Summary from the Literature of Bacteriological Findings in Reported Cases of Benign Gonococcaemia

	No. of Cases	Cervix and/or Urethra. Smear or Culture	Blood Culture	Skin Lesions Smear	Skin Lesions Culture
Abu-Nassar *et al.* (1963)	14	10 of 12*	0 of 11	6 of 7	0 of 7
O'Sullivan (1964)	2	2 of 2	0 of 2	0 of 1	0 of 2
Fred *et al.* (1965)	6	6 of 6†	0 of 1	3 of 3‡	1 of 4
Ackerman *et al.* (1965)	1	0 of 1	1 of 1	1 of 1§	0 of 1
Ackerman and Calabria (1966)	1	1 of 1	1 of 1	1 of 1	0 of 1
Björnberg and Gisslén (1966)	9	9 of 9	1 of 5	—	0 of 7
Danielsson and Michaëlsson (1966)	3	3 of 3	0 of 1	1 of 1	0 of 3
Frichot and Everett (1967)	1	0 of 1	0 of 1	—	1 of 1
Keiser *et al.* (1968) (Cases with skin lesions)	15	11 of 14	5 of 12	3 of 8	0 of 11
Grossman and Roos (1968)	1	1 of 1	1 of 1	—	0 of 1
Present Series	3	3 of 3	2 of 3	0 of 3	0 of 3
Totals	56	46 of 53	11 of 39	15 of 25	2 of 41
%Positive in each category		87	28	60	5

*Approximate figure, as paper merely states that 5 out of 11 cultures and 10 out of 12 smears were positive.
†This figure is implied but not stated.
‡The paper states, "Histology and Gram-staining suggestive."
§Demonstrated histologically only.

skin lesions are not usually present. The rapid response of the benign type to penicillin in adequate dosage is characteristic of the disease and distinguishes it from Reiter's disease (Partain *et al.*, 1968).

Skin Lesions.—When the lesions are haemorrhagic and appear mainly on the distal parts of the extremities, the diagnosis is more likely to be considered than when the eruption is non-specific, consisting of papules and pustules generally distributed as in Case 3. Other types of skin lesion have been reported, such as purpura (Abu-Nassar *et al.*, 1963), painful reddened areas (Danielsson and Michaëlsson, 1966), and erythema-nodosum-like lesions with central papules (Grossman and Roos, 1968). The last should be distinguished from erythema nodosum due to other causes. Chronic meningococcaemia and low-grade staphylococcal septicaemia may be indistinguishable from benign gonococcaemia.

Treatment

Our three cases responded rapidly to treatment with penicillin. The optimum dose is not known, but it seems logical to use a large one intramuscularly for two weeks to ensure elimination of the organisms from all foci. Too small a dose may result in the carrier state or, by suppressing the organism, make diagnosis difficult.

We wish to thank Dr. B. Gottlieb, consultant physician at St. Mary Abbots Hospital, for permission to publish details of Case 1 and for advice in the preparation of this paper. We also wish to thank Dr. M. Patricia Jevons, consultant bacteriologist at St. Stephen's Hospital, for writing the section on bacteriology which she had carried out.

ADDENDUM.—Since this paper was written another patient with benign gonococcaemia was admitted to the Western Hospital, on 13 October 1969. She was a girl, aged 19, who had had an intermittent pustular eruption of her legs and recurrent painful swelling of both her ankles for six months. *N. gonorrhoeae* was isolated from the cervix and the blood. The blood had been taken soon after the cervix had been swabbed.

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Preliminary Communications

Thyroid-stimulating Hormone Response to Synthetic Thyrotrophin Releasing Hormone in Man

British Medical Journal, 1970, **2**, 274–277

Summary: Synthetic thyrotrophin-releasing hormone, L-pyroglutamyl-L-histidyl-L-proline-amide, has been administered intravenously to euthyroid subjects in doses ranging from 1 to 200 μg. Its effect was assessed by serial measurements of serum thyroid-stimulating hormone (T.S.H.). A rise in serum T.S.H. was detectable five minutes after administration of 50 μg. of thyrotrophin-releasing hormone, reaching a maximum in 15 to 30 minutes, and then gradually declining over the next 120 minutes. Doses of 100 and 200 μg. of thyrotrophin-releasing hormone produced even greater rises of T.S.H. in some cases. The only side-effect noted was transient nausea with doses greater than 50 μg. Measurement of serum T.S.H. levels after administration of thyrotrophin-releasing hormone should prove a useful test of pituitary T.S.H. release and may help to distinguish pituitary and hypothalamic lesions.

INTRODUCTION

There is now clear evidence that the hypothalamus produces a regulating substance, thyrotrophin-releasing hormone, which controls the release of thyroid-stimulating hormone (T.S.H.) from the anterior pituitary. The releasing hormone is stored in the median eminence of the hypothalamus and released into the portal blood system which flows from the hypothalamus to the pars distalis of the anterior pituitary (Harris, 1955; Martini and Ganong, 1967). The release of T.S.H. from the pituitary is stimulated by thyrotrophin-

releasing hormone and inhibited by raised levels of thyroid hormones (Bowers *et al.*, 1968a).

The existence of a thyrotrophin-releasing factor was first postulated on the basis of physiological experiments in which it was shown that electrical stimulation of the preoptic area of the hypothalamus increased T.S.H. release, and that destruction of areas of the hypothalamus resulted in reduced T.S.H. output (Harris, 1955; Bowers *et al.*, 1968a). The identification of the factor was first claimed by Shibusawa *et al.* (1956), but this work did not receive wide acceptance. Harris (1963), Schreiber *et al.* (1962), and Reichlin (1964) observed that extracts of median eminence increased thyroid function in mice and rabbits. More convincing evidence for the existence of such a factor was produced by Guillemin *et al.* (1962, 1963, 1965) and Schally *et al.* (1966a, 1966b, 1966c), who recovered and purified a thyrotrophin-releasing factor and other hypothalamic releasing substances from fragments of porcine, ovine, bovine, and human hypothalamic tissue. The yield of this thyrotrophin-releasing factor, however, was very small; Schally obtained only 7·2 mg. of purified material from 265,000 porcine hypothalami, and Guillemin obtained an even smaller quantity from 750,000 ovine hypothalami.

Schally *et al.* (1966a) showed that porcine thyrotrophin-releasing factor contained three amino-acids, histidine (his.), glutamic acid (glu.), and proline (prol.). Once characterized, they suggested that this thyrotrophin-releasing factor should be renamed thyrotrophin-releasing hormone (Schally *et al.*, 1968). Schally *et al.* (1969), using degradation techniques, found the amino-acid sequence to be glu-his-prol: Two other groups of workers, Burgus *et al.* (1969) and Gillessen *et al.* (1970) independently screened various synthetic sequences of the three amino-acids and found that L-pyroglutamyl-L-histidyl-L-proline-amide had the full biological activity of the isolated thyrotrophin-releasing hormone and appeared to be identical with it. Our paper describes the effects of this substance on T.S.H. release in euthyroid male subjects.

Materials and Methods

Thyrotrophin-releasing Hormone.—The thyrotrophin-releasing hormone used in this study was synthesized by the joint efforts of Dr. Guillemin and the Roche Chemical Departments of Basle and Nutley, and supplied by Roche Products Ltd.* It was presented as pyroglutamyl-histidyl-proline-amide in the form of the acetate salt. The molecule is protected on both the amino and carboxyl ends. One milligram of pure powder was made up in 0·9% sodium chloride to a concentration of 10 μg./ml. and was stored at −20°C. in 1-ml. sterile ampoules until use.

Thyroid-stimulating Hormone Immunoassay.—Serum T.S.H. levels were measured by a modification of the double antibody method of Odell (Raud and Odell, 1969; Hall *et al.*, 1970) with guinea-pig anti-human T.S.H. in the presence of human chorionic gonadotrophin and using rabbit anti-guinea-pig gammaglobulin as second antibody. National Pituitary Agency human T.S.H. was used for iodination by the method of Hunter and Greenwood (1962), iodinated human T.S.H. being purified by a modification of the Quso method of Berson and Yalow (1968). Medical Research Council human T.S.H. Standard A was used for reference. In all tubes the serum content was kept constant by the addition of canine serum (0·1 ml. of serum in a 0·5-ml. system). Incubation damage was quantitated by the addition of excess first antibody to duplicate reaction tubes 24 hours before addition of the second antibody.

Thyroid Hormone Levels.—An indirect estimate of the blood thyroid hormone concentration was made with Thyopac-3 (Radiochemical Centre, Amersham) (Clark and Brown, 1970). The serum protein-bound iodine (P.B.I.) was estimated by the Technicon AutoAnalyzer technique of Riley and Gochman (1964).

Thyrotrophin-releasing Hormone Administration.—Thyrotrophin-releasing hormone was administered intravenously to four healthy male volunteers (age 25 to 38 years), who had no clinical or laboratory evidence of thyroid disease. The hormone was administered through a No. 18 indwelling Graham's Viggo needle from which all blood specimens were also withdrawn. After withdrawal of a basal blood specimen for T.S.H., P.B.I., and Thyopac-3 estimations, 5 ml. of 0·9% sodium chloride solution was injected as a control and a further blood specimen removed five minutes later. Then the thyrotrophin-releasing hormone was injected as rapidly as possible. Serial blood samples were taken at the times indicated in Table I for a further two hours.

Results

The results presented in Table I and Figs. 1 and 2 show that there is a significant rise ($P<0·05$) in T.S.H. levels in all the subjects given 50 μg. or more of thyrotrophin-releasing

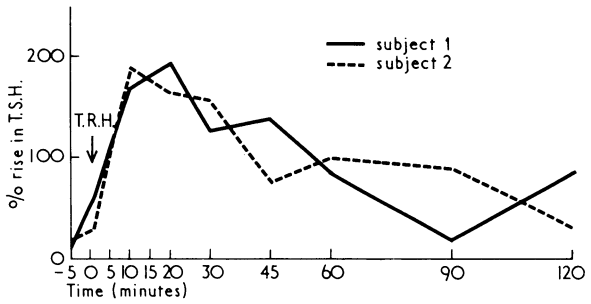

FIG. 1.—T.S.H. response to injection of 50 μg. of thyrotrophin-releasing hormone.

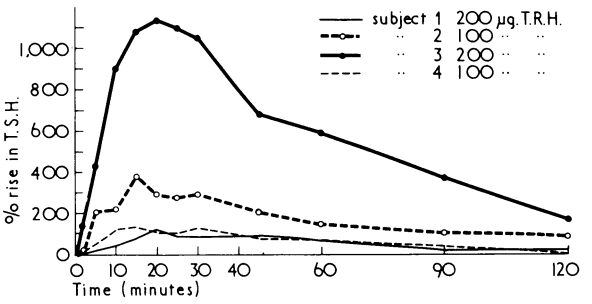

FIG. 2.—T.S.H. response to injection of 50 μg. of thyrotrophin-releasing hormone.

hormone. The T.S.H. response appeared to be related to the quantity of thyrotrophin-releasing hormone administered, though there was a considerable individual variation in response. Subject 2 responded to a dose of 100μg. with a rise of >381%, while Subject 4 responded to the same dose with a rise of only 137%. The maximum rate of rise in T.S.H. levels occurred between 5 and 15 minutes and the peak response was noted between 15 and 30 (mean 20) minutes after injection of the thyrotrophin-releasing hormone. A peak T.S.H. level of 12·3 μU./ml., which is a rise of >1130% over basal levels, was obtained in Subject 3 with an injection of 200 μg. of thyrotrophin-releasing hormone. The other subject who received 200 μg. had a rise from undetectable basal levels of T.S.H. to 2·2 μU./ml. (>120%). Following the peak the values of T.S.H. gradually decreased

* This material was released by Roche Products Ltd. for use in animals. The company is in no way implicated in the administration to volunteers

TABLE I.—*Effect of Thyrotrophin-releasing Hormone (T.R.H.) on Serum T.S.H. Levels*

Subject	Dose T.R.H. (μg.)	Basal level		Time After T.R.H. Injection (Minutes)									
				+2		+5		+10		+15		+20	
		T.S.H. (μU./ml.)	% Change	T.S.H. (μU./ml.)	% Change	T.S.H. (μU./ml.)	% Change	T.S.H. (μU./ml.)	% Change	T.S.H. (μU./ml.)	% Change	T.S.H. (μU./ml.)	% Change
1	10	< 1·2	—	1·1	0	1·5	> 25	1·2	0	—	—	< 1·2	0
	50	1·3	—	2·1*	62	2·2*	69	3·5*	169	—	—	3·8*	192
	200	< 1	—	< 1	0	< 1	0	1·4*	> 40	1·7*	> 70	2·2*	> 120
2	10†	< 1·3	—	< 1·1	0	< 1	0	< 1	0	—	—	< 1	0
	50	1·7	—	2·2	29	3·2*	88	4·9*	188	—	—	4·5*	165
	100	< 1·1	—	< 1·3	< 18	3·2*	>191	3·5*	>218	5·3*	> 381	4·3*	> 291
3	10†	< 1	—	< 1	0	< 1	0	< 1	0	—	—	< 1	0
	200	< 1	—	2·4*	> 140	5·3*	>430	10·0*	>900	11·8*	>1080	12·3*	>1130
4	10	2·2	—	2·5	13·6	< 2	0	1·2	− 45	—	—	2·3	4·5
	100	1·9	—	2·1	10	3·0*	58	4·2*	121	4·5*	137	4·0*	111

Subject	Dose T.R.H. (μg.)	Time After T.R.H. Injection (Minutes)											
		+25		+30		+45		+60		+90		+120	
		T.S.H. (μU./ml.)	% Change	T.S.H. (μU./ml.)	% Change	T.S.H. (μU./ml.)	% Change	T.S.H. (μU./ml.)	% Change	T.S.H. (μU./ml.)	% Change	T.S.H. (μU./ml.)	% Change
1	10	—	—	< 1	0	< 1	0	< 1·4	< 17·9	< 1	0	< 1	0
	50	—	—	2·9*	123	3·1*	138	2·4*	84	1·5	15	2·4*	84
	200	1·9*	> 90	1·9*	> 90	1·9*	> 90	1·7*	> 70	1·2*	> 20	< 1·2	< 20
2	10†	—	—	< 1	0	< 1·3	0	< 1	0	< 1	0	< 1	0
	50	—	—	4·4*	159	3·0*	76	3·4*	100	3·2*	88	2·4	41
	100	4·1*	> 273	4·3*	> 291	3·3*	>200	2·7*	>145	2·3*	> 109	2·1*	> 90
3	10†	—	—	< 1	0	< 1	0	< 1	0	< 1	0	< 1	0
	200	12·0*	>1100	11·5*	>1050	7·8*	>680	6·9*	>590	4·7*	> 370	3·7*	> 270
4	10	—	—	4·6	109	2·1	−4·5	1·8	− 18	1·9	−13·6	− 1·7	−22·7
	100	3·8*	100	4·3*	126	3·4*	79	3·2*	68	2·7	42	1·8	− 5

*Level significantly raised above basal value ($P < 0.05$).
†Subjects pretreated with triiodothyronine 120 μg. daily for two weeks.

over the next 90 minutes. In 3 out of 10 experiments, however, the T.S.H. value had not returned to basal levels within 120 minutes of infusion.

The effect of thyrotrophin-releasing hormone on serum P.B.I. levels up to two hours after the dose is shown in Table II. There was a rise in P.B.I. in two out of four subjects who

TABLE II.—*Effect of Thyrotrophin-releasing Hormone on Serum P.B.I. Levels*

Subject	Dose (μg.)	Time in Minutes					
		−10	+20	+30	+60	+90	+120
1	50	7·3*	6·2	7·8	7·5	6·6	7·5
	200	7·4	6·9	6·9	6·9	8·5	9·3
2	10†	1·8	1·5	1·9	1·6	1·7	1·6
	50	5·2	5·4	5·1	4·9	5·5	5·6
	100	5·7	5·3	5·1	5·2	6·0	6·6
3	10†	1·7	2·6	2·9	—	2·0	1·0
	200	5·2	4·8	4·6	4·7	5·2	5·8
4	10	7·7	7·2	7·8	7·5	7·7	8·1
	100	7·0	7·7	7·7	11·3	11·2	8·5

*P.B.I. values in μg./100 ml.
†Subjects pretreated for two weeks before this dose of thyrotrophin-releasing hormone with 120 μg. of triiodothyronine daily.

received more than 50 μg. of thyrotrophin-releasing hormone, but this response was not consistent. There was no change of Thyopac-3 ratio.

DISCUSSION

A synthetic thyrotrophin-releasing hormone preparation caused a significant rise in serum T.S.H. levels in normal subjects. These results are in agreement with the report by Bowers *et al.* (1968b), who used a purified preparation of porcine thyrotrophin-releasing hormone in three cretins. The time course of the T.S.H. response in the two studies is similar, with a detectable rise within five minutes, a further rise between 6 and 30 minutes, with a peak at 15 to 30 minutes, followed by a gradual fall over the next 120 minutes. Bowers *et al.* (1968b) found that 300 μg. of their purified thyrotrophin-releasing hormone gave a rise of more than 300% at 30 minutes over control values in their most responsive case, They estimated that 300 μg. of their preparation was equivalent to 20 μg. of pure thyrotrophin-releasing hormone. In the euthyroid subjects reported in the present paper no consistent response was obtained with a dose of 10 μg. of pure thyrotrophin-releasing hormone, a significant response was obtained with 50 μg., and in some cases a greater response occurred with doses of 100 μg. and over. It is suggested that the higher doses required in this report may be due to the inhibitory effect of endogenous thyroid hormone on T.S.H. release.

The drug did not produce any significant short-term side-effects. The blood pressure, pulse, and respirations remained unchanged. No side-effects at all were noted with doses lower than 50 μg., but each of the four subjects given 100 μg. or more experienced a mild, transient nausea coming on 30 seconds after administration and lasting 3 to 10 minutes. No abnormalities were detected in the blood count, urine analysis, or liver function tests 7 to 10 days after injection.

It is now recognized that more information can be obtained with dynamic tests of pituitary function than with basal urinary or plasma assays (Greenwood *et al.*, 1966). Attempts to develop such a "stress" test for T.S.H. release have previously been unsuccessful. Odell *et al.* (1968) and Raud and Odell (1969) were unable to demonstrate a consistent rise in serum T.S.H. in response to methimazole or propylthiouracil (7-28 days), glucose administration, meals, exercise, fasting, fever, surgery, cold exposure, arginine, or vasopressin administration. Hall *et. al.* (1970) also failed to produce a rise in serum T.S.H. using carbimazole 40 mg. daily for one month (three subjects); carbimazole 40 mg. daily along with

potassium iodide 60 mg. daily for three weeks (five subjects), lysine vasopressin 10 pressor units intravenously over two hours (five subjects), and acute lowering of central body temperature by 3·6° F. (2°C.) (one subject).

Administration of thyrotrophin-releasing hormone causes a rise in serum T.S.H. and so should provide a useful test of the function and reserve capacity of the thyrotroph cells of the anterior pituitary. The clinical and laboratory diagnosis of minor degrees of pituitary T.S.H. deficiency can be particularly difficult. All thyroid function tests may be within the conventional normal range and yet the patient may benefit from thyroid hormone medication. Failure of serum T.S.H. levels to rise in response to thyrotrophin-releasing hormone should therefore provide a more refined diagnosis of T.S.H. deficiency. Since thyrotrophin-releasing hormone acts directly on the pituitary it could also be used to distinguish between pituitary and hypothalamic lesions affecting T.S.H. release, a distinction which cannot be made with available tests.

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Medical Memoranda

Congenital Dilatation of Intrahepatic Biliary Ducts with Cholangiocarcinoma

British Medical Journal, 1970, **2**, 277–278

Congenital dilatation of the intrahepatic ducts is rare. The condition was first described by Caroli *et al.* (1958). The following account of a further case records three features not previously described: obstructive jaundice, the development of severe osteoporosis during the latter part of the illness, and the occurrence of a cholangiocarcinoma arising from one of the dilated ducts.

CASE REPORT

In September 1959 the patient (then aged 23) developed recurrent attacks of painless obstructive jaundice. In 1962 a cholecystectomy was performed at another hospital but no definitive evidence of cholelithiasis was found. She continued to have attacks of jaundice, now accompanied by epigastric and right subcostal pain. In 1964 a laparotomy showed no abnormality of the biliary tree. Because of the continuance of symptoms she was admitted to Manchester Royal Infirmary in September 1965. Percutaneous cholangiography showed a fistula between the biliary tree and the proximal duodenum. Review of *x*-ray films showed air in the biliary tree previous to cholecystectomy. At laparotomy a fistula was found between the proximal duodenum and a large cystically dilated biliary duct at the porta hepatis; this contained 400 ml. of colourless mucus. Digital exploration showed considerable dilatation of the intrahepatic biliary ducts. A Roux-en-Y anastomosis was fashioned between the dilated biliary duct and the jejunum. Over the next four months her serum bilirubin subsided from 27 to 2·4 mg./100 ml., and she first complained of backache. In 1967 she noticed a loss in height of 5 cm. Because of continuing jaundice and pyrexia she was readmitted to hospital in April 1968. She was icteric and had one-finger-breadth hepatomegaly and kyphosis of the lower thoracic and upper lumbar vertebrae.

Investigations.—Haemoglobin 11·7 g./100 ml.; serum iron 65 µg./100 ml.; white cell count 14,300/cu. mm.; E.S.R. (Wintrobe) 49 mm. in 1 hour; serum bilirubin 1·4 mg./100 ml.; serum alkaline phosphatase 200 King–Armstrong units/100 ml.; 5-nucleotidase 190 units; serum albumin 3·4 g./100 ml.; serum globulin 6·3 g./100 ml.; electrophoresis showed a pronounced rise of gamma-globulin; serum cholesterol 200 mg./100 ml., with normal lipid pattern; serum electrolytes normal; serum calcium 9·0 and serum inorganic phosphorus 3·4 mg./100 ml.; and 24-hour urine calcium was 56 mg. Faecal fat excretions varied between 13 and 23 g./day at the above serum bilirubin level. *X*-ray examination of