Wood (1949). This high γ-globulin, which may be a reflection of antibody formation, probably accounts for the abnormal liver-function tests. γ-globulin has also been shown to increase the E.S.R. (Hardwicke and Squire, 1952), which in this case remained high long after clinical recovery, and made it, therefore, an unsatisfactory index of progress.

The successful treatment of localized actinomycosis with antibiotics has been widely reported, but recovery after pyaemic dissemination seems to be extremely rare. *A. israeli* is sensitive to penicillin and rarely develops resistance (Boand and Novak, 1949); streptomycin resistance usually develops rapidly. Sulphonamides are usually given with penicillin, although there is no direct evidence of synergistic action between these substances. In the present case penicillin and sulphatriad were used in combination for six months; the streptomycin given in the seven days before the identity of the organism was established had little effect. Several cases have been reported, however, of the successful use of streptomycin in those rare instances in which the strain is penicillin-resistant (Torrens and Wood, 1949; Pemberton and Hunter, 1949). The majority of strains of *Nocardia* are penicillin-resistant (Drake, 1946), but have been shown to be highly sensitive to sulphonamides and moderately sensitive to streptomycin (Glover *et al.*, 1948).

Summary

A case of generalized pyaemia with miliary pulmonary infiltration due to *Actinomyces israeli* is described.

The organism, described in detail, was unusual in showing free growth in aerobic culture in CO_2.

During the illness gross abnormalities of the serum proteins were observed by electrophoresis on paper strips.

The patient was treated with penicillin and sulphonamides for six months and made a full recovery.

We wish to acknowledge our gratitude to Dr. Ernest Bulmer for permission to publish this case, to Mr. V. Brookes for the surgical details, and to Dr. J. Hardwicke, in receipt of a Medical Research Council grant in the Department of Experimental Pathology, University of Birmingham, for the detailed protein studies.

REFERENCES

Benbow, E. P., Smith, D. T., and Grimson, K. S. (1944). *Amer. Rev. Tuberc.*, **49**, 395.
Biggart, J. H. (1934). *Johns Hopk. Hosp. Bull.*, **54**, 165.
Boand, A., and Novak, M. (1949). *J. Bact.*, **57**, 501.
Cope, Z. (1938). *Actinomycosis*. London.
Drake, C. H. (1946). *J. Bact.*, **51**, 199.
Glover, R. P., Herrell, W. E., Heilman, F. R., and Pfuetze, K. H. (1948). *J. Amer. med. Ass.*, **136**, 172.
Harbitz, F., and Grondahl, N. B. (1911). *Amer. J. med. Sci.*, **142**, 386.
Hardwicke, J., and Squire, J. R. (1952). *Clin. Sci.*, **11**, 333.
Holm, P. (1950). *Acta path. microbiol. scand.*, **27**, 736.
Israël, J. (1878). *Virchows Arch. path. Anat.*, **74**, 15.
Kay, E. B. (1948). *Amer. Rev. Tuberc.*, **57**, 322.
Kirby, W. M. M., and McNaught, J. B. (1946). *Arch. intern. Med.*, **78**, 578.
Kunkel, H. G., and Tiselius, A. (1951). *J. gen. Physiol.*, **35**, 89.
Marrack, J. R., and Hoch, H. (1949). *J. clin. Path.*, **2**, 161.
Morris, E. O. (1951). *J. Hyg., Lond.*, **49**, 46.
—— (1952). Thesis, Department of Bacteriology, University of Birmingham.
Pemberton, H. S., and Hunter, W. R. (1949). *Lancet*, **1**, 1094.
Peters, J. P., and Van Slyke, D. D. (1932). *Quantitative Clinical Chemistry*, **2**, 697. London
Shrewsbury, J. F. D. (1928). *Bgham med. Rev.*, **3**, 372.
Sullivan, H. R., and Goldsworthy, N. E. (1940). *J. Path. Bact.*, **51**, 253.
Torrens, J. A., and Wood, M. W. W. (1949). *Lancet*, **1**, 1091.
Weed, L. A., and Baggenstoss, A. H. (1949). *Amer. J. clin. Path.*, **19**, 201.
Weichselbaum, T. E. (1946). Ibid., **16**, Tech. Sect. 40.

At the official opening of the 38th Nurses and Midwives Conference and Exhibition in London on October 12, Mrs. Iain Macleod said that, although there were more nurses in the Health Service than ever before (147,000 full-time and 27,500 part-time, as compared with 118,000 and 17,000 respectively in June, 1948), there was still a great need for more nurses in mental hospitals and tuberculosis wards. This difficulty was being partly overcome, as more nurses were now being trained in sanatoria, but there was still a shortage in mental institutions.

ACTION OF THIOURACIL AND THYROXINE ADMINISTRATION ON ADRENAL FUNCTION

BY

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Many recent studies have shown a relation between adrenal and thyroid functions, though its nature has not yet been defined. Depression of thyroid has been found when the adrenal is stimulated by A.C.T.H., by stress, or by adrenaline, or when cortisone is given; a few authors have reported benefit to the exophthalmos of Graves's disease from cortisone administration,[1 26] which others deny.[27 28 29] On the other hand, in Addison's disease thyroid function is apparently also low, as shown by basal metabolic rate (B.M.R.), by plasma-protein-bound iodine (P.B.I.), and by radio-iodine uptake[1 25]; when such patients are given cortisone there is initially thyroid stimulation, but later thyroid depression.[25] In myxoedema are usually found low indices of adrenal function, low urinary 17-ketosteroids, low urinary reducing and formaldehydogenic steroids, and impaired eosinophil response to A.C.T.H.[1 4 5 6 24]; and partial correction of these abnormalities has sometimes been reported after treatment.[1 7] In thyrotoxicosis, involvement of the adrenal function has been long suspected, but its nature and its degree are still ill defined: 17-ketosteroid excretion is usually below normal in that condition[4 5 7]; the excretion of reducing steroids is said to be raised,[5 6] but low formaldehydogenic steroid output has been reported.[8] In animals, thyroxine administration has been found to induce a hypertrophy of the adrenal cortex.[9 10 12 13 17] Thiouracil or thyroidectomy is said by most authors to cause an atrophy of the adrenal cortex,[9 10 11 12 13 14 16 18 19 20] though a few have observed no change.[15 21 22]

This paper reports some measurements of adrenal function in thyrotoxic patients, both when untreated and after control by thiouracil. To assist in differentiating any effects due solely to the thiouracil, and not dependent on its effect on thyroid function, similar measurements have also been made in patients with primary myxoedema and in one normal subject at two or more levels of thyroid dosage.

Procedure

The thyrotoxic patients were first tested in hospital untreated, and then again when the thyrotoxic features had subsided—that is, after three to six weeks' treatment and while still receiving methylthiouracil. Five out of 10 patients received methylthiouracil, 200 mg. thrice daily; the remaining five had this dosage plus L-thyroxine, 0.45 mg. daily, and 10 mg. of potassium iodide daily. The pre- and post-treatment test procedures were planned to be an identical sequence, and were performed as follows: the patients were kept in hospital for two to three days; on the first morning, after a night's rest in hospital, the first 24 hours' collection of urine was started and the eosinophil depression test with A.C.T.H. carried out. The next morning the second 24 hours' collection of urine was started, and the eosinophil depression test with adrenaline performed.

The treated myxoedematous patients under full thyroid treatment were tested in the same way on what had been

established as the maintenance dose (thyroid, 1–4 g. (65–250 mg.) a day). They were again tested after three to six weeks' treatment with an increased thyroid dosage (usually doubled dosage).*

The untreated myxoedematous patients were also tested in the same way before institution of the treatment and after about three weeks on thyroxine, 0.1 mg. a day.

One normal subject was tested for three weeks before and after 500 mg. of "thyranon" daily, which led to symptoms of overdosage (tachycardia, sweating, nervousness, and some loss of weight). The B.M.R. rose from −1% to +30%, and the plasma cholesterol fell from 295 to 145 mg. per 100 ml.

The Patients

Nine of the 10 thyrotoxic cases (seven female, three male) were uncomplicated, typical, and clinically obvious; the other had thyrotoxic myopathy. The diagnosis was confirmed in all by the B.M.R. estimation, the urinary radio-iodine excretion test, and the subsequent therapeutic response.

The nine treated myxoedema patients (eight female, one male) had been previously diagnosed as typical instances of severe primary myxoedema. At the time of the study they had been on a fixed and apparently optimal dosage of thyroxine for months and did not show any features of thyroid deficiency. The three untreated myxoedema patients were also typical instances of severe primary myxoedema.

Test Methods Used

Eosinophil Depression Test.—Carried out during the morning. Capillary blood was taken before and four hours after an injection of 25 mg. A.C.T.H. intramuscularly, and stained with a mixture of two-thirds of phloxine, and one-third of methylene blue diluted in 50% water and 50% propylene glycol. Each sample was counted eight times in Fuchs-Rosenthal cells. The patients fasted from the preceding evening, but the last cases were allowed to eat their breakfast after the A.C.T.H. injection and then fasted during the following four hours, the test being performed in the same condition before and after treatment. The Thorn adrenaline test was usually performed with 0.4 mg. of adrenaline subcutaneously the following day.

17-ketosteroids.—The method used resembles in all essentials that recently published by the M.R.C. Committee on Clinical Endocrinology.[30] Ethanolic potassium hydroxide stabilized with ascorbic acid[31] was used for the colour reaction; all readings of optical densities were made on the Hilger-Spekker absorptiometer, using Ilford 604 and 601 filters; the colour correction equation of Talbot *et al.*[32] was applied. Readings were made against a reagent blank. The standard used was an ethanolic solution of dehydro-*iso*-androsterone. At least two determinations were performed before and after treatment or modification of the treatment; but, whenever possible, more determinations were made if too much discrepancy between our creatinine figures made us suspect mistakes in collection of urine.

Results

Thyrotoxic Patients Tested Before and After Treatment with Methylthiouracil (see Table).—The pre-treatment 17-ketosteroids were low normal (from 14.9 to 2.48 mg.), but the post-treatment levels were significantly lower (T, 3.11; P, under 0.02). The pre-treatment eosinophil depression after A.C.T.H. was normal in nine out of ten, but after treatment the fall was diminished in seven out of nine, though not significantly so. No consistent change was discernible in the eosinophil depression test with adrenaline or in the levels of excretion of reducing steroid. It is worth pointing out that none of these patients except one showed any features of hypothyroidism at the second test.

Myxoedematous Patients, under Apparently Adequate Thyroid Treatment Tested Before and After an Increase in Thyroid Dosage (see Table).—In eight of the nine patients, judged clinically to be euthyroid, the initial 17-ketosteroid excretions were surprisingly low; the tests after the higher dosage gave a higher mean value which was not statistically significant. The initial eosinophil depression with A.C.T.H. was slight in three out of nine, and abnormally slight in one out of nine. On the higher dosage, in eight out of nine the eosinophil depression was greater, though again not statistically significant. The changes in eosinophil depression with adrenaline or in the excretion of reducing steroids were less consistent.

Some Measures of Adrenal Function before and after Treatments Raising or Lowering Thyroid Function

Group	No. of Cases	Pretreatment Tests of Adrenal Function*				Change in these after Treatment† (Untreated—Treated)			
		Urinary 17-ketosteroids	Reducing Steroids	Eosinophil Depression 0–4 Hours		17-ketosteroids	Reducing Steroids	Eosinophil Depression 0–4 Hours	
				25 mg. A.C.T.H.	Adrenaline			25 mg. A.C.T.H.	Adrenaline
Thyrotoxicosis (before and after thiouracil)	10	7·8 (2·5–14·9)	4·19 (2·0–6·7)	63·2% (35–73%)	58·2% (36–77%)	−1·5‡ (fall in 9/10)	−0·5 (fall in 3/6)	−9·6 (fall in 7/9)	−1·3 (fall in 5/7)
Treated myxoedema (before and after extra thyroid)	9	4·5 (2·19–9·16)	4·10 (3·37–4·90)	54·5% (18–74%)	50·3% (20–64%)	+1·06 (rise in 6/9)	−0·5 (rise in 2/3)	+5·9 (rise in 8/9)	+4·3 (rise in 5/9)
Normal subject (before and after excess thyroid)	1	12·2	—	45%	11%	+4·95	—	+5	−9
Untreated myxoedema (before and after thyroid)	3	2·78 (1·15–4·40)	2·30	42% (26–54%)	40%	+1·05 (rise in 3/3)	+1 (rise in 1)	+19 (rise in 3/3)	+19 (rise in 1)

* Mean value and (range) shown. † Mean value and (number showing same trend) shown. ‡ Fall significant: T=3·11; P<0·02.

The clinical reactions of the nine patients to the raised dosage of thyroxine were variable, but six of them showed slight clinical features of hyperthyroidism. The B.M.R. increased slightly and the blood cholesterol fell in all but one.

Normal Subject Tested Before and After Large Doses of Thyroid.—The eosinophil depressions were slightly subnormal before treatment, and changed little after thyroid administration; both tests were repeated, with similar findings. The 17-ketosteroids rose after the thyroid administration.

Untreated Hypothyroid Patients Given Small Doses of Thyroxine (see Table).—The pre-treatment 17-ketosteroids were very low; after treatment slight rises were observed in two out of three patients. The pre-treatment eosinophil depression was below normal in two of the three patients; after treatment the eosinophil depression following A.C.T.H. was greater in all three.

Discussion

In general, in this study there has been agreement between the 17-ketosteroid and A.C.T.H. eosinophil depression tests: where one has decreased the other has usually also done so. However, the adrenaline eosinophil depression test and particularly the urinary reducing steroid assay have

*Four patients went from thyroid 200 to 400 mg. (3 to 6 gr.) a day; three from thyroid 50 to 200 mg. a day; one from L-thyroxine 0.3 to 0.6 mg. a day; and one from thyroid 65 to 200 mg. (1 to 3 gr.) a day.

given variable and inconsistent results. All our reducing steroid results have been in the normal range,[23] and differences between two extracts of the same urine, or from day to day, have been commoner than as the result of treatment.

These tests suggest a fall in adrenal function when the thyrotoxic patients have been treated with methylthiouracil; the group is small, but the fall in 17-ketosteroids is significant and that in the A.C.T.H. eosinophil depression approaches significance in the small group. Further, when extra thyroid has been given, either to one normal or to nine myxoedema patients on a maintenance thyroid dosage, the opposite trend has usually been seen, though the changes are not significant in these small groups. Thus a lowering of raised thyroid function towards normal levels apparently causes an immediate decrease of adrenal function; and the change observed with the thyrotoxic patients is probably not merely a non-specific effect of the thiouracil. No such non-specific effect of thiouracil on the adrenal has been seen in animals, for with animal experiments it has been observed that the simultaneous administration of thyroxine prevents the adrenal atrophy seen with thiouracil.[9 13 19]

Our results with the few untreated myxoedema patients conform to those already published[1 7]—an increase of the lowered ketosteroid excretion and eosinophil depression. Thus our findings suggest that the immediate effect of raising thyroid function is to stimulate the adrenal cortex, and of lowering thyroid function to depress it. The low 17-ketosteroid excretion of thyrotoxicosis suggests that prolonged hyperthyroidism may have a different effect.

Summary

When 10 thyrotoxic patients were tested before and after control with thiouracil 17-ketosteroid secretion fell significantly and eosinophil depression after A.C.T.H. also fell, though not significantly.

When extra thyroid was given to nine myxoedema patients on a basic maintenance dosage and to one normal subject 17-ketosteroid excretion and eosinophil depression after A.C.T.H. rose, but not significantly.

In three untreated myxoedema patients 17-ketosteroid, and eosinophil depression after A.C.T.H., rose slightly following a few weeks of the initial thyroid dosage.

I am greatly indebted to Dr. Russell Fraser for allowing and helping me to carry out this study at the Postgraduate Medical School of London; and to Dr. C. L. Cope, Dr. W. Klyne, Dr. R. Haslam, and Miss I. Broadbent for advice in various chemical matters. I wish to thank Dr. Fanard for a gift of thyranon; I am also grateful for the co-operation of the nursing staff, who made adequate urine collection possible.

References

[1] Hill, S. R., Reiss, R. S., Forsham, P. H., and Thorn, G. W., *J. clin. Endocr.*, 1950, **10**, 1375.
[2] Paschkis, K. E., Cantarow, A., Eberhard, T., and Boyle, D., *Proc. Soc. exp. Biol., N.Y.*, 1950, **73**, 116.
[3] Selye, H., *J. clin. Endocr.*, 1946, **6**, 117.
[4] Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H., and Reifenstein, E. C., Ibid., 1941, **1**, 234.
[5] Shadaksharappa, K., Calloway, N. O., Kyle, R. H., and Keeton, R. W., Ibid., 1951, **11**, 1383.
[6] Talbot, N. B., Wood, M. S., Worcester, J., Christo, E., Campbell, A. M., and Zygmuntowicz, A. S., Ibid., 1951, **11**, 1224.
[7] Engstrom, W. W., and Mason, H. L., Ibid., 1944, **4**, 517.
[8] Daughaday, W. H., *et al.*, Ibid., 1948, **8**, 166, 244.
[9] Florentin, P., Martin, R., and Sadoul, P., *C.R. Soc. Biol., Paris*, 1947, **141**, 177.
[10] Deane, H. W., and Greep, R. O., *Endocrinology*, 1947, **41**, 243.
[11] Baumann, E. J., and Marine, D., Ibid., 1945, **36**, 400.
[12] Pekkarinen, A., and Hortling, H., *Acta endocr., Kbh.*, 1951, **6**, 193.
[13] Freedman, H. H., and Gordon, A. S., *Proc. Soc. exp. Biol., N.Y.*, 1950, **75**, 729.
[14] Zarrow, M. X., and Money, W. L., *Endocrinology*, 1949, **44**, 345.
[15] Williams, R. H., Weinglass, A. R., Bissell, G. W., and Peters, J. B., Ibid., 1944, **34**, 317.
[16] Arvy, L., and Gabe, M., *C.R. Soc. Biol., Paris*, 1946, **140**, 945.
[17] Wallach, D. P., and Reineke, E. P., *Endocrinology*, 1949, **45**, 75.
[18] McClosky, W. T., Lillie, R. D., and Smith, M. I., *J. Pharmacol.*, 1947, **89**, 125.
[19] Glock, G. E., *Nature, Lond.*, 1945, **156**, 508.
[20] Kowalewski, K., and Bastenie, P. A., *Ann. Endocr., Paris*, 1950, **11**, 284.
[21] Leblond, C. P., and Hoff, H. E., *Endocrinology*, 1944, **35**, 229.
[22] Glock, G. E., *J. Endocr.*, 1949, **6**, 6.
[23] Cope, C. L., and Bain, M., *Clin. Sci.*, 1951, **10**, 161.
[24] Statland, H., and Lerman, J., *J. clin. Endocr.*, 1950, **10**, 1401.
[25] Thorn, G. W., Forsham, P. H., Bennett, L. L., Roche, M., Reiss, R. S., Slessor, A., Flink, E. B., and Somerville, W., *Trans. Ass. Amer. Phys.*, 1949, **62**, 233.
[26] Lederer, J., and Hambresin, L., *Ann. Endocr., Paris*, 1950, **11**, 634.
[27] Koepf, G. F. Quoted by G. W. Thorn *et al.* in *New Engl. J. Med.*, 1950, **242**, 865.
[28] Engel, F. L. Discussion of Reiss *et al.*: "Adrenal Thyroid Relationship." *Proceedings of the First Clinical A.C.T.H. Conference*, edited by John R. Mote, p. 203. Blakiston, Philadelphia, Pa., 1950.
[29] Fredrickson, D. S., Forsham, P. H., and Thorn, G. W., *J. clin. Endocr.*, 1952, **12**, 541.
[30] Medical Research Council, *Lancet*, 1951, **2**, 585.
[31] Wilson, H., and Carter, P., *Endocrinology*, 1947, **41**, 417.
[32] Talbot, N. B., *et al.*, *J. biol. Chem.*, 1942, **143**, 211.

A TUBERCULIN SURVEY IN STOKE-ON-TRENT

BY

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Tuberculin surveys of the population of the United Kingdom have been performed sporadically, usually on small and selected samples, over the last 30 years or more. Following a decision of the Ministry of Health authorizing the use of B.C.G. vaccine, the Medical Research Council organized a survey on a national scale to estimate the incidence of natural primary tuberculous infection in young people before the results of tuberculin-testing could be materially affected by the widespread use of B.C.G. vaccine.

The M.R.C. report (1952) describes in detail the organization of the survey, and Stoke-on-Trent was one of the 22 areas chosen for the test, which was carried out during the winter months of 1949–50. The present paper is an account of the findings in Stoke, and special attention has been given to the factors peculiar to the district which it is felt had a bearing upon the results obtained.

Present Survey

Stoke is an urban district some 10 miles by 4 in rural surroundings. The density of the population in 1949 was given as 13.05 persons per acre, but this figure is misleading, as a good deal of agricultural land is included in the city's boundary: in the 28 wards of the city it ranges between 4.82 and 37.15 per acre. The area covered by this survey and known collectively as the "Potteries," comprising the townships of Tunstall, Burslem, Hanley, Stoke, Fenton, and Longton, is highly industrialized. Housing is mainly of the small four-roomed terraced type, in which serious overcrowding is common. Among a variety of industries there are two in which the bulk of the population is engaged—pottery manufacture and coal-mining: in 1948, of a total population of 274,500, 56,000 were employed in the former and 15,000 in the latter. Both these occupations are attended by a serious although decreasing risk of pneumoconiosis, often complicated by pulmonary tuberculosis.

About half the people employed in the pottery industry are exposed to dust contamination, and of those who develop silicosis half may be expected sooner or later to become infected with tuberculosis. Approximately 750 cases of silicosis are existent at one time, and about 60 new cases are reported each year. Death from silico-tuberculosis is almost the normal termination of the disease in potters. Pneumoconiosis in miners is less often attended by superimposed open tuberculosis, and death from the combination of the two conditions is less common. There is thus a potential source of infection, especially in potters, which is peculiar to the district. It seemed that this was a factor