

Kahane himself, however, finally gives as his own opinion that it should be ranked among the acropathies, which he defines as those affections which are localized in the peripheral parts of the limbs and as the ultimate basis of which are assumed lesions of a vaso-motor nature. There is great difficulty in determining whether the nerves or the vessels form the starting point, whether we have to do with an irritation of the vaso-dilators or a paralysis of the vaso-constrictors. He says, in conclusion of a long and careful consideration of the question, that there are two points that one can be sure of: 1st, that erythromelalgia belongs clinically to the group of acropathies; 2d, that it is to be referred to a disturbance in the relation between the systems of the nerves and blood-vessels quite without regard to the question whether it is of functional or anatomical, central or peripheral nature. In his conception it is a phase of disease that occurs in one series of cases independently and in another as an attendant phenomenon of other diseases.

Sachs had found the blood-vessels diseased in most cases, but the nerves not in many; the changes in the latter he believed to be secondary. He says erythromelalgia occurs as an independent group of symptoms, even if not an individual disease. In uncomplicated cases it is probably to be referred to disease of the peripheral arteries. The obliterating arteritis may be indirectly connected with central disease, but may be wholly independent of such influences. In 1901, Elsner, on examination of the arteries in cases that he saw, found them the seat of occasional slight thickening of the intima, but the nerves normal. He calls attention to several cases in which gangrene of the extremities occurred. He believes that erythromelalgia cannot at present be defined as a disease *per se*. Cassirer, on the contrary, is constrained to place himself among those who believe the disease to have a certain idiopathic character, while recognizing like others one class of cases of a peripheral and a second of a central origin. Allchin and Saville regard the disease as of vaso-motor origin, probably allied to Raynaud's disease, the former speaking of it as an expression of vaso-motor ataxia. Shaw in 1903 analyzes nine cases and reports the results of the examination of amputated toes in three cases, stating that "vascular change was present in all, mostly an increase in the intima of the arteries and occasionally thrombosis and changes in the inner coat of the veins. The nerves were investigated even to their terminations, and no degeneration was found, nor was there any suggestion of increase of fibrous tissue in the trunk of the nerves." (Compare Mitchell.) He says: "In no case has recent degeneration of nerve fibres been demonstrated, and in not one of the nine cases analyzed was anesthesia ever present." He concludes that erythromelalgia when occurring independently of central nervous change is associated with but one morbid picture, that of local vascular change. Taubert finds erythromelalgia traceable to disease in the lateral and posterior columns of the cervical cord (see Eulenburg and others). Reynolds calls the disease a vaso-motor neurosis, and argues in favor of the theory of primary vaso-motor dilatation of the arteries followed in the way of compensation for this vaso-motor paralysis by thickening of the coats of the arteries so as to narrow the lumen and stream of blood (quoting Delafield, Thoma, and Barlow in support of his views). Starr, sketching the phenomena of the "vascular storm," says: "The dilatation of the arteries in the extremities results in an extreme condition of redness and sensation of heat and pain. After hours of this the extremities may suddenly become cold, pale, or blue and shrivelled up, presenting the appearance of the hands after long soaking in hot water; and this alternation of distention and contraction of the blood-vessels constitutes the symptomatology of the disease. It appears to be a pure vaso-motor neurosis, but it is rarely if ever attended by any trophic disturbances of the skin or nails, such as occur in neuritis, and no pathological observations are at hand to establish the hypothesis that there is a true neuritis of the vaso-motor nerves."

If, therefore, we should venture upon a rough summing

up of the principal pathological features of erythromelalgia as indicated in the preceding brief synopsis of recent authorities we should say that opinion was settling upon the following beliefs: (1) The disease is considered a vaso-motor neurosis (angioneurosis, Oppenheim); (2) the attribution of the group of symptoms to disease of the posterior and lateral spinal gray matter, when it would be called secondary, and to as yet undetermined causes of peripheral origin, where some would call it clinically idiopathic or *sui generis*; (3) its association with the acropathies and sometimes with Raynaud's disease; (4) there is much more evidence connecting the disease locally with alterations of the blood-vessels than of the nerves, but good authorities deny that we are yet in position to pass finally upon its pathology.

The TREATMENT of erythromelalgia can hardly be said to aim with hopefulness at more than the alleviation of some of its most distressing symptoms, proof of which is found in the long list of the various means employed. Weir Mitchell's recommendation of rest, cold, and elevation of the limb affected has been found of value, based as it is upon well-known observations of patients that the opposites of these increase their sufferings. Other measures to be noted are hydrotherapy, electricity (Eulenburg and Schütz found benefit from the use of the constant current), massage (although Barlow says it is of doubtful value and unbearable during the paroxysms). Of course antisiphilitic remedies are indicated in cases in which that disease is believed to underlie or complicate erythromelalgia, and among drugs which are more or less approved are arsenic, antipyrin, the bromide of potassium, morphine (Morgan reporting a case of recovery after hypodermic injections of morphine and atropine twice a day for three weeks), the salicylates, atropine, and ergot internally as well as ichthyol externally. It should also be remembered that spontaneous recovery has taken place in some cases. Further than this, the several cases referred to above are evidence that surgical measures, such as the stretching of nerves, their resection, and the amputation of toes and fingers, have brought relief in certain instances. It should be noted, however, that gangrene followed operative procedures upon nerve and vein in one case of Weir Mitchell's and upon amputation of a toe in another.

The references given below are mainly to the chief articles of the last three years, the reader being referred to the essays of Lewin and Benda and of Kahane for full bibliographies.

J. Haven Emerson.

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EUCAINE is a name applied to two different but closely allied local anesthetics distinguished as *Alpha-eucaine* or *Eucaine "A"* and *Beta-eucaine* or *Eucaine "B"*.

The anæsthetic effect of cocaine, which is methyl-benzoyl-ecgonine, $C_{17}H_{21}NO_4$, was found to depend on the presence of both the methyl and the benzoyl groups and not on the ecgonine radical. So with the desire of obtaining the anæsthetic effect of cocaine without its toxicity, other methyl-benzoyl compounds were designed. Of these Eucaine "A" was submitted to the profession, and was for a time extensively employed; but its very irritating effects have so militated against its desirability that it has been largely replaced by its congener, Eucaine "B," a compound of less toxicity and less irritating properties.

Alpha-eucaine, $CH_3.N.C_2.(CH_3)_2.(CH_3)_2.(CH_2)_2.CC_6H_4.COO.COCH_3$, is methyl-benzoyl-tetra-methyl-hydroxy-piperidine-carbonic-acid-methyl-ester, a derivative of tri-acetone-amine. Its hydrochloride occurs as a bitter white crystalline powder soluble in 10 parts of cold water, 7 of boiling water, less than 2 of alcohol, and 13 of glycerin, and is very slightly soluble in ether and the fixed oils.

Beta-eucaine, $H.N.C_2.HCH_3.(CH_3)_2.(CH_2)_2.C.C_6H_5.COO.H$, benzoyl-vinyl-diacetone-alkamine, is also a bitter white crystalline powder, and its hydrochloride dissolves in 23 parts of water, 12 of boiling water, 30 of alcohol, and 35 of glycerin. It is insoluble in ether and almost insoluble in the fixed oils.

Both eucaines have the nature of alkaloids, and their hydrochlorides have been the salts in common use; but the acetate of beta-eucaine is now recommended as it is readily soluble in water. The solutions of eucaine salts are not decomposed by boiling, so may be sterilized.

The pharmacological action of the eucaines has been studied by Cushman, Vinci, Ver Eecke, and others. The salts are not absorbed by the unbroken skin, but, applied to mucous membranes or injected into the tissues, they paralyze the sensory nerves and their terminal endings at the site of application and are powerful local anesthetics. They are said to produce local congestion in mucous membranes.

In large dose they weaken the heart by direct depression of the cardiac muscle and its contained ganglia, and in addition lower blood pressure by dilatation of the arterioles. The respiratory centre is at first stimulated, later paralyzed, so that death takes place from asphyxia (paralysis of respiration). The cerebral centres are stimulated with the production of tonic and clonic convulsions; later they are paralyzed. There is no dilatation of the pupil or disturbance of the accommodation of the eye, but the conjunctiva is congested. The superficial epithelium of the cornea is not affected. The kidney cells are stimulated and the quantity of urine is increased, with increased elimination of nitrogen, phosphorus, and chlorides. The drug is not found in the urine, and apparently undergoes decomposition in the body.

To produce general poisoning in rabbits and guinea-pigs it requires 0.15-0.2 gm. of eucaine "A" per kilo, and 0.4-0.5 gm. of eucaine "B." Cocaine is four times as poisonous as eucaine "B," and only slightly more toxic than eucaine "A."

The uses of beta-eucaine as a local anæsthetic are practically those of cocaine, so we need not here enumerate its therapeutic applications. The consensus of opinion among surgeons (Bier, Bainbridge, Moyer) would seem to indicate that it is weaker as an anæsthetic than cocaine, whether employed subcutaneously or in spinal analgesia. Wallis found that the amount required for a small operation averaged 3 i.-iss. (4-6 c.c.) of a four-per-cent. solution, but G. W. Crile performed a painless duodenotomy with 8 c.c. (5 ij.) of a two-per-cent. solution.

Nearly all writers agree that eucaine tends to increase a hyperemia of the conjunctiva or nasal mucous mem-

brane, and Dawbarn and others prefer it for the removal of tonsils, adenoids, and other hypertrophied tissues, as it does not cause a shrinkage like cocaine. Poole prefers cocaine in iritis, as eucaine increases, or at least does not decrease, the anterior congestion.

In our experience eucaine applied to mucous membranes is slower in its action and much weaker than cocaine; used subcutaneously it is somewhat weaker. We had several cases of local gangrene following its hypodermic use in abdominal and pleural tapping, though in each of these instances the injection had been preceded by the ethyl-chloride spray. Cocaine under similar conditions never produced a slough. Da Costa noted a slow, persistent sloughing, especially in fatty tissue, bursa, or tendon sheaths. He also noticed inflammation following its use in the bladder. Shastid reports the occurrence of amblyopia, rapid pulse, and delirium following the application of a five-per-cent. solution to the inferior turbinate.

Beta-eucaine is, then, a drug of anæsthetic action resembling that of cocaine, but somewhat weaker. It produces hyperemia rather than the ischaemia of cocaine, and has no effect on the pupil, accommodation, or the corneal epithelium. In the ordinary dosage it is non-toxic, and is reported to be well borne where there is an idiosyncrasy against cocaine. Lilienthal has frequently used four to ten grains without unpleasant consequences. No eucaine habit is known. The drug keeps indefinitely and can be sterilized by boiling.

Solutions of one- to four-per-cent. strength in normal salt are commonly employed, but stronger solutions, obtained by heating the liquid and using warm, are sometimes preferred. Von Mikulicz uses the following: β Cocainæ hydrochloridi, 0.5 gm. (gr. viiss.); beta-eucainæ hydrochloridi, 0.5 gm. (gr. viiss.); sodii chloridi, 2 gm. (gr. xxx.); aquæ, q.s. ad 1,000 c.c. (3 xxxii).

W. A. Bastedo.

EXOPHTHALMIC GOITRE.—(Synonyms: Graves' disease; Basedow's disease.) These names have been indifferently used during the last sixty or more years to express a fairly well-defined disease in which more or less enlargement of the thyroid, protrusion of the eyes, and certain nervous disturbances (including tachycardia) form the prominent symptoms. The Irish physician, Graves, who described the coexistence of palpitation of the heart with enlargement of the thyroid as an affection more or less related to hysteria, was antedated in his observations by Parry, who mentioned the same combination together with exophthalmos in 1825. Some years later Basedow also observed the existence of exophthalmos in similar cases, and gave the description which has connected his name with the disease. Charcot, too, in 1844 and 1845 described such cases at the Salpêtrière. Since their time an enormous literature has appeared in which, while the objective descriptions remain very constant, the most divergent theories have been advanced to account for the symptoms. These we may detail in discussing the etiology of the disease.

Exophthalmic goitre is an affection which occurs most frequently in women, although cases are by no means rare in which the same phenomena are seen in men. No very precise age limits can be set, but the majority of the cases appear to begin after the age of puberty, and to increase in number as the climacterium is approached, the onset being most frequent, according to Osler, between the ages of twenty and thirty. No particular station in life seems to predispose to the disease, but it is usually observed that the individuals belong to neuropathic families in which cases of epilepsy, hysteria, chorea, or even some form of insanity have occurred. Combinations of epilepsy and exophthalmic goitre in the same person have been described, in which cases the epileptic seizures usually give place to the symptoms of the other disease. Exophthalmic goitre is a very widespread disease, not at all localized in certain areas, as is the case with other forms of goitre and with endemic myxœdema or cretinism. Indeed, although cases in which exophthalmic

symptoms supervene after the long existence of the ordinary type of goitre are not unknown, the disease seems to be no more frequent in those regions where goitre is endemic than elsewhere, and the coincidence of the two conditions must be considered accidental. Instances of the coexistence of exophthalmic goitre with myxedema have also been observed,² which, although probably accidental and not indicating any close relationship between the two conditions, have a significance which will appear later.

SYMPTOMS.—The onset is sometimes very slow and gradual, in other cases it is extremely sudden, and the symptoms reach their maximum of intensity in a very short time. Usually, but not always, such an onset is ascribed to sudden violent emotional disturbances, such as a fright or great sorrow, etc., after which the patient feels demoralized and incapable of effort, and the palpitation of the heart and tremors begin. Prominence of the eyeballs may be the first thing observed, and is noticed by the friends before the patient herself appreciates it.

Of all the symptoms perhaps the most constant are those referable to the heart and circulatory system in general, and these may be considered under several heads. First of all and most noticeable is the violence of the heart's action—a pounding heart beat that may sometimes be violent enough to keep the patient awake can be felt over a wide area. Loud systolic bruits can often be heard over the apex and base of the heart and along the vessels. The pulsation of the arteries is extraordinarily violent in many cases and is readily visible in the extremities. There is usually a widespread dilatation of the capillaries also, and sometimes a venous pulsation can be made out. The dilatation and violent pulsation of the vessels are especially noticeable over the enlarged thyroid and in the eye grounds.

Then next in prominence is the tachycardia, which may reach the highest degree. Usually this develops gradually and the pulse rate increases from normal up to 130 to 150 or more in the minute. In a case recently observed in the Johns Hopkins Hospital, a rate of 200 per minute was maintained for days. The tension in such cases usually remains high, and the volume full. F. Müller³ gives a sphygmographic tracing in a case whose pulse rate at the time was 176, in which this is illustrated, there being a sharp initial elevation with frequent bigeminal pulsation. Recent researches seem to show (Donath,⁴ Spiethoff⁵) that the blood pressure is in some cases increased, in some diminished, but by no means always increased.

Variations in the pulse rate are very marked, and excitement or exertion has a much greater influence than in a normal individual. In some instances it is impossible to escape from the idea that exhaustion of the heart muscle must play a part in the final dissolution of the patient.

Referable to the central nervous system more directly we find a variety of symptoms, of which perhaps the most prominent is the tremor. This is involuntary and fine for the most part, leading to a fine trembling of the hands, muscles of the face, and indeed of any and all of the muscles indifferently. It is most noticeable to the patient in the attempt to perform fine co-ordinated movements. Writing becomes difficult or impossible, and the characters show a tremulous irregularity. Fibrillary twitchings of the tongue are usually present, and may be so extensive as to produce a wave-like undulation over the surface of that organ. Definite spasms and twitchings of various muscles may occur too, even producing in some cases the condition of tetany, such as has been described in thyroidectomized animals. Epileptiform seizures are not unknown, and may suggest an extreme manifestation of the tetanic condition. The explanation of these phenomena will be further discussed in treating of the etiology.

The other symptoms referable to the nervous system are chiefly psychical. Early in the disease the patients feel themselves to be irritable and excitable. The friends observe a change of disposition, very different from that observed in the development of myxedema. Instead of

becoming sluggish and apathetic, with all the mental faculties dulled, these patients are keenly susceptible to every outward stimulus, and the mental reaction is a relatively intense one. In some respects this receptive and reactive state may resemble in a mild way that seen in the maniacal stage of the maniacal-depressive insanity. A feeling of anxiety often dominates the mental state and the excited patient becomes a prey to groundless fears. Insomnia may be persistent, much to the exhaustion of the patient. In other cases fantastic dreams occur with great frequency, and may pass over into the waking state, so that the patient has but to shut her eyes to see all sorts of forms move about her, or even in broad daylight the hallucinations may occur. Delirium and the wildest maniacal excitement, or stupor and even unconsciousness may come on late in the disease.

The exophthalmos is not an invariable feature, although it is very frequently present (Fig. 5134, *A* and *B*); it may be unilateral, but is usually bilateral. In its onset it becomes, as a rule, gradually more and more noticeable, but sometimes, as it is alleged, after a sudden emotional shock it may appear and reach a high grade within a very short time. The actual extent of the protrusion of the eyeball it is difficult to measure, although methods have recently been devised which will render such measurements more exact. It is most noticeable in the widening of the aperture of the lids which it produces, and by the staring expression which it gives to the face; but it must not be forgotten that the individual variations in normal people in this respect are very great. In extreme cases, however, such as one of Basedow's, the eye may be actually dislocated from the orbit. Many consequences of this protrusion have been noted in the literature, and as signs of the exophthalmos they bear the name of their observers. Graefe, for example, noticed that in lowering the eyes the upper lid did not follow and keep the sclera covered as in the normal eye—the so-called Graefe's sign. Stelwag's sign consists in the widening of the palpebral aperture; Möbius' sign, in the lack of normal convergence of the eyes.

Pupillary changes are rarely if ever seen, and no definite retinal alterations have been found, nor is there any disturbance of sight from the exophthalmos proper. Winking is much less frequently carried out, however, than in the normal eye, and in cases in which the eye projects far from its socket the eyelids never quite cover the eyeball. The consequence may be that the proper moistening of the surface is interfered with, and a band-like area across each eye, passing over the cornea, becomes dried and opaque. Ulceration and infection of this dried area, which becomes wider with the increased protrusion, leads to complete opacity of the cornea and loss of vision in that eye. The infection may even go on to involve the whole eye and result in its entire destruction.

The absence of pupillary disturbances is particularly significant in connection with one of the theories as to the etiology of the disease, as will appear later.

No special disturbance of the urinary secretion seems to occur with this disease, although glycosuria has been observed in some cases and polyuria in others.

Digestive disorder and disturbances of the general metabolism, however, are almost constant, and have an extremely important bearing upon the prognosis.

Loss of appetite is very common, and the patients waste away perhaps as a result of this. On the other hand, a ravenous, insatiable appetite is sometimes observed, but strangely enough with the same progressive emaciation. F. Müller⁶ describes most graphically this curious phenomenon. "The food prepared for this patient, quite enough for the nourishment of a robust person, was not enough for her, and she gathered up every scrap of food that was left by the other patients in the ward. One found her almost always eating, and it was curious to see her, as with wide open, eager eyes she stared into her plate and ceaselessly chewed and swallowed."

There are, however, variations in this emaciation, such

that while at times the patient loses rapidly in weight, there come periods during which she recovers almost all that was lost, and Huchard speaks accordingly of "crises d'amaigrissement." The loss of weight may be enormous

son's disease. An instance of this is the above-mentioned case of von Schrotter. So, too, urticaria, erythema, localized oedema, scleroderma, loss of hair, swelling of joints, atrophy and hypertrophy of breasts, etc., occur,



A.



B.

FIG. 5134.—Case of Exophthalmic Goitre showing Exophthalmos and Goitre. A, Front view; B, side view.

and astoundingly rapid. One of Müller's patients lost fifty pounds in nine months, reaching then a weight of fifty-four pounds. Curiously enough the emaciation may not be general but limited to one portion of the body, either to one side or to the upper part, while the lower extremities remain unaltered. von Schrotter⁷ describes such a case in which the very fat legs contrasted sharply with the wasted chest and shoulders.

Diarrhoea, of a most persistent character, is often observed, and may aid greatly in producing the emaciation. It seems possible that it may be due to an increased activity of peristalsis dependent upon some such nervous influence as produces the general tremor. Incidentally, too, it may be remarked that it seems possible that in those cases of persistent diarrhoea which are associated with tetany there may be an underlying cause for both, similar to that at work in the production of the disease under discussion.

Symptoms from the genital apparatus are very inconstant and difficult to explain. There is sometimes a cessation of the menses, and there have been instances in which pregnancy has had a favorable influence upon the course of the disease.

Changes in the skin are frequent and of many sorts. Very characteristic is the profuse and continued sweating, which is no doubt due to the central irritation of the secretory nerves. It is frequently such as to bathe the patient constantly and to keep the skin in a sodden condition, from which results the increased electrical conductivity noted by Charcot and others. Annoying sensations of heat, accompanied by flushing of the skin, frequently occur, while the general temperature is normal. Other changes, difficult to explain, also appear, such for example as the extensive pigmentation of the skin, which may be almost like that observed in Addi-

and are usually explained as dependent upon disturbances of the trophic nerves.

Dyspnoea and labored breathing may come on, especially after exertion, and occasionally there is a dry cough which is very wearing, but which seems not to depend upon any actual pulmonary lesion.

Finally the thyroid shows fairly constant changes, which are recognizable clinically (Fig. 5134, *A* and *B*). The enlargement is usually diffuse and bilateral, but may not be extreme. Frequently it is so slight as to be hardly noticeable.

In all cases, however, the thyroid is somewhat increased in consistence and may sometimes become very hard. The vessels which course over it are generally widely dilated and pulsate violently, and to this great vascularity and hyperæmia is due in large part the enlargement of the gland.

PATHOLOGY.—Numerous autopsies have been performed on these cases, and the most painstaking examination of the viscera made without as yet any constant lesion having been discovered which can be considered explanatory of all these symptoms. Especial attention has been directed to the nervous system and to the thyroid, and the description of the changes in these can therefore be made more minute.

In the central nervous system no definite constant changes have been discerned in the cerebral cortex nor in the lower portion of the brain or cord. Only Mendel⁸ and his students have found atrophy of the corpus restiforme on one side with a similar atrophy of the solitary bundle on the other side, and this he brings into causal connection with the disease. It is, however, far from constant, and it is hard to explain a general condition by a one-sided lesion.

The sympathetic ganglia in the neck have also been

examined with great care, but Ehrich,⁹ who from his cases was able to find degenerative changes, thinks them entirely secondary. Others find no alterations whatever in these ganglia and nerves.

Müller found degenerative changes in the trunk of the vagus nerve, but decided that these were secondary.

The alterations in the heart are by no means constant nor characteristic. Dilatation is sometimes found at autopsy, hypertrophy occasionally, while degenerative changes are frequent.

It is in the thyroid that the most characteristic and constant changes are met with. The gland is usually but not always enlarged, and its consistence much increased. No adequate idea of the vascularity is gained from the inspection of the specimen after death, but at operation it is found to be extraordinarily rich in widely distended vessels, which pulsate violently, and which from the friability of their walls (Kocher,¹⁰ Ehrich¹¹) render the operation for the extirpation of the gland a difficult one. The surface is often somewhat nodular and the capsule thickened. Section of the gland shows that it has not the translucency and brownish-red color of the normal gland, nor its gelatinous elastic consistence. Instead it is hard and resistant, and of an opaque pinkish-gray color, the cut surface having a rather lobular, roughened appearance. (Figs. 5135 and 5136.)

Microscopically there is usually made out a great increase in the connective tissue throughout the gland. Strands of fibrous tissue run through it from the capsule and produce a sort of indefinite lobulation. More striking, however, is the alteration in the alveoli. Instead of preserving a more or less uniform roundness, they are distorted into the most complicated forms, and their



FIG. 5135.—Exophthalmic Goitre. Thyroid lobe in section from case illustrated in Fig. 5134.

walls plicated and corrugated until the outline is an extremely irregular one. By many authors papillary outgrowths from the walls have been described, but Ehrich claims that these appearances are merely due to the irregular line of section of folds in the wall.

The cells are irregular in height and outline, and are often vacuolated and ragged, and contain more abundant

fat globules than normal. There is much variation in the size of the alveoli, the distended irregular ones being frequently long drawn out and sometimes even com-

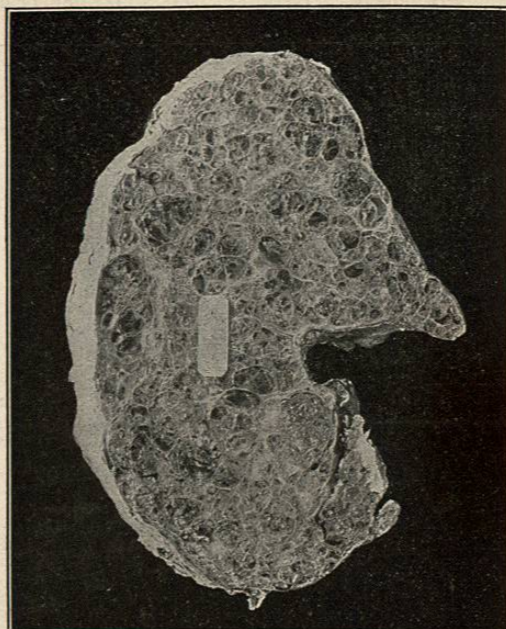


FIG. 5136.—Adenoma of Thyroid, or Colloid Goitre.

municating with one another, while others are small and so packed with cells that there is no real lumen. Mitotic figures are rare. Indeed Ehrich states that proliferation occurs only by amitotic division, and is not a prominent feature, but that the enlargement of the gland is largely due to the distention of the alveoli. The general trend of opinion, however, is toward the idea that there is a hypertrophy by cell proliferation.

We may pass over the histological details of the process of secretion as observed in these cases by Farner, Ehrich, Haemig, and others. Suffice it to say that while in some cases the process of secretion seems active enough, and the alveoli are filled with a stainable colloid material, in the majority the secretion of this stainable colloid is not evident, the cells have become high and vacuolated, and whatever secretion there is, is of the non-staining or chromophobe type of Andersson. The alveoli in these cases are empty of colloid, and contain only the débris of cells and fine ragged strands of granular material.

As to the removal of the colloid material from the gland there is still some doubt. Many authors have described the presence of a material staining like colloid in the lymphatics and interstitial spaces, while others have even declared its presence in the veins and arteries. Thus Farner¹² explains the lack of colloid in the follicles by the rapidity of its export. Ehrich, however, with right, suspects that the colloid-like substance in arteries and veins is merely the coagulated serum. Indeed he denies that any secretion escapes from the gland, and thinks the whole process a retrogressive one. Support is lent to Ehrich's views by the work of Oswald (*Virchow's Archiv*), who finds a decreased percentage of iodine in the thyroid in exophthalmic goitre, and considers the change a decrease in functional activity.

There is no statement in the literature as to any changes in the parathyroids in this affection, but an enlargement of the thymus is fairly constant, and in most of the cases a swelling of the cervical lymph glands has been observed. In a case recently dissected at the Johns Hopkins Hospital the hæmolymph glands in the neck were especially prominent.

The other organs show, as far as is known, no constant lesions. Askanazy has described certain degenerative changes in the voluntary muscle, but investigations confirmatory of his results seem not to have appeared.

ETIOLOGY.—Several distinct theories as to the etiology of the disease have been proposed, but they all fail to account satisfactorily for all the symptoms.

According to one, which has been defended by Buschan, exophthalmic goitre is a general neurosis in which the psychic and vaso-motor functions are predominantly affected; but constant changes in the thyroid cannot be explained on this idea.

Möbius is the chief defender of the theory of hyperthyroidization, in which the thyroid forms the starting-point for all the symptoms. Certain authors have shown that unpleasant symptoms—flushing, tachycardia, etc.—may follow the excessive administration of thyroid extract in normal animals, and it has been conceived that in this disease the enlarged thyroid is in a state of great secretory activity, pouring into the lymphatics far more of its secretion than normal, and thus bringing about the characteristic symptoms. This view seems further supported by the results of surgical extirpation of part of the gland—the relief of the symptoms being frequent. Not all the symptoms can be produced by injection of thyroid extract into normal animals, however, nor can all of the symptoms of exophthalmic goitre be relieved by extirpation of the active gland. For example, the exophthalmos can neither be produced by thyroid extract nor always relieved by thyroidectomy. There is much in favor of this theory, but also several arguments opposed to it are difficult to answer. The disease is considered to be a sort of general antithesis to the condition of myxœdema, which we know to be due to loss of the thyroid, and hence again the idea that such a reversal of the symptoms of myxœdema must be due to hyperthyroidization. But histologically we cannot say with certainty that the gland is secreting actively. Indeed, of the usual colloid we see little or nothing at all. The theory fails to explain several important symptoms. The results of the operation for extirpation of part of the gland are not uniformly good, and indeed not especially better than the rest in bed and regular régime alone; and finally cases of exophthalmic goitre in combination with myxœdema have been described—a condition which must directly contradict and disprove the theory of hyperthyroidization.

Ehrich thinks that the enlargement of the thyroid, and indeed most of the other symptoms, are due to the arterial hyperemia, but he fails to explain this itself.

Mendel's theory of a lesion in the corpora restiformia falls on account of the inconstancy of such a lesion.

Finally, a theory has been based upon the effect upon the eyes of stimulation of the cervical sympathetic, ascribing the exophthalmic goitre, or at least many of its symptoms, to a lesion of the sympathetic. Now it was stated above that lesions of the sympathetic are by no means constant or even common, but the theory is not plausible upon the face of it for the following reasons: Section of the sympathetic causes pallor of that side of the face, retraction of the eye, and narrowing of the pupil, while stimulation causes a flushing of the face, sweating on that side, protrusion of the eyeball, widening of the palpebral fissure, and dilatation of the pupil. Those symptoms of exophthalmic goitre might therefore correspond with the results of a constant stimulation of the sympathetic, but even then the pupillary disturbances are absent in exophthalmic goitre, while they form the most striking consequence of stimulation of the nerve.

The nature of the exophthalmos has given rise to much discussion in this connection. It is by no means proven that it is due to distention of retrobulbar vessels; nor can it be shown that it is due to stimulation of the sympathetic, perhaps by pressure of the enlarged thyroid, for removal of the goitre influences it very little. Protrusion of the eyeball is, however, not impossible to the normal individual, and experiments of Filehne¹³ and Dur-

dufi¹⁴ have shown that irritation of the corpus restiforme will produce exophthalmos even after the sympathetic is cut through. So also Kotschanowski¹⁵ claims that it may be produced by stimulation of certain anteriorly placed cortical centres.

The theory of sympathetic irritation, being as it is without anatomical basis, explains only haltingly a few of the symptoms. It is impossible to make the lack of pupillary change agree with this conception, and the general tremors, general sweating, and vaso-motor disturbances, as well as the metabolic disorders and psychical symptoms, are not explained at all by such a theory.

Recent experimental work upon the thyroids and parathyroids seems to promise some light upon the subject. Briefly stated it has been found (Moussu,¹⁶ Vassale and Generali,¹⁷ Schiff,¹⁸ and Gley¹⁹) that extirpation of the thyroids produces certain disturbances of nutrition which lead to the condition of myxœdema or cachexia strumipriva, while extirpation of the parathyroids leads, and in a far shorter time, to the death of the animal from symptoms of violent poisoning of the central nervous system—tetanic convulsions, dyspnoea, etc.—and that the tetany, which was previously ascribed to the removal of the thyroids, is really due to the simultaneous removal of the parathyroids, which are closely associated with them. Certain changes in the thyroid are said to occur after parathyroidectomy, and the tetany so produced is ameliorated by the removal or partial removal of the thyroids.

Slight exophthalmos sometimes occurs in the animals from which the parathyroids have been removed, and altogether the symptoms are rather suggestive of those of exophthalmic goitre. The suggestion has therefore been made (Gley, *British Med. Jour.*, 1901, September 21st), and is now being put to the proof, that possibly the development of this disease depends upon some lesion which destroys the parathyroids, and that it is nothing more than a long-continued parathyroid insufficiency. Indeed, one promising but incomplete attempt at the relief of the symptoms by parathyroid therapy has been made by Moussu.²⁰ As stated above, there appears to be but a very meagre description of the parathyroids in exophthalmic goitre in the literature (Benjamin's, "Ziegler's Beiträge," Bd. xxxi.), but in several cases which have recently occurred in the Johns Hopkins Hospital it was found possible to isolate parathyroids in four, although the glands were small, degenerated, and sclerotic. In a fifth and fatal case no parathyroid tissue was found at autopsy. It can readily be understood on this theory that the cases of combined myxœdema and exophthalmic goitre offer no difficulties. They are readily explained as cases in which the destruction of the thyroid produces the myxœdema, while destruction of the parathyroid independently produces the exophthalmic symptoms.

The theories as to the etiology are thus as yet not entirely satisfactory, although the last mentioned seems at least to offer some promise.

COURSE OF THE DISEASE; PROGNOSIS; TREATMENT.—The disease runs sometimes a very rapid course, terminating fatally after an illness of a few days only. In most instances it drags on for years and may end in recovery. The prognosis indeed is by no means very unfavorable, and a considerable proportion of the cases get quite well. There have been cases reported in which some sudden emotional shock is followed by intense symptoms, such as have been described, which after a short time disappear completely. In the cases in which the most intense symptoms are developed, however, and in which the clinical picture is complete, recovery without surgical interference is rare. The greatest variety of procedures has been employed in the attempt to cure these cases. From the medical point of view none are very satisfactory. Rest in bed, freedom from emotional disturbances, and the regular régime of the hospital seem to afford great relief in many cases, and are extremely important in the cure. The tachycardia is apparently not influenced by digitalis, although strophanthus is said

to have some effect. Ergot and belladonna have been warmly recommended by some authors, and may do some good. Electricity, too, applied to the spine and peripheral nerves has been advocated by Erb and others.

Based on the remarkable results obtained by the administration of the thyroid gland in myxœdema numerous cases of exophthalmic goitre have also been treated in this way regardless of the theory of hyperthyroidization, but the effects have been either actually harmful or entirely negative. The cases in which thyroid therapy has produced untoward results have therefore been brought forward as a strong support of the idea that the thyroid is already secreting too profusely, and thereby causing the symptoms.

From the fact that the thymus is usually found enlarged in exophthalmic goitre extracts of thymus have been given in these cases, sometimes with remarkable temporary results, but without any permanent advantage to the patient. In the case referred to above, which occurred in the Johns Hopkins Hospital, administration of the thymus extract reduced the pulse rate at once from 200 per minute to normal. When it was discontinued the pulse rose again to 200, and was again brought to normal by the thymus extract. After a time, however, its effect disappeared, and the pulse rate remained high until the death of the patient. In another case there occurred a remarkable reduction in the size of the goitre during its use. Since the parathyroid lies embedded in the thymus in the ox and certain other animals, it seems possible that it may be included in the extract manufactured from the thymus of these animals and may be responsible for the above results.

It was stated above that one attempt has been made to influence the symptoms by parathyroid feeding, and indeed the great amelioration following its use seemed very promising. The patient, however, died of tuberculosis before any definite result was attained. It is quite difficult to procure the glands in sufficient quantity for such treatment, but as soon as a parathyroid extract is on the market, it will be possible to give this remedy a thorough trial.

Quite recently Lanz,²⁵ Möbius,²¹ Goebel,²² Schultes,²³ and others have proposed and carried out a treatment which is based on other principles, and which they claim to be very successful. On the idea that the thyroid is concerned in the neutralization of poisons produced elsewhere in the body, and that in exophthalmic goitre it is so active that not only does it neutralize these poisons but further poisons the organism by the excess of this antitoxin (!), these authors attempt to supply this overactive thyroid with poison for neutralization by injecting the serum of thyroidectomized sheep, in which supposedly much of the poison must have accumulated, or by feeding them on the milk of such thyroidectomized animals. The chances for fundamental error in the conception of this treatment seem very great, for it is by no means proven that in exophthalmic goitre the thyroid is overactive; nor, on the other hand, is it proven that the function of the thyroid lies in the neutralization of poisons elaborated elsewhere.

In recent years the surgical treatment of exophthalmic goitre has become very prominent. It also is based upon the idea that the enlarged thyroid is overactive in pouring its secretion into the lymphatics, and the cases are therefore subjected to the partial extirpation of the thyroid.

The operation is a serious one, hemorrhage being very difficult to control. The patients do not take the anæsthetic well and many have died on the table.

Of late years, however, many of these operations have been performed under a local anæsthetic. Kocher²⁴ has reported fifty-nine cases, in which the results have been on the whole very satisfactory, often with almost complete or complete relief of all the symptoms. Usually the exophthalmos persists or disappears gradually, and often the improvement in the symptoms does not immediately follow the operation, but appears later. Much anxiety has been expressed from time to time as to the dangers of allowing the escape of thyroid secretion into

the wound during such an operation, and the fever which sometimes follows the operations has been ascribed to this. Lanz,²⁵ however, has shown experimentally that the most violent crushing and laceration of the thyroid which is then left *in situ* is not usually followed by any rise in temperature nor by any special untoward symptoms.

Ehrich has reported eight cases of operative extirpation of part of the thyroid in exophthalmic goitre, but is far less enthusiastic about the results. Many of these were not relieved, or suffered a recurrence of all the old symptoms after a temporary relief. He thinks that on the whole the good results are due mainly to the regular régime of the hospital for a time after the operation and to the suggestive effect of the operation.

In some instances merely ligation of the vessels of the thyroid has been performed, often with favorable results.

In none of these operations has any attention been paid to the condition of the parathyroids.

Operations for the section or removal of the cervical sympathetic trunks have been performed (Jaboulay,²⁶ Balacescu²⁷), with results which they claim to be quite as good as those obtained by the extirpation of the thyroid.

A definite opinion as to the value of these different methods of treatment must, however, be reserved until our knowledge of the results is more extended.

William G. MacCallum.

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EYEBALL, ENUCLEATION AND EVISCERATION OF.—I. ENUCLEATION.—By enucleation is meant a shelling of the eyeball out of Tenon's capsule with preservation of the relation between the conjunctiva, ocular tendons, and the other contents of the orbit.

History.—In 1841 Bonnet, of Lyons, first described and recommended true enucleation. The operation had been performed in a very crude manner by Bartisch, of Saxony, in 1583, by passing a sharp spoon behind the eyeball and thus gouging it out of Tenon's capsule. Bonnet's operation had the great merit of preserving the capsule of Tenon and disturbing as little as possible the soft parts of the orbit. It became justly popular. Like most surgical procedures it has been variously modified by different operators. During the past few years it has been greatly improved and its cosmetic effect enhanced by suturing the tendons of the four straight muscles to the conjunctiva.

Operation.—The following instruments are required: A stop speculum, fixation forceps, toothed forceps, strabismus scissors, strabismus hook, a strong pair of scissors curved on the flat for cutting the optic nerve, a needle-holder, fine curved needles, and black silk for sutures. A general anæsthetic is advisable, although the operation may be performed under local anæsthesia.

The lids being held apart with a stop speculum, the surgeon incises, with strabismus scissors, the conjunctiva and adjacent fascia all around as close as possible to the corneal margin, and dissects the same from the sclerotic as far as the insertions of the tendons of the straight muscles. The tendon of each straight muscle, beginning with the internal rectus, is then, in succession, raised upon a strabismus hook and secured with a suture of black silk, after which the tendon is severed with strabismus scissors as close to the eyeball as possible. The anterior portion of the eyeball being now free from all attachments, may be dislocated forward by pressing the stop speculum back. The curved enucleation scissors are next introduced with the points closed and are pushed backward between the eyeball and the detached conjunctiva until the optic nerve is felt. After the exact position of the optic nerve is found, it is included between the blades and cut close to the sclerotic by one strong cut. The eyeball now readily protrudes and is held by the fingers of the left hand, while the tendons of the two oblique muscles and all adherent tissue are severed close to the globe. A small ball of sterilized gauze is inserted in the capsule of Tenon for the purpose of checking hemorrhage and of aiding the next step, the suturing of the tendons of the straight muscles to prevent their retraction. Each rectus tendon is now drawn forward and fastened to the margin of the conjunctiva by the same suture which was inserted just before the division of the tendon. The sterile gauze should now be removed, the margins of the conjunctiva and capsule of Tenon united with several interrupted sutures, and a dry antiseptic dressing applied. Both eyes should be bandaged for twenty-four hours and the patient kept in bed for a couple of days. The socket should be washed out once daily with physiologic salt solution until after four or five days, when all dressings may be discontinued.

The technique of the operation, as above described, has been varied by different operators. The most important variations relate to methods of preparing the stump after enucleation, which will best secure motility of the prosthesis and furnish cosmetic results. The following method has been brought forward by G. F. Suker: After removing the eye, the severed tendons of the recti muscles are brought together by means of the silk guides and sutured one to the other with either catgut or silk. The conjunctiva from above and below is then brought over the muscle stump and sutured with a continuous or interrupted suture. H. V. Wurdemann, who was one of the first ophthalmologists to point out the advantages of a properly prepared stump, makes a pouch suture by weaving the needle along the cut edges of the divided conjunctiva and Tenon's capsule. In passing the recti tendons, each one is picked up on the needle.

H. Schmidt has suggested the following method: Each tendon of the recti muscles is secured by a catgut suture, and, after division, is fastened to a slit made in the conjunctiva over the site of the tendon's insertion. The opposite edges of the conjunctiva are then brought together with a continuous suture.

Priestley Smith has described the following method of suturing the tendons to the conjunctiva: A narrow horizontal fold of the conjunctiva over the internal rectus is pinched up so as to include the subjacent connective tissue and muscle, and a black silk thread is carried through these structures by means of a curved needle. The suture is then tied firmly but not too tightly. A second suture is applied in like manner to the external rectus. The upper and lower recti may be treated in the same way, but this is of less importance. The enucleation is then carried out and the conjunctival aperture may or may not be closed by one or more vertical sutures.

Complications and Accidents.—Hemorrhage, occasionally severe and persistent, may occur during the operation or later. In enucleating an inflamed eye, there is always a good deal of hemorrhage, particularly where there has been extension of inflammation into the surrounding tissue. The hemorrhage in this case is beneficial. Hemorrhages following an enucleation may require repeated packing of the orbit with antiseptic gauze. Occasionally a secondary hemorrhage occurs, when the dressings must be removed and the orbit packed with gauze. In these cases the tissues of the orbit may become greatly swollen from infiltration with blood. In chronically inflamed eyes, dense adhesions, binding the conjunctiva and its underlying fascia to the sclerotic and the tendons of the straight muscles, may be encountered. These cases often require a most careful dissection in order to expose the tendons, but by taking time and keeping the sclerotic always before him, the surgeon may perform the operation without accident. In enucleating an eyeball that has been perforated, or one soft from any cause, great care must be taken to remove it without leaving portions of the sclera and choroid behind. When an eyeball is enucleated because it contains a malignant growth, the posterior orbit should be carefully explored with the finger and probe before severing the optic nerve; and if a tumor is found, it should be removed along with the eyeball. As much of the optic nerve as possible should be removed with the globe. In very rare cases, enucleation has been followed by fatal meningitis, especially when performed on an eye within which suppuration was taking place. Up to 1900 G. E. de Schweinitz had collected fifty-two cases of fatal meningitis following enucleation, "thirty-three of which certainly—and a larger number probably—had followed enucleation for one stage or another of suppurative disease within the globe." The risk of a fatal termination from any cause after enucleation is about one in sixteen hundred. Meningitis after enucleation of a non-suppurating eyeball is exceedingly rare. In 1898 the Committee of the Ophthalmological Society of the United Kingdom could not find a single instance among 10,734 cases gathered from various sources.

Indications for Enucleation.—There are certain affections of the eye for the relief of which enucleation is demanded and cannot be replaced by any other operation. Enucleation is demanded in all cases of malignant tumor of the globe except in those rare cases of tumors which grow at the limbus and on the conjunctiva or iris. It is also required in cases of malignant tumors of the orbit which cannot be removed without sacrificing the eye. Enucleation is to be performed in those cases of sympathetic ophthalmitis in which the sight of the exciting eye has been lost. It is also demanded in the cases of eyes so injured that they are likely to excite sympathetic ophthalmitis, if two weeks or more have elapsed since the injury; for while enucleation cannot prevent all cases of sympathetic ophthalmitis, it is the operation which holds out the best chance for the prevention of the disease.

On this account enucleation should be performed in the case of an eye with a wound so situated as to involve the ciliary region, and so extensive as to have destroyed the sight or to make its ultimate destruction by iridocyclitis reasonably certain. It is also indicated in the case of an eye with a wound in the ciliary region, complicated by severe inflammation of the iris or ciliary body, even if sight is not destroyed; or of an eye containing a foreign body, which judicious efforts have failed to extract, and in which severe iritis is present, even if sight is not destroyed. Enucleation is also to be performed in the case of an eye in which the wound has involved the cornea, iris, or ciliary region, and in which persistent sympathetic irritation in the fellow-eye has occurred, or in which there have been repeated relapses of sympathetic irritation; in the case of an eye long blind from injury which has become red and painful; in cases of painful phthisis bulbi, and in those in which the choroid has undergone calcareous changes. Enucleation is also indicated