. Total serum cholesterol varied in seven determinations from 120 to 145 mg./100 ml. Serum alkaline phosphatase was 4.1 Bodansky units. Albumin was 4.3% and globulin 2.3%. Paper electrophoresis of the serum proteins gave a value of 31.2% for albumin, 8.5% for α_1 -globulin, 13.5% for α_2 -globulin, 17.4% for β -globulin, and 29.4% for γ -globulin. The serum protein-bound iodine (P.B.I.) was 8.9% and 10.6% on two occasions before tracer ^{131}I studies were made.

The B.M.R. was on two occasions +10% and +14%. Urinary 17-ketosteroids were 4.6 mg./24 hours. Less than 30 m.u. of follicle-stimulating hormone was excreted per litre of urine, showing that there was no primary testicular insufficiency, in which much higher values are obtained. Radiological examination of the bones of the upper limbs showed that the bony age corresponded to a chronological age of 9 years; the epiphyseal lines were wide open. The skull and the sella turcica were radiologically normal. The electroencephalogram was also normal.

Radioiodine Tracer Studies

Radioiodine tracer studies with doses of 50 μC . were undertaken on three different occasions before treatment was started and under identical conditions. The results are summarized in the Table.

The first test gave a distinctly hyperthyroid pattern with high thyroid uptakes, high plasma concentration of ^{131}I , low urinary excretion, and low salivary concentration.

In the second test, while the thyroid uptake and urinary excretion were still at the lower limit of the hyperthyroid range, the total plasma concentration of ^{131}I was normal and the salivary concentration of the isotope was at the upper normal limits. The protein-bound ^{131}I conversion ratio (protein-bound ^{131}I /total ^{131}I in the plasma, according to the method of Clark) was at 24 hours 11%, a low value which was compatible with the value for the salivary concentration of ^{131}I (Freinkel and Ingbar, 1953, 1955; Thode *et al.*, 1954; Jaimet and Thode, 1956; Stein *et al.*, 1957).

The third test showed a further decrease of thyroid uptake to normal values at 24 hours. Salivary concentration of ^{131}I was low, probably indicating a higher conversion ratio than in the previous test.

In addition to the spontaneous changes from a hyperthyroid to a euthyroid pattern of ^{131}I uptake and release,

Results of ^{131}I Studies (50 μC .)

	Thyroid Uptake (% of Dose)		Urinary Excretion (% of Dose) 24 hrs.	Total Plasma Concentration (μC ./litre) 24 hrs.	Salivary Concentration (μC ./litre) 24 hrs.	Remarks
	2 hrs.	24 hrs.				
Normal Range	11 $\pm$ 4	40 $\pm$ 10	50 $\pm$ 5	0.07 $\pm$ 0.03	5 $\pm$ 3	
1. Tracer 12/12/56	25	62	27.5	0.19	3.0	Before treatment
2. Tracer 13/1/57	19.2	49	33.8	0.08	7.05	
3. Tracer 13/2/57		35.9	58	0.08	2.4	
4. Tracer 12/6/57	10.4	14	80.4	0.27	26.9	During T_3 therapy 20 days after cessation of T_3
5. Tracer 28/7/57	12.7	30.1	55.8	0.09	5.2	

differential counting during the radioiodine tracer tests showed conspicuous differences of radioactivity between the three lobes of the thyroid. At 24 hours after the first tracer dose the relative radioactivities of the isthmus, the right lobe, and the left lobe were respectively 100, 60, and 20, taking the isthmus radioactivity as 100. At the third test at 24 hours the respective values were 100, 25, and 2.5; these differences then tended to diminish, and at 96 hours the isthmus and the right lobe had the same radioactivity, while the left lobe was still 2.5 times less radioactive.

During the fifth radioiodine tracer test the acid butanol extractable radioactivity (Roche *et al.*, 1954), determined on serum taken 24 hours after the ^{131}I dose, was only 15.6% of the total serum radioactivity (average of duplicate determinations), as compared with normal values of 85% and higher.

Results of Treatment

Triiodothyronine (T_3) was given during 57 days in daily doses of 60 μg . (a total of 3.42 mg.). During that period the patient put on 2 kg. in weight, and grew 5.5 cm. in height.

FIG. 1
FIG. 2
FIG. 3
An 18-year-old youth with "thyrogenic" infantilism. Fig. 1, before treatment. Fig. 2, after five weeks of T_3 (60 μg . a day). Fig. 3, after eight weeks of T_3 .

His bony age developed, and corresponded to the chronological age of 11–12 years at the end of the period of treatment. The penis grew to 6–7 cm. in length and became much broader. The testicles also grew to 4.5 by 3 cm. Pubic hair started to appear soon after the beginning of treatment and progressively became fairly dense. A slight moustache appeared (Figs. 2 and 3). The voice became deeper. Libido was awakened in the course of treatment, and on occasion sexual behaviour became excessive. At the end of the period of treatment the 24-hour urinary excretion of 17-ketosteroids had increased to 10.6 mg., a value normal in our laboratory for the chronological age of the patient.

At no time during treatment was there an indication of thyroid hormone overdosage (no tachycardia) except for a transient rise of the B.M.R. to +51% five days after starting T_3 . The B.M.R. fell within the next 11 days to +21%, despite the continuation of the same daily dose of hormone. Another 18 days later it was +17% and has shown no change since.

Throughout the period of treatment the size of the heart shadow, which was radiographically determined at weekly intervals, showed no change whatsoever. Since it has been shown that under T_3 therapy the size of the myxoedema

heart returns to normal in 3-15 days (Zondek *et al.*, 1955), the cardiac enlargement could hardly be interpreted as a manifestation of a "myxoedema heart" (Zondek, 1918, 1919).

A radioiodine tracer test during treatment (see Table) revealed, as expected in clinically euthyroid patients, a distinctly hypothyroid pattern and also a uniform distribution of the radioactivity over the three lobes of the thyroid. A fifth tracer test performed three weeks after the cessation of treatment showed a return to a euthyroid pattern. Directional counting on this occasion showed that the isthmus of the thyroid again had concentrated far more ^{131}I than either lateral lobe—an abnormal distribution similar to that which had been observed before treatment.

Discussion

This case fits in well with the original description of the syndrome of "thyrogenic" infantilism proposed by Zondek (1923) on purely clinical grounds—that is, the beneficial effects of thyroid therapy. In both the present and the original cases there was only somatic and sexual developmental arrest. None of them displayed signs of thyroid insufficiency. Laboratory findings in the present case were also either in the euthyroid or even hyperthyroid range. Nevertheless, all patients responded to thyroid therapy dramatically—the previously reported ones to desiccated thyroid and the above case to triiodothyronine.

A gross abnormality of the present patient's circulating thyroid hormone was its extremely low extractability into acid butanol, presumably indicating that the circulating iodine compound contained only very small quantities of thyroxine and triiodothyronine. It is also possible that the serum contained the normal hormonal constituents, but in an abnormally bound form, or, alternatively, that the serum contained an abnormal iodine compound in an abnormal binding.

Be that as it may, it appears that the circulating iodine compound was able to maintain the normal activities of thyroid hormone in the adult, but was not available for the anabolic functions which thyroid hormone normally fulfils in the growing organism, such as its maturing effects on the skeletal and genital system. This remarkable discrepancy may be explained either by assuming that the abnormal circulating iodine compound was in itself able to maintain most though not all functional activities of the normal thyroid hormone, or by assuming a failure of certain target organs to transform the abnormal circulating iodine compound into the peripherally active thyroid principles (peripheral theory, Zondek, 1924). The possibility may also be considered that the abnormal circulating thyroid hormone was not available to the pituitary, which was thus prevented from producing growth hormone (Eartly and Leblond, 1954) and gonadotrophins.

It should be mentioned that abnormalities of the circulating thyroid hormone have previously been observed in cases of thyroid cancer (Robbins *et al.*, 1952, 1955; Tata *et al.*, 1956), of Hashimoto's disease (Owen and McConahey, 1956), of non-goitrous (Whitelaw *et al.*, 1956) and of goitrous cretinism (Stanbury *et al.*, 1955, 1956a, 1956b; Querido *et al.*, 1956). Two recently described cases of infantilism in girls (diGeorge and Paschkis, 1957; Werner *et al.*, 1957) had low acid-butanol-extractable iodine and high serum P.B.I.-levels as in the above case. However, the former differed from the latter by having an easily visible and palpable goitre and some evidence of hypothyroidism such as a high serum cholesterol and a low serum alkaline phosphatase.

Another interesting feature in the present case was the spontaneous variability of thyroid function in the radioiodine tracer tests, with regard both to the overall activity of the thyroid and to that of its three lobes. This was very remarkable indeed, as careful clinical examination revealed, throughout the whole course of observation, a normal homogeneous gland—that is, the absence of either a diffuse or a

localized increase in volume. Under such conditions similar differences in ^{131}I uptake and release, which must be attributed to a failure of the normally active regulative mechanisms of thyroid activity, have to the best of our knowledge not been recorded.

As to the diagnosis of thyrogenic infantilism, it should not be inferred from our description of the syndrome that every case of somatic and sexual developmental arrest characterized by the absence of hypothyroid manifestations should be classified as "thyrogenic" and should be expected to benefit from thyroid therapy. We have now two patients under observation who, although their clinical picture is suggestive of "thyrogenic" infantilism, are completely refractory to thyroid therapy. It is true the pattern of thyroid function observed in them does not conform to the above outlined abnormalities of thyroid function and of the circulating thyroid hormone. However, it is as yet too early to say whether these phenomena are pathognomonic of "thyrogenic" infantilism or only related to the above case. At the present stage of knowledge only the positive response to thyroid therapy should be regarded as decisive for the diagnosis of the syndrome.

Summary

A case of "thyrogenic" infantilism in an 18-year-old youth is reported. The characteristic features of the syndrome are: (1) marked retardation of somatic and sexual development and a corresponding retardation of the bony age; (2) no clinical or laboratory signs of thyroid hypofunction; and (3) a dramatic response to thyroid therapy, resulting in body growth, with a corresponding development of the bony age and sexual maturation.

In the case described the serum protein-bound iodine was high and the extractability of the circulating iodine compound into acid butanol was extremely low.

Regardless of the nature of the abnormal circulating iodine compound, it was apparently able to maintain the normal activities of thyroid hormone except for those on somatic and sexual development.

There was a spontaneous change from a hyperthyroid to a euthyroid pattern in repeated radioiodine tracer tests and large differences in the radioactivity taken up by the three lobes of the thyroid, notwithstanding a lack of clinically demonstrable general or localized volume increase of the thyroid tissue at any stage of the observation. Whether these abnormalities of thyroid function and of the circulating iodine compound are related to the syndrome of thyrogenic infantilism or only to the case reported here is not known at present and will be the subject of further investigations.

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CARDIOMYOTOMY FOR ACHALASIA OF THE CARDIA

THE EXPERIENCE OF THE MIDDLESEX AND HAREFIELD HOSPITALS UP TO 1955

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Although cardiomyotomy for achalasia of the cardia was described by Heller in 1914 it was not widely practised in Britain or America until 30 years later. Writing from the Mayo Clinic in 1940, Gray and Skinner reported that Heller's operation had not been used in the treatment of 1,200 cases of achalasia seen there up to that time. Grey Turner (1946) did not recommend cardiomyotomy for achalasia.

The first report of the successful use of cardiomyotomy in this country came from Barlow (1942), who described four operations. Barrett (1950) and Allison (1950) advocated Heller's operation as the surgical treatment of choice. Several further papers (Wangensteen, 1951; Effer and Rogers, 1955; Brewer *et al.*, 1956) confirmed Barrett's opinion that Heller's operation should replace the more radical operations because it is not followed by peptic oesophagitis. Other recent evidence, however, has suggested that Heller's operation may also be followed by the symptoms and complications of gastro-oesophageal reflux (Hawthorne and Nemir, 1953; Hawthorne *et al.*, 1956).

This paper is an attempt to cast further light on the value and limitations of cardiomyotomy and the incidence of post-operative peptic oesophagitis by reviewing the combined experience of the surgeons of the Middlesex and Harefield Hospitals from its introduction in 1947 until 1955. The results have been assessed by physicians who have not been concerned in the treatment of most of the patients.

Material

Cardiomyotomy was performed on 26 patients at the Middlesex Hospital and nine patients at Harefield Hospital between April, 1947, and August, 1955. Between May, 1956, and March, 1957, 27 of these were interviewed, examined, and weighed by one of us (E. D. A.), and a barium swallow examination was made of each. Of the remainder, two are dead, four could not be traced, one was too disabled by chronic lung disease to leave her home, and one lived at too great a distance to attend for examina-

tion. We have incomplete information about the present health of the latter two patients from their family doctors. Of the four who were untraced, two attended the outpatient department for 19 and 20 months after operation respectively. The other two patients have not been heard of since leaving hospital. The two patients who died attended hospital until shortly before their deaths.

Thus we have complete data in 27 cases, incomplete information in a further six, and no information about two patients (Table I).

TABLE I.—Material

No. interviewed	27
Dead (information up to time of death)	2
Traced, but unable to attend (information from family doctors)	2
Untraced:	
Some information	2
No information	2
	35

Eight patients were male and 27 female, and the average age of the group at operation was 45 years. The average duration of symptoms before operation was 10 years 5 months (range 1 to 51 years). Nineteen of the 35 patients in the series had received previous treatment with Hurst's mercury bougies, with the Negus hydrostatic bag, or had undergone oesophagoscopy and dilatation. In 17 of these the pre-operative treatment had been given a fair trial and had failed. In one case dilatation through an oesophagoscope and in another dilatation with a Negus bag had been performed within the fortnight immediately before the operation; there had been no other previous treatment. In three other cases octyl nitrite had been taken with temporary benefit. In the remaining 13 cases there is no evidence of any treatment having been given before cardiomyotomy was performed.

The mean period which elapsed between the date of operation and the date of interview was 3 years 10 months. Fig. 1 shows the distribution of the cases from this point of view.

FIG. 1.—Length of time from operation to interview. Cases not interviewed are shown in black.

Associated Conditions.—Fourteen patients (40%) gave a history of respiratory infection. In 4 (11%) there was evidence of rheumatoid arthritis. This supports the impression of Allison (1950) and Wooler (1948) that there may be an association between rheumatoid arthritis and achalasia of the cardia.

The Operation

Seven different surgeons performed the 35 operations in the series; four were thoracic and three general surgeons. The thoracic surgeons performed 17 operations, of which 13 were successful, and the general surgeons 18, of which 15 were successful. The cardia was approached through the thorax in 22 cases and from the abdomen in 3. In 10 cases the incision involved both thorax and abdomen. In each case a single longitudinal incision was made in the oesophagus down to the submucosa. The length of the incision was recorded in the operation notes in 27 of the 35 cases. It varied from 1½ to 6 in. (3.8 to 15 cm.), mean 3.1 in. (7.87 cm.). Information concerning the extension of the cut on to the wall of the stomach was incomplete. In this series no correlation has been found between the length of the cut in the oesophageal wall, as recorded in the operation notes, and the clinical success of the operation. However, in view of the doubt about the methods used for the measurement of the incision at operation, it would be unwise to draw definite conclusions.