evacuate the greater part of the vitiated blood (in the dog a very considerable quantity of such venous and chloroform-charged blood comes away); and in the second place we reduce the resistance in the arterial system sufficiently to allow of the enfeebled heart resuming its beat. This method of combined artificial respiration and arterial bleeding would appear to be applicable not only to the treatment of chloroform collapse in man, but possibly also to the treatment of carbonic acid poisoning, drowning, and asphyxia. In the case of man, it would be well to divide both temporal arteries, and to allow the hæmorrhage to go on unchecked until a certain amount of arterIALIZED blood had run away.

In conclusion, it may not be inappropriate to direct the earnest attention of the practitioner to the eminent utility of preliminary injections of atropine as a means of preventing the fatalities which occur in the early stages of chloroform administration. This method, which was recommended originally by Dr. J. Harley,¹ but which was first placed on a scientific basis by Dastre and Morat, does not appear to have come into general use yet. The method is based upon perfectly sound physiological principles, inasmuch as it is directed to the prevention of the heart stoppage, which in the case of early chloroform collapse appears generally to be brought about by the inhibitory action of the vagus. The atropine² removes this source of danger by paralysing the nerve endings of the inhibitory fibres in the heart. In the case of dogs and rabbits, this atropine method is of almost absolute efficacy against the otherwise frequent fatalities of the early stage of chloroform administration.

SOME EFFECTS OF THYROIDECTOMY IN LOWER ANIMALS.³

By GEORGE R. MURRAY, M.A., M.B.CAMB.,
M.R.C.P.Lond.,

Heath Professor of Comparative Pathology in the University of Durham;
Pathologist to the Hospital for Sick Children, Newcastle-on-Tyne.

THE relative importance of the thyroid gland in different species of animals is a subject of considerable interest, for the comparative pathology of this gland is not as yet clearly understood. The importance of this gland to the well-being of any given species can be most readily determined by observing the effects which follow the removal of it alone or together with any accessory thyroid glands which may exist in that particular species. The effects of thyroidectomy have now been studied in a good many different species of animals, and although the results have been negative in some cases, they appear to show more and more clearly the importance of the thyroid gland in many different animals. In the lower vertebrata experiments indicate that the gland is not so important as in the higher vertebrata.

In fishes O. Lanz⁴ found that no changes followed the removal of the thyroid gland in 50 dog-fish (*scyllium catulus* and *canicula*). In lizards, however, we already have evidence that the thyroid gland exercises an important function, for although Lanz did not observe any change in 12 lizards (*lacerta viridis*) after thyroidectomy, Christiani⁵ found that lizards do not survive the removal of the thyroid gland more than six weeks, and that they generally die within a month. Christiani has also shown that in adders thyroidectomy is followed by loss of appetite, loss of strength and activity, shedding of the skin, and death. In rabbits, of which I wish specially to speak, the results obtained by different observers have varied considerably. Schiff, Colzi, Tizzoni, Ughetti and Mattei, and Rogowitch all obtained negative results, and thus a general opinion was formed that rabbits could live quite well without the thyroid gland, and that consequently it did not exercise any very important function in that particular species of rodent. This, however,

is not the case, for the rabbit enjoys no special immunity from the effects of thyroidectomy.

Gley⁶ has found that when the accessory thyroid glands which are present in the rabbit are removed along with the principal gland, very acute symptoms are induced, which in the great majority of his experiments—14 out of 16—ended fatally. The chief symptoms of this acute cachexia are muscular tremor commencing in the masseter muscles, clonic and often tetanic contractions of the voluntary muscles, paralysis, first of the extensors of the fore feet, then of the hind limbs, difficult and often rapid respiration, copious flow of saliva, dilatation of the pupils, and rise of temperature. Death is rapidly followed by the onset of rigor mortis.

Gley found that no symptoms followed removal of either the thyroid gland or of the accessory thyroids alone, whereas when both the principal and the accessory glands were removed, either simultaneously or on different occasions, the acute symptoms rapidly followed. This, however, is not the only effect of thyroidectomy in rabbits, for under certain conditions a slowly-developing chronic condition occurs analogous to the myxœdema which follows total thyroidectomy in man. I have found that removal of the thyroid gland alone in adult rabbits may be followed after a long interval by this peculiar condition, and shall now describe two experiments to illustrate this:

1. On January 12th, 1893, the thyroid gland was removed from a grey buck rabbit while the animal was under the influence of chloroform. The wound healed rapidly by first intention. No change was noticed in the condition of the animal until three weeks had elapsed, when it was found to be less lively and slower in its movements than before. A

Fig. 1.—Showing the myxœdematous swelling of the head and the bare patches of skin due to loss of hair.

month after the operation the appetite began to fail. During March and April the rabbit remained in a somewhat dull and apathetic condition, and often sat still for long with the eyes half closed. When roused it could run about quite well. The temperature remained normal. The appetite diminished, but during these two months it only lost 4 ounces in weight. No further change took place in this rabbit for a long time, as it remained in much the same condition until the following winter. Early in December, about 11 months after the operation, it became more apathetic, and would no longer run about when let out on the grass. When forced to move it did so less actively than it had during the summer. The face, and especially the upper lips, became swollen. The hair began to come out rapidly, and a very light pull was sufficient to detach whole tufts of it. Bare patches of dry scaly skin were left at the lower part of the outer border of each ear, and the hair on the back of the neck became very scanty. The genital organs were swollen, and bare patches appeared

¹ BRITISH MEDICAL JOURNAL, vol. i, 1868, p. 320.

² For use in man Dastre (*Les Anesthésiques*, Paris, 1890) recommends the injection of 1 milligramme (= *circa* $\frac{1}{10}$ grain) of sulphate of atropine combined with 1 centigramme (= *circa* $\frac{1}{10}$ grain) of hydrochlorate of morphine twenty minutes before the administration of the chloroform.

³ Read in the Section of Pathology at the Annual Meeting of the British Medical Association held in London, July-August, 1895.

⁴ *Zur Schilddrüsenfrage*, Leipzig, 1894.

⁵ *Archives de Physiologie*, April, 1895, p. 356.

⁶ *Archives de Physiologie*, Tome iv, 1892.

on the posterior surface of the hind limbs. The gait became slow and awkward; the temperature was low, 99.8° F. In the middle of December an abscess formed in one of the hind feet, and the temperature rose to 102° . After suitable treatment the temperature came down, and on December 18th fell as low as 96.4° ; four days later the temperature was only 95° . A photograph (Fig. 1) was taken and the animal was killed. The swelling of the face and the bare patches of skin are shown in the photograph. *Post mortem* the subcutaneous tissues of the neck and shoulders were found to contain a considerable amount of soft gelatinous infiltration. The pericardium was distended with clear fluid. No trace of the thyroid gland was found, showing that it had been completely removed. No accessory glands were found. The hypophysis cerebri only weighed 0.01 g., and so was not hypertrophied.

2. On February 10th, 1893, the thyroid gland was removed from a black and white doe rabbit in the same manner as in the last experiment. The wound healed by first intention. A month after the operation the rabbit had become rather dull and inactive, but it could be easily roused to active movements. A week later the appetite diminished considerably. Two months after the operation the animal remained in much the same condition, and was generally found sitting still with the eyes half closed.

Fig. 2.—Illustrating the loss of hair, the dry scaly condition of the skin, and especially the dry cracked condition of the edges of the ears.

On March 1st the weight was 4 lbs. $15\frac{1}{2}$ ozs., and by April 26th it was 5 lbs. 1 oz. After this no further change took place until a year after the operation, then during February, 1894, a good deal of the hair on the ears and nose was shed. The edges of the ears became dry, rough, and cracked. At the beginning of May the condition remained much the same, though the weight had increased to 5 lbs. $13\frac{1}{2}$ ozs., or nearly 1 lb. more than it had been fourteen months before, but during the following two months it diminished to 3 lbs. $12\frac{1}{2}$ ozs., so that in this short period the animal lost more than one-third of its weight. The ears felt cold to the touch except after handling, when they became flushed and warm. The skin of the ears was dry and rough. The superficial layers of the epidermis formed grey scales which could easily be detached. The posterior border and half the anterior border of each ear was thickened, dry, and cracked. The hair came out easily when pulled.

During the summer the animal regained weight up to 4 lbs. $8\frac{1}{2}$ ozs., and became more lively, but in other respects remained as before. As the weather became cold towards the end of October it lost flesh again, and soon weighed only 3 lbs. $5\frac{1}{2}$ ozs. At the end of October it had become weak, and walked unsteadily. The peculiar condition of the ears had become more marked, and is well shown in Fig. 2. They were dry and rough as before, the outer edge especially being dry, and cracked in many places to a depth of $\frac{1}{4}$ in. In some places pieces of the dried margin of the ear had broken off so that the edge was rough and irregular. The rabbit began to suffer from uterine hæmorrhage, and so it was killed after having survived the operation for nearly twenty-one months. At the *post-mortem* examination, four small fragments of thyroid tissue were found in the thyroid region, probably pieces of the gland left at the time of the operation. All put together, however, they would scarcely be equal in bulk to half of one lobe of the original gland. No accessory glands were found. The hypophysis cerebri was considerably enlarged, and weighed 0.05 g. The rabbit was found to be pregnant.

The chief points of interest in these two experiments are: The early development of hebetude and loss of appetite; the absence of any further change for the long period of eleven months in one case and twelve months in the other; the similarity between the condition developed and that which develops in man and in monkeys after thyroidectomy as shown by the hebetude, swelling, loss of hair, dryness of skin, and low temperature. It is also to be noted that warmth diminished and cold increased the severity of the symptoms, and also that the doe became pregnant even when the symptoms were well marked. Gley has observed the development of this same condition in three rabbits but under rather different conditions. In the first of his experiments the spleen was first removed, then the thyroid gland some three weeks later, and rather more than two months afterwards the hypophysis cerebri was injured. In the second the thyroid gland was first removed, and the two accessory glands on two subsequent occasions. In the third both the principal and the accessory thyroid glands were removed at the same time, and an injection of thyroid extract was made into the peritoneal cavity. In each of these rabbits a condition like that I have described in my own experiments was developed. In each of Gley's experiments something more than removal of the principal gland was done, whereas in mine that was the only operation.

Hofmeister,⁷ who experimented with young rabbits from 5 to 16 weeks old, found that removal of the thyroid gland alone was followed by remarkable changes. The growth of the bones, and especially of the long bones, became arrested. The skin became rough, the hair was shed, and the abdomen became swollen; in fact, a condition of cretinism was developed.

The negative results obtained by many observers are most probably due to the period of observation not being sufficiently long. If a fragment of the gland is left at the time of the operation, it may become sufficiently hypertrophied to prevent the onset of any symptoms. In one of my experiments no change followed the operation, although the rabbit was kept for two years and three months. When it was killed I found that the experiment had been imperfectly performed, as a piece of the thyroid gland had been left and had become hypertrophied till it was as large as one lobe of the original gland, which fully accounted for the absence of any symptoms during life. Thus in rabbits we may have either an acute or a chronic cachexia occurring as a result of thyroidectomy, the acute symptoms apparently being induced by complete loss, and the chronic by a partial loss of thyroid gland tissue. These facts support the conclusion that the thyroid gland performs as important a function in the rabbit as in the monkey and in man, as the rabbit, like them, may suffer according to circumstances from myxœdema, cretinism, or acute cachexia strumipriva when deprived of this gland.

Dr. A. G. AULD insisted that in connection with the pathology of the thyroid gland, it was of much interest and importance

⁷ *Fortschritte der Medicin* February 15th 1892 Bd 7, p. 121.

to note the condition of the remaining "blood-vascular" or ductless glands. The state of the pituitary and thymus glands had received considerable notice in connection with morbid alterations of the thyroid, but Dr. Auld suggested a more systematic examination of the suprarenal gland. In a case of fully-developed exophthalmic goitre in a young woman, aged 25, in whom death occurred from an inter-current malady, he had had an opportunity of examining this organ. He was much interested to find that the medullary portion of the gland was much hypertrophied, and the nuclei of many of the glandular cells were undergoing division. At the meeting of the British Medical Association last year at Bristol, Dr. Auld had pointed out that the function of the medulla of the suprarenal was the elaboration of a special secretion. In the case of exophthalmic goitre referred to, there was much colloid-like substance in the gland and particularly in the veins, existing in them in the form of small coagula. It seemed to him that this condition of the suprarenal in Graves's disease was compensatory. He believed the secretion of the suprarenal had a trophic action on the sympathetic nervous system, and that the sympathetic system was much disordered in Graves's disease. Hence it would seem likely that the secretion of the suprarenal gland was antagonistic to the secretion of the thyroid.

DIABÈTE BRONZÉ.¹

By V. HANOT, M.D.,

Professeur Agrégé in the Faculty of Medicine; Physician to the Hospital of St. Antoine, Paris.

IN 1882, in collaboration with Dr. Chauffard, I described a disease in which two distinct morbid conditions were present namely, diabetes and hypertrophic cirrhosis with pigmentation.²

In 1886 I named this combined disease *diabète bronzé*.³

In my second series of cases the liver was not appreciably enlarged, the normal volume and pigmentation being fully maintained.

M. Chauffard agreed with me in considering the pigmentary cirrhosis as a consequence of the diabetes, and I admitted that under the influence of the glycosuria caused by the original condition, and of the obstructed circulation due to the diabetic endarteritis, the hepatic cell became stimulated with regard to its chromatogenic functions, and became the seat of a pigmentary hypergenesis. The pigment was developed in the liver, and then became diffused in the form of minute emboli through the whole organism. Since then, other authors have described the disease, namely, MM. Letulle,⁴ Brault and Galliard,⁵ Barth,⁶ Gonzalez Hernandez,⁷ Palma,⁸ Mossé,⁹ de Massary and Potier,¹⁰ and Marie.¹¹

M. Letulle holds a different opinion from that advanced by Chauffard and myself. He does not admit the hypergenetic action of the liver cells, as those which are most pigmented are the dead ones; he considers, therefore, that they store it rather than form it. Further, he does not think that the pigment present in other organs is originally formed in the liver. The pigment which he has found outside the liver, for instance in the cardiac muscle, is, he thinks, formed *in situ*,

owing to a reduction of the hæmoglobin either of the blood or of the muscle.

MM. Brault and Galliard consider that the production of the pigment is due to the fact that the degenerated blood pigment, supplied daily to the altered hepatic cell itself, cannot be readily elaborated and utilised by the latter, and hence accumulates both in the blood and in other organs. "We think," they say, "that the cirrhosis is primary and the degeneration secondary. The pigmentation occurs in consequence of the cirrhosis, without which this degeneration would not exist."

M. Gonzalez attributes to a purely mechanical effect of the pigment, when once it has been formed, a preponderating part in the evolution of the malady.

M. Mossé, who has examined for the first time the histological changes which occur in the skin, the mode of distribution of the pigment in the Malpighian bodies, has observed a glycogenic infiltration of the liver and a histological change in the suprarenal capsules. Mossé expresses himself as follows: "In our opinion, whilst admitting that the pigment accumulated in the liver, in proportion to the specialisation of the liver cell to a biliary function and to the large volume of blood which traverses the organ, may be the source of the pigment emboli, yet we are led to believe that the pigmentary impregnation is above all a secondary phenomenon, and that the embolic process has only a restricted part as a causal factor of the general melanosis. The localisation of the pigment in the deeper layers of the cells of the Malpighian bodies, which is so evident in this disease; the abundance of granulations and pigmentary accumulations in the vascular network of the skin; and the recent observations of Gonzalez and Reiner concerning the chemical composition of the pigment (ferruginous pigment), appeared to us sufficient to establish the fact that the pigmentary granulations, which in the aggregate constitute the brown or black masses, doubtless do not proceed from a disintegration of the hepatic cell, but develop in the vessels at the expense of the altered hæmoglobin."

M. Mossé has laid stress upon the lesions, not only of the liver, but of the pancreas, the kidney, and even of the suprarenal capsules; he admits that the diabetes is an important factor in pigmentary cirrhosis; the diabetes causes the change in the blood, which produces the pigmentation and the glycosuria and the melanoderma, whilst the sugar and pigment contained in the vessels give rise probably to perivascular changes, which result finally in cirrhosis.

The change in the suprarenal capsules is of the same kind as the diverse vascular changes in other organs, and does not justify for a single instant the hypothesis of Addison's disease, which differs from *diabète bronzé* in many points, especially in the pigmentation of the mucous membranes.

MM. Massary and Potier think it probable that the changes in the liver, the chromatogenic functions of which have been proved, are necessary for the production of the pathological pigment, "but we think," they say, "that this pigment is not simply separated from the blood in the hepatic gland, and that it does not pass from the liver in the form of emboli to other organs. It is separated from the blood in the organs themselves, as, for instance, in the pancreas, the suprarenal capsules, the sweat glands, and the Malpighian layer" of the skin. In M. Marie's opinion, *diabète bronzé* is neither a pigmentary cirrhosis in diabetes mellitus nor a *cachexie bronzée*, but a true clinical and pathological entity, in fact a new disease.

Two recent cases which I have observed lead me to agree with M. Marie's opinion. Two patients, one of whom was an avowed alcoholic (as in M. Brault's case) came to consult me; up to that time their health had only been affected for a month at most. The urine already contained sugar. In the alcoholic patient the liver extended beyond the margin of the ribs by barely two fingers' breadth; in the other the organ was evidently of normal size. I watched, rapidly develop, under my own eyes as it were, at the same time hepatic hypertrophy and melanoderma and cachexia, all of which may legitimately be considered as equally important consequences of one and the same cause. However that may be, hepatic cirrhosis in *diabète bronzé* is a vascular, and generally a hypertrophic, cirrhosis.

In different cases the liver weighed from 1,800 to 3,500 g.

¹ Read in the Section of Medicine at the Annual Meeting of the British Medical Association, held in London, July-August, 1895.

² Hanot and Chauffard, Cirrhose hypertrophique pigmentaire dans le diabète sucré (*Revue de Méd.*, 1882, p. 385, avec planches).

³ Hanot and Schachmann, Cirrhose pigmentaire dans le diabète sucré—Diabète bronzé (*Archiv. de Physiol.*, 1886, 90, avec planches).

⁴ Letulle, Cirrhose pigmentaire de foie chez le diabétique (*Sem. Méd.*, 1885, p. 408).

⁵ Brault and Galliard, Sur un cas de cirrhose pigmentaire dans le diabète sucré (*Archiv. gén. de Méd.*, January, 1888).

⁶ Barth, (*Soc. Anat.*, 1888).

⁷ Gonzalez Hernandez, La cachexie bronzée dans le diabète (*Thèse de Montpellier*, 1892).

⁸ Palma, Zwei Fälle von Diabetes mellitus und Lebercirrhose (*Berliner klin. Wochens.*, April 21st, 1893).

⁹ Mossé, Diabète maigre et melanodermie (Diabète bronzé) Cirrhose pigmentaire du foie et du pancréas. Examen histologique de la peau (*Congrès de Méd. et d'Hygiène.*, p. 777, 1894).

¹⁰ Massary and Potier, Sur un cas de diabète bronzé (*Soc. Anat.*, April, 1895).

¹¹ Marie, Sur un cas de diabète bronzé, avec autopsie (*Sem. Méd.*, May 22nd, 1895).