

arteries. The cardiac enlargement is presumably secondary to the hypertension present in this condition."

The prospective recruit was examined by Lt.-Col. Walter H. Scott, the medical consultant for the Edmonton district, and I am indebted to him for the following copy of his notes: "No history of illness. Has done hard work all his life making ties. Examination shows forcible pulsations visible and palpable in neck and arms. Whole neck pulsates. Cardiac enlargement. Systolic murmur at all valves but faint at apex, tricuspid and aorta, and long and louder at pulmonic cartilage. Blood pressure: left arm 185/100; left leg 120/100; right arm 200/120; right leg 115/100. Systolic murmur well heard at apices of both lungs posteriorly. Summary. Coarctation of the aorta. Unfit."

**Comment.**—Case 2 is almost a repetition of Case 1. The condition was accidentally found during an x-ray examination of the chest done with no thought of coarctation being present. The diagnosis was based in Rösler's sign of erosion of the ribs. A clinical examination done later confirmed the x-ray diagnosis by discovering visible and palpable pulsations due to the dilated collateral anastomosis, hypertension in the upper extremity and disparity between the blood pressures of the brachial and femoral arteries.

The roentgenogram of this case shows a prominent bulb.

The case report supplied by Dr. Malcolmson was also of a recruit. He showed the pathognomonic rib defects in the roentgenogram and had secondary cardiac enlargement. Physical examination discovered marked hypertension in both arms with a much lower tension in the femoral arteries. Bruit was easily detected over the anastomosing branches in the scapular and upper thoracic areas.

This case is almost a duplicate of Case 2 above.

The condition had been overlooked in the first routine medical examination upon application.

#### SUMMARY

- Coarctation of the aorta is one of the more rare anomalies of the cardiovascular system. Although present during infancy and childhood it usually does not become manifest till adolescence or early adult life.

- The most important change occurring in the vascular system is the development of a collateral circulation between the proximal and distal aortic segments. This is chiefly by the scapular, mammary and intercostal arteries.

- Clinically, the condition is diagnosed by the hypertension in the upper portions of the body contrasted with hypotension in the lower, coupled with evidence of dilated collateral arteries.

- Radiologically, the findings of smooth notching in the inferior surfaces of the ribs is pathognomonic. This so-called Rösler's sign is not present in all cases. It is due to the dilated tortuous intercostal arteries which take part in the collateral circulation.

- Three cases of coarctation of the aorta discovered accidentally and confirmed by subsequent clinical examination are reported.

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### HYPERTHYROIDISM TREATED BY OESTROGENS

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IN 1933 Benazzi<sup>1</sup> found that an oestrogen administered to young rats induced an inactive phase in their thyroids. He pointed out that several Italian physicians had treated Grave's disease successfully, even before that time, by the use of oestrogens. Karp and Kostkiewicz<sup>2</sup> found colloid degeneration of the thyroid gland in rabbits similarly treated. Heyl, de Jongh and Kooy<sup>3</sup> observed decreased thyroid activity in the human subject after injections of an oestrogen and ascribed this effect to a decreased secretion of the thyrotropic hormone from the anterior pituitary. This explanation has been

confirmed since by other workers. From all the foregoing it appeared to one of us (E.V.S.) that there might be some justification for a trial of oestrogenic therapy in the preoperative management of a patient preparing for her third operation for exophthalmic goitre.

#### CASE 1

Mrs. J.J., aged 25 years, was first seen in the Endocrine Clinic at Victoria Hospital on September 19, 1936. She had had a bilateral ligation of the thyroid vessels in August, 1930. The operative wound became infected and drained for months. After preparation with Lugol's iodine for two weeks, she had had the right lobe removed at a second operation in October, 1932. In March, 1936, her hyperthyroid

symptoms recurred one month after her second still-birth (this one was ascribed to *placenta prævia*). She was put on Lugol's iodine on May 4th, and this was continued until her third operation on December 2, 1936. When seen by us in September she exhibited marked exophthalmos, restlessness, tremor, hyperactive reflexes, undue perspiration and she had lost a good deal of weight in the preceding months. She tired readily, but there was no undue cold tolerance.

An electrocardiogram in May had shown a normal sinus rhythm and a sinus tachycardia of 125. This pulse rate had not decreased in the interval—when we saw her it was 152. Her weight was 132. On October 1st her basal metabolic rate was plus 20. On October 6th her blood oestrogen was negative,<sup>4</sup> and accordingly she was given 10,000 international units of progynon B hypodermically each week. On October 20th, her weight was 134, pulse 136, and she "felt 100 per cent better". The progynon B was given twice as often thereafter. On November 2nd, her basal rate was still plus 25, but her pulse rate was only 92 and her weight was still 134 pounds. On November 5th an iodine tolerance test showed a lower curve than normal. For example, in 30 minutes there was 65 per cent of iodine in the blood, in two hours only 1 per cent, and in four hours none remained. On November 27th she was admitted to hospital. On the 29th her non-protein nitrogen was 31, her blood sugar 88, her blood count was normal, her blood pressure was 135/78, basal rate plus 24, and weight 133½ pounds. The thyroidectomy was performed on December 2nd. Her convalescence was uneventful. On December 29th her basal rate was plus 11 and on January 8, 1937, it was

minus 6. By that time she had developed constipation and had an undue heat tolerance and other evidences of hypothyroidism. On April 13, 1937, her weight was 141 pounds and her pulse 100. In July, 1937, her basal rate was minus 1 and her weight 136. In June, 1938, she completed a normal pregnancy. She seemed quite well in June, 1940, except for residual exophthalmos, and her energy was sufficient to take adequate care of her child.

At each operation the gross appearance of the gland was that of exophthalmic goitre. The appended microphotographs illustrate the differences between the appearance of the gland at the last two operations. This appears to be the only illustration of a human thyroid gland after oestrogen treatment that has been published; it corresponds closely to the picture of the rabbit thyroid gland similarly treated by Karp and Kostkiewicz. In the 1936 gland there is much more uniform distribution of colloid in the acini and the lining cells are cuboidal rather than the tall columnar seen in the earlier (1932) gland. There were many more lymph nodes throughout the 1936 gland and these were larger. There were scarcely any hyperplastic areas to be seen, in contrast to the picture in the gland in 1932, which showed many large areas of intense hyperplasia.

Before our study of this case had been completed, both Spence<sup>5</sup> and Cookson<sup>6</sup> reported small series of such hyperthyroid patients treated by oestrogens. They, too, found some decrease in the pulse rate and an increase of body weight, but observed no change in basal rate, exophthalmos, size of the thyroid, tremor or skin moisture. Both concluded that there was little to recommend this therapy. Later, Donald<sup>7</sup> used oestrogens preoperatively on three hyperthyroid women and obtained considerable improvement as a result. Jonas and Markalous<sup>8</sup> reported that hyperthyroid women having menstrual irregularity had a decreased output of oestrogens in the urine and were helped both with respect to the goitre and the menses by the administration of oestrogens. Goldman and Kurzrok<sup>9</sup> treated seven menopausal hyperthyroid women with large doses of oestrogens. Their protocols show definite help in only one or at most two of this group. The animal work of Benazzi and others cited above has since been amply confirmed by Gessler, Zain, and Sherwood.

We have recently seen other hyperthyroid patients whose clinical histories suggest that a favourable effect can sometimes be obtained by the use of oestrogens.

#### CASE 2

Mrs. J.C., 50 years old. Her hyperthyroid symptoms dated back about 12 years. In May, 1936, her first thyroidectomy was done. However, by November, 1937, her symptoms had recurred, with a basal rate of plus 75, and a second thyroidectomy was performed. She then felt well until December, 1939, when she lost 14 pounds in weight very quickly and was put on Lugol's iodine, which she continued until June, 1940. She was first seen by one of us (E.V.S.) on December 9, 1940. At that time there was no palpable thyroid gland, the pulse was small and the pulse rate 104.

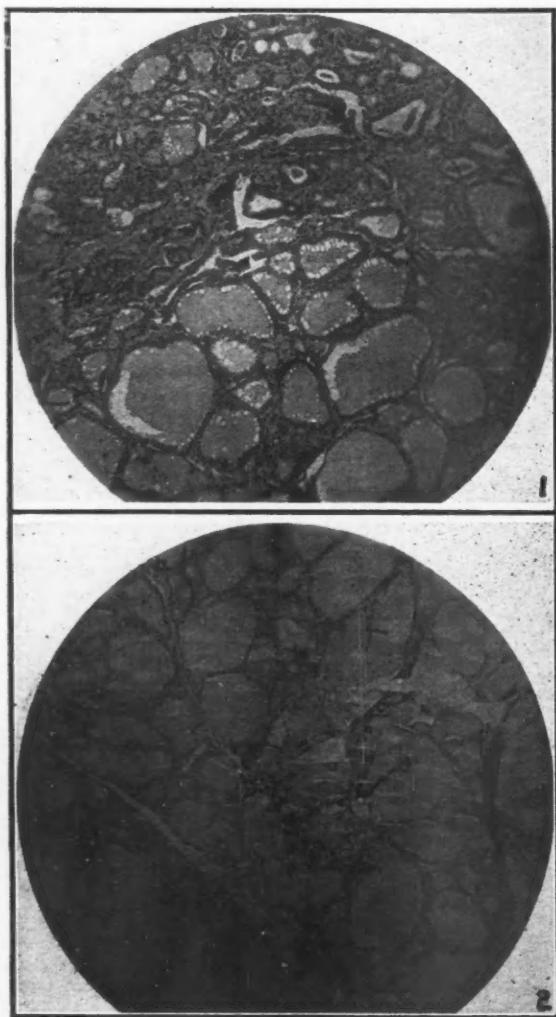


Fig. 1.—1932 gland. Fig. 2.—1936 gland.

There was considerable exophthalmos with poor convergence and much lid lag. There was a fine tremor of the hands. She had had menorrhagia all her life, it should be noted in passing. Her basal rate was plus 45, her weight was 157 pounds, and her blood oestrogen was positive. She was given 50,000 rat units of progynon B twice weekly for four doses, despite this last finding. After each injection she felt very weak for about a day and a half, and became equally apathetic mentally. Then she was put on two milligrams of stilbæstrol (B. & W.) each day. She observed an increased urine output, as has been seen to occur after the administration of estrogens to eclamptics.<sup>10</sup> On December 19th her weight was 162 pounds. On January 10, 1941, her weight was 166, she was very tired and depressed, but she had stopped perspiring, had much less tremor, was constipated, and had a normal pulse rate. On the 13th her basal rate was plus 22, and her weight was still 166 pounds. An attempt was made to maintain her thereafter on one milligram of stilbæstrol per day as it was suspected that the first dose had been excessive and had thrown her into too marked a hypothyroid state. She was enthusiastic about her improvement and gained three pounds which she has held since.

In February, 1941, she fractured her tibia. She continued her stilbæstrol but began to bleed vaginally. This went on intermittently until she was given an x-ray menopause on May 2nd. It was necessary to adjust her stilbæstrol dosage because of nausea, and finally it was changed to ovocyclin, 0.5 mg. per day. If she got more than 0.5 mg. of ovocyclin she became dizzy and more than 1 mg. of stilbæstrol she was nauseated. She felt very, very weary all the time, but could tolerate the hottest summer weather without discomfort. Her weight remained at 165. Her basal rate on June 9th was plus 11. Her pulse rate varied greatly, from 90 to 150. She was digitalized finally, but the pulse was still very erratic and variable. There was no further vaginal bleeding and no subjective menopausal reaction to the x-ray treatment. Her blood pressure throughout remained at about 190/90. On July 7th her basal rate was plus 30, and she said she felt "too tired to live". She contended that the lack of energy was worse than the palpitation and heat intolerance of her worst hyperthyroid state. She was told that she must make that choice.

### CASE 3

Mrs. W.H., aged 62 years. She had had increasing evidence of recurrent hyperthyroidism for three years past together with a weight loss of 10 pounds. She had had x-ray therapy to the thyroid gland in 1927 and had experienced considerable relief thereafter. She was first seen by Dr. C. K. Stuart on January 14, 1941, complaining of an itchy area of psoriasis on the right lower leg. At that time she had dyspnoea on exertion, had had constant palpitation of the heart for the previous three years (worse in the last six months) and definite heat intolerance. She flushed readily and felt weak. She had no exophthalmos. Her blood pressure was 220/118 and her pulse rate 108. Her heart was enlarged to the left. Her hands were always warm. The thyroid gland was bilaterally enlarged and the lower poles could not be felt on either side. There was a tendency to stare and a fine hand tremor. There was slight œdema of the legs. Her blood oestrin was positive, her basal rate was plus 35, her white count 3,500, and red count 3,900,000. Her weight was 122 pounds.

She was given 50,000 international units of progynon B intramuscularly and then put on two milligrams of stilbæstrol per day for six days, with one milligram a day thereafter. On February 4th her weight had risen to 129, her pulse was 86 and her blood pressure 230/108. She said she felt stronger and had lost the palpitation of the heart she had felt steadily for months past. Her hands were cold and dry. She was given Lugol's iodine, ten minims three times a day. Her improvement has been maintained since.

### CASE 4

Mr. G.P., aged 29 years. This man was first seen April 15, 1941, giving a history of tremor, increased nervousness, palpitation of the heart, great fatigability, insomnia, and great heat intolerance, dating back a little more than a month. He had nycturia twice a night, polyuria and increased thirst. He had lost 20 pounds weight during this time, although his appetite had become enormous. His previous medical history was unimportant. Examination revealed nothing beyond some lid lag, a diffusely enlarged thyroid gland of about twice the normal size, a pulse rate of 120, blood pressure of 140/80, and a coarse tremor of the hands. There was nothing abnormal in the urine.

On April 22nd, a basal metabolic rate done at the Guelph General Hospital measured plus 42. His blood oestrin was strongly negative. His temperature occasionally rose to 99 during his nine days' stay in hospital under observation. His pulse fell to 90, his weight remained constant, he began to sleep well and lost some of his tremor in the hospital. His only treatment during this period was with 5 mg. of stilbæstrol per day. He was nauseated on this dose and so was given ovocyclin, 4.0 mg. per day, instead; 30,000 rat units of progynon B seemed to have about the same effect as this huge dose of oral oestrogen. On May 1st, when he was discharged, his basal rate was plus 24.

He was readmitted May 12th for thyroidectomy. He had continued up till this time to take his daily ovocyclin (œstrone). His pulse was 125. He had gained 8 pounds of weight. He seemed to be in good pre-operative condition. On the fourth day after admission he suddenly developed a left lower lobe pneumonia. In the next five days his ovocyclin was stopped and sulfathiazole controlled the pneumonia. Indeed in 48 hours after it was first given his temperature returned to normal and his pulse fell to 90. The thyroid gland shrank to about 50 per cent in size and became definitely nodular, his tremor and nervousness improved and he was discharged, since operation seemed unnecessary and even hazardous, on May 22nd, with a basal rate of minus 2.

He has been seen weekly since that time and has made slight, steady improvement. His daily ration of ovocyclin is unchanged. On July 16th he returned from a vacation during which he motored over 1,000 miles and camped in his own trailer. He gained 5 pounds, felt much improved, had a pulse of 90 to 100, a slight tremor—and his thyroid gland felt normal in both consistency and outline!

### DISCUSSION

All of these cases were ambulatory throughout our observation of them. Three had undergone previous unsuccessful surgical or roentgenological procedures, and presumably could be regarded as unusually difficult problems. The doses used in all but the last case were not huge and the clinical improvement was very prompt. Two had recently or concurrently had Lugol's iodine, but although this is unfortunate from the viewpoint of the observer, the clinical effect produced was very obviously not ascribable to the use of the iodine and occurred much too rapidly to be due to that. There was no change in exophthalmos and other eye symptoms or in any hypertension which existed, but all other symptoms and signs of hyperthyroidism subsided partially or completely. Two of these

patients already had high oestrogen values; apparently this was a compensatory effort of the organism in order to adjust itself to the thyroid assault upon it. The second case had demonstrated this high oestrogen level clinically for years both before and during her surgical phase by her consistent functional menorrhagia. We merely lent Nature help by raising the oestrogen level of these people still higher.

The second case must be regarded as a therapeutic failure; there were so many economic and domestic difficulties coincident with the residual hyperthyroidism that one could never tell what was thyroid improvement and what was less unhappiness, or what was dejection and what was weakness from overtreatment.

It is difficult to ascribe the regression of the thyroid gland in the fourth case to either the estrogens administered or to the drug used in treating the pneumonia. However, it is obvious that the oestrogens used had improved the hyperthyroid state even before the onset of the pneumonia. Further experience must settle the other problems raised by this unique case history.

The microscopic picture of the oestrogen-treated human thyroid appears to be so closely parallel to corresponding animal findings that there is good reason to expect that the clinical improvement secured in the human should be as thorough and prolonged as that seen in animals, if treatment is continued. All or nearly all endocrine therapy, of course, as in diabetes for example, needs to be kept up almost indefinitely to effect "cure".

It would seem that the therapeutic method used in this small group deserves further trial, at least in the preparation of hyperthyroid patients for operation, and in the pregnant woman where surgical complications are especially un-

desirable. It might be suggested here that the increased blood oestrogen level characteristic of advanced pregnancy may serve a useful purpose in controlling the tendency to hyperthyroidism suggested by the rise in basal metabolic rate in late pregnancy. It is remarkable that the latter so very rarely gives evidences of clinical hyperthyroidism.

#### SUMMARY

Three out of four hyperthyroid patients treated with oestrogens were improved.

The authors thank Dr. L. J. Fallis, Superintendent of Victoria Hospital, London, for permission to publish the case report of Mrs. J.J.; Schering's (Canada) for the progonon B; British Drug Houses of Canada for the stilboestrol; and the Ciba Company for the ovocyclin used in this study. Dr. G. K. Wharton collaborated in the management of the first case, and we are indebted to Dr. C. K. Stuart for the record of the third case.

N.B.—Patient 2 on November 10, 1941, had a blood pressure of 190/76. She had tried to stop her stilboestrol but found she felt worse and returned to it. She felt fairly well thereafter.

Patient 4 is now doing very heavy manual labour as a welder.

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**COST OF LIVING IN GERMANY.**—According to the official index for the cost of living in Germany (*Dtsch. med. Wschr.*, September 26, 1941, p. 1074) during July the prices of goods in daily demand were 1.5 per cent higher than in June. This increase is attributed to seasonal influences. The figure for the total cost of living in July was 136.1 (taking the cost in 1913-14

as 100) as against 134.1 for June. The figure for food rose from 130.6 in June to 134.2 in July—an increase of 2.8 per cent. This was ascribed to the more general use of new potatoes which were of course dearer than the old ones. The price of other fresh vegetables also increased. The cost of clothing rose from 158.1 in June to 158.7 in July—an increase of 0.4 per cent.—*The Lancet*.