down," accurately and precisely, these masked forms of tuberculosis in the eye, in the nose, in the larynx, and even in internal organs and systems, at a time when diagnosis is otherwise extremely difficult and treatment relatively easy. Certainly in such cases the effects of tuberculin used as a remedy by an expert are often magical in suddenness and completeness.

General hospitals, and some special hospitals, might help earnest students and suffering humanity by establishing a special ward and an out-patient department for the study of chronic tuberculosis in both its common and erratic forms.

ENDOCRINE IMBALANCE AND ITS RELATION TO CHRONIC ARTHRITIS.*

BY

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THE views and opinions of the ancient authorities before the days of cellular pathology and bacteriology are of distinct interest in the light of our present knowledge. Hippocrates laid down the axiom that "Gout never occurred in women until the menses had ceased." Trousseau¹ and Charcot² believed that chronic articular rheumatism was associated with the beginning and end of menstruation and with pregnancy. Orde,³ in 1879, suggested that there was evidence to show that there was some relationship between uterine disorders and rheumatoid arthritis—such as severe arthritis with dysmenorrhoea and arthritic paroxysms coincident with menstruation—views with which I am in full accord.

At all these stages in a woman's life considerable strain is being thrown on the endocrine glands. These glands begin to assert themselves in early foetal life, and as they have no function in respect of external relation, their secretions must be entirely occupied with internal regulation, so that from the first any endocrine defect must disturb the balance. In childhood the endocrine system retards maturity to give time for further development, and utilizes glands such as the thyroid, subsequently katabolic in action, in the service of active growth. As puberty advances, the retarding gland—the thymus—atrophies, and the katabolic glands, like the thyroid, take on their own action. During pregnancy all the endocrine glands are working at full capacity, though some are antagonistic to each other. This continues during lactation, whilst at the climacteric the ovarian hormone disappears and more work is thrown on the thyroid, which itself is on the down grade.

There are two groups of endocrine glands:

1. Parasympathetic or extended vagus—anabolic in action—the cell-islets in the pancreas, and the parathyroids.

2. The sympathetic—katabolic in action—adrenals, thyroid, and pituitary.

The rhythm of life largely depends on the fluctuating balance between these two.

All the ductless glands, especially those co-operating with the sympathetic nervous system, participate in the development of sexual characters, the thyroid and possibly the post-pituitary tipping the balance towards femininity, the adrenal cortex and the anterior pituitary towards virility. Thus the thyroid shows increased activity at puberty, the catamenia, marriage, and pregnancy, and undergoes partial involution at the climacteric.

There is a close association between the gonads and the pituitary: neither appears to be able to get on and develop without the help of the other. The internal secretion of the ovary stimulates the secretion of pituitrin, and the development of a corpus luteum in pregnancy checks this process on behalf of the foetus until the time for the uterus to contract and for the milk to flow.

Llewellyn⁴ first drew attention to the association of the endocrines and chronic rheumatism, especially of the chronic villus type occurring in women at the menopause, expressing views which have been corroborated by Ribierre,⁵ Rosen,⁶ H. K. Thompson,⁷ Cecil and Archer,⁸

and many others. At a discussion on climacteric arthritis⁹ the subject was considered under the wider term of "hypoglandular arthritis." It was pointed out that this condition of joints was by no means confined to women at the climacteric, but that it was seen in young women due to thyro-pituitary failure. Cumberbatch concluded that there is a type of arthritis closely associated with, if not entirely due to, disturbance of the endocrine function of the ovary, and gave the following reasons for these conclusions.

1. Some of the cases occurred in young women in whom the menstrual function was being established. They developed arthritis of the rheumatoid type and amenorrhoea occurred. There was no evident primary focus of infection. The application of diathermy to the interior of the pelvis brought the arthritis to an end and menstruation returned.

2. Other cases occurred in women at the other end of menstrual life. In many the climacteric commenced at an early date and menstruation ceased. In these, again, there was no evident primary focus of infection. The application of diathermy usually arrested the arthritis and menstruation recommenced, in the cases in which the onset of the climacteric was premature.

Robinson considered that arthritis is directly or indirectly due to inactivity of the corpora lutea of the ovary. This inactivity may occur at any time after puberty, and may or may not be associated with absence of menstruation. Heating the ovary by diathermy increases the activity of the ovarian function.

Returning to the view of Trousseau and Charcot that chronic arthritis is a disease associated with the commencement and cessation of menstruation and also with pregnancy, I have seen quite a number of young girls in their teens in whom the start of menstruation had been delayed, or who had had one or two periods and then stopped. They were large, fat, well-developed girls, who complained of pains in joints and muscles.

One girl, aged 12½, had for six months complained of pain in her right knee; she was listless, had never menstruated, and had all the appearances of thyro-pituitary deficiency. X rays showed a small rarefied area just beneath the articular face of the cartilage of the tibia. Her tonsils were found to be septic, and removal was advised; this was carried out, and thyroid in small doses was also given. This case did not begin to improve until six months after the enucleation, when she started to menstruate, pain ceased, and she resumed her previous activity. Her mother suffered from chronic villus arthritis of the menopause.

In another case the patient's mother suffered from Raynaud's disease, which was not of a severe type. This girl was very much like the previous case in appearance; she was over-developed, was affected by amenorrhoea, and the rheumatic condition was more in the nature of a fibrositis of the erector muscles of the spine, though there was some doubt as to the condition of the dorsal vertebrae as seen with x rays. When I first saw this patient she had had her tonsils enucleated about fourteen days previously and was in a markedly hyperthyroidic state, with rapid pulse, muscular tremor, and thyroid gland slightly enlarged.

Crammer¹⁰ remarks that "it is well known that acute infections are sometimes followed by symptoms which may not unreasonably be attributed to disturbances of the thyroid-adrenal function. The stimulation produced by these toxins may develop into a Graves's disease." The thyroid is one of the defensive agents against infection, and I believe in this case the removal of the septic tonsils produced a flooding with thyroxine, the patient having most probably been hypothyroidic before.

Langdon Brown¹¹ points out how frequently tonsillar sepsis may be a factor in producing hypothyroidism in childhood. We are familiar with the fact that tonsillar sepsis is likely to excite hyperthyroidism after puberty, but until the gland has experienced the activating effect of puberty—that is, before the gland has taken on its katabolic duties—it is apparently more easily exhausted than excited to over-activity. Once the thyroid has taken on its katabolic duties we find patients with all the symptoms of rheumatoid or atrophic arthritis—as, for instance, the young woman in the early twenties.

Llewellyn had frequently pointed out that the early symptoms of rheumatoid disease, prior to the development of joint swellings, are very similar to the secondary features of Graves's disease and also Raynaud's disease, and he believes that all these diseases are due to endocrine instability or imbalance. McCarrison had pointed out that in the goitrous regions of the Himalayas rheumatoid arthritis is very common.

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In my experience also I believe that a history of thyroid enlargement and rheumatoid arthritis is extraordinarily common. When you examine the patient there may be no evidence, but on inquiry into the past history it is astonishing how often you will get a history of goitre. I have recently had under treatment a case with the following family history.

Maternal grandmother suffered from goitre; mother had a goitre as a girl and died at 76, bedridden with arthritis, high blood pressure, and attacks of angio-neurotic oedema. The patient has three sisters—all of whom suffered from Graves's disease, one developing the disease a week after marriage. A brother was laid up for a long time, and it was thought he was going to develop Graves's disease, but he is now quite fit. The patient when 12 to 13 years of age had a very large goitre, and did not start menstruating until she was 17, when she had considerable dysmenorrhoea. At 19 the heart was said to be weak, and for the last few years she has suffered from tachycardia, auricular flutter, and fibrositis.

Association of Pregnancy with Rheumatoid Arthritis.

For years I have been struck with the fact that a patient with rheumatoid arthritis will give you the following history: that she became pregnant, and that during pregnancy she was very much better, but that during the puerperium all the symptoms returned with increased severity. This clinical fact has given me much thought. Now the thyroid is an active accelerator of metabolism, and its close connexion with reproduction is shown by its frequent physiological enlargement in the female—at puberty, marriage, and pregnancy, and sometimes at menstruation, and by its partial involution at the climacteric. During pregnancy great strain is thrown on the thyroid and the patient often becomes hypothyroidic for the time being. Then there is the association of the secretion of the corpus luteum and the pituitary, the internal secretion of the ovary stimulating the secretion of pituitrin; when the corpus luteum develops in pregnancy it checks this process in the interest of the foetus. Langdon Brown points out that the blood sugar curves of pituitary glycosuria and the glycosuria of pregnancy are similar, and suggests that the latter condition is due to pituitary disturbance, which is comprehensible, since pituitrin directly inhibits the action of insulin. This suggests that the normal holding up of pituitrin during pregnancy allows sugar to be stored up more readily in the interest of the offspring through the unchecked action of the insulin. Again, Cumberbatch and Robinson put forth the hypothesis that arthritis is directly or indirectly due to inactivity of the corpora lutea.

It is worth considering, therefore, whether the exhausted thyroid tends to reproduce the symptoms of rheumatoid disease, which have been held up in some way by the corpus luteum's inhibitory action on the posterior pituitary, and has thus restored the endocrine balance during pregnancy with amelioration of all the arthritic symptoms.

Arthritis of the Menopause.

The loss of the internal secretion of the ovary along with the partial involution of the thyroid produces a mild myxoedematous or hypothyroidic state. Clinically we know definitely that these cases improve with small doses of thyroid extract, some with the addition of ovarian extract and others with the addition of pituitary extract. I have particularly noticed how frequently these arthritic symptoms occur in cases where an artificial menopause has been induced and how improvement takes place under the above treatment.

Llewellyn¹² holds that there is a definite rheumatic diathesis due to endocrine instability, an instability which is observed in children and which is the forerunner of acute rheumatism. He bases his opinion on the following points, believing that:

1. The tendency of rheumatism to change its facies with the onset of puberty, the predilection of rheumatoid arthritis for the reproductive period and of osteo-arthritis and gout for the menopause or pre-senile epoch, suggest that the endocrine changes associated therewith account for the superficial diversity, but fundamental unity, of these affections.
2. Rheumatic children are all hypothyroidic.
3. Thyroid swelling very often ensues at the outset of acute rheumatism.
4. There is a definite geographical overlapping of goitre and acute rheumatism.

5. Acute rheumatism is an example of endocrine heredity. He quotes McCarrison: that the victims of simple toxic goitre are not only liable to Graves's disease, but, worse still, hand on to their children a condition of thyroid instability.

6. Both hypo- and hyper-thyroidism may follow acute rheumatism.

7. There is a higher incidence of rheumatism in goitrous than in non-goitrous children.

8. It is a clinical fact that some cases of acute rheumatism do not improve on salicylates until thyroid extract is added.

9. Subthyroidism spells suboxidation, and vasomotor instability implies irregularity in the supply and distribution of oxygen to the tissues.

Now, some may ask, where do infection and septic foci come in, and how is it that if you remove the septic foci the patient so frequently improves? The thyroid gland is one of the great defences against infection, and if the patient is already suffering from instability of the thyroid—either hypo- or hyper-thyroidism—the presence of an infective focus will not improve matters, and its removal may, and probably does, in many cases restore stability, in the same way as the removal of septic tonsils is so often the commencement of improvement in a case of Graves's disease.

Others may ask why it is that vaccines and protein shock are beneficial in these cases. Crammer answers this question when he says that the fact that many bacterial toxins stimulate the thyro-adrenal apparatus illustrates the curious and as yet unexplained phenomenon that in some infections the injection of non-specific vaccine, and even proteins, may have a striking therapeutic effect. The effect of the injection of these substances is to produce a typical rigor. The rationale of this so-called non-specific vaccine therapy, and protein therapy, would be that it elicits an increased functional activity from the thyroid adrenal apparatus—in fact, "sympathetic fever," which is one of the normal reactions of the organism against bacterial infection.

There is another point worthy of consideration—patients frequently tell us that their symptoms of rheumatoid arthritis commenced after a nervous shock, as an air raid, the death of a parent, an accident, etc. I have always believed that there is a psychological element in many cases of arthritis and endocrine imbalance, especially of the katabolic glands; their close association with the gonads supports this view. I have never been satisfied that septic foci were the sole causes of these diseases, but that behind it all there was a soil or diathesis which I believe to be connected with endocrine instability or imbalance.

REFERENCES.

- ¹ Troussseau: New Sydenham Society Publications, vol. iv, *Clinical Medicine*.
- ² Charcot: New Sydenham Society Publications, 1881.
- ³ Orde: Clinical Society, February, 1879.
- ⁴ Llewellyn: *Arthritis Deformans*, 1809.
- ⁵ Ribierre: *British Medical Journal, Epitome*, para. 323, December 13th, 1913.
- ⁶ Rosen: *Therapie der Gegenwart*, lviii, p. 81, 1917.
- ⁷ H. K. Thomson: *Boston Med. and Surg. Journ.*, April 2nd, 1925.
- ⁸ Cecil and Archer: *Journ. Amer. Med. Assoc.*, 1925, lxxxiv, 75.
- ⁹ Climacteric Arthritis, *Proc. Roy. Soc. Med.*, January, 1925.
- ¹⁰ Crammer: *Brit. Journ. Exper. Path.*, vol. vii, No. 3, p. 95.
- ¹¹ Langdon Brown: *The Endocrines in General Medicine*, 1927.
- ¹² Llewellyn: *Aspects of Rheumatism and Gout*, 1927.

SEA-SICKNESS AND ITS TREATMENT.

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SEA-SICKNESS in its milder forms may be regarded as an occasion for jesting by those whom it does not trouble, but for some sufferers its anticipation may poison the prospect of a voyage, and it may cause prolonged discomfort or even death. A woman, aged 40, rather debilitated by fever, travelling in a ship in which I was a passenger many years ago, died after ten days of continual vomiting which no treatment could check. Such a catastrophe may be rare, but cases occur too frequently where suffering is prolonged for many days and the patient is reduced to a state of extreme mental and physical prostration.

No age, no condition of life, is exempt. Old people going on a voyage for the first time, sailors who have used the