

tive appreciation of the lesion presenting and the method of treatment.

1. Many of these men were admitted with an obvious lesion of a major vessel. The limb at the site of the lesion was tense but not too tense. The distal circulation was fair or reasonably good. There was no obvious persisting hæmorrhage requiring immediate attention. Sometimes there was some question of a distal pulse. The vessel may have been partly torn, and, in spite of this and an overlying blood clot a moderate amount of blood was passing down the limb beyond the wound in the artery. With penicillin and sulfonamides available, sepsis was probably not a great factor. One might, under careful observation, postpone operation for a period of 12 to 24 hours and thus allow the collateral circulation to more adequately adapt itself to its increased load. Where persisting hæmorrhage was a factor there was of course no alternative but immediate surgery.

2. Patients were admitted with an obvious lesion of a major vessel. The limb at the site of injury may or may not have been tense. Persisting hæmorrhage was not a factor. There was no apparent circulation in the distal portion of the limb, collateral or otherwise. The limb was white and cold, often passively immobile, and muscles were already tense, firm and tender. Observations and questioning revealed the fact that this state of affairs occurred very early following injury—a matter of 2 to 3 hours. Obliteration of deep circulation alone did not seem responsible. Something had happened to the collateral circulation—call it spasm or what one will—which did not seem to recover in spite of any method of approach. The limb was doomed. There seemed to be some other factor involved—one which is not at all clear.

3. Repair of a wounded vessel can at times be done and continuity re-established and maintained with or without heparin. Collateral circulation can adapt itself quickly as a result of the diminution of the lumen and in a reasonable period of time, assume the entire load and permit ligation of the wounded vessel. The procedure is however a dangerous one and demands careful postoperative supervision and prolonged retention in hospital. Such is not always possible.

4. The use of tubes and grafts must be considered further, if for no other reason than to maintain circulation for a sufficient period to allow collateral circulation to take over the load.

Any method one might employ requires time and careful postoperative care. There are some cases ideally suited for and likely to benefit from this method of treatment. It can be employed even in time of battle in forward areas but with limitations and accompanying hazards.

5. The postoperative care would seem most important no matter what type of treatment had been used. Further immediate transport is definitely contraindicated. Only when distal circulation is well established should these patients be moved. Exposure of limb to room temperature is indicated. The application of heat to a limb hovering between life and death will soon tip the scales toward the latter. Splints where required must be effective but minimal. A position of dependency or one closely approaching the level of the body would seem desirable.

LOCALIZED (PRETIBIAL) MYXŒDEMA ASSOCIATED WITH GRAVES' DISEASE*

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THROUGH common usage, the term myxœdema has become practically synonymous with hypothyroidism. Actually, myxœdema is a pathological condition involving the skin and other tissues, one cause of which is hypothyroidism. It is not generally known that the disorder can be associated with hyperthyroidism, particularly that of the exophthalmic goitre type.

Although the preceding literature described the occurrence of œdema complicating Graves' disease,^{1, 2} the earliest reference to the observed co-existence of myxœdema and Graves' disease which could be found was in a paper by Sollier,³ in 1891. Referring to the association of the two abnormalities, Putnam⁴ in 1894 admitted that myxœdema might co-exist with Graves' disease but he quite reasonably questioned the likelihood of the former condition developing while the thyroid was secreting an excess of its active principle.

Subsequent observations have established the fact that the type of myxœdema which is most

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commonly associated with Graves' disease is a localized condition affecting the lower extremities, and which may originate during the stage of active thyrotoxicosis. Apparently, the first published record of this variety of non-pitting œdema was made by Hektoen⁵ in September, 1895, when he noted in the report of a post-mortem examination of a case of exophthalmic goitre that the skin over the anterior aspect of the lower third of each leg was swollen and elastic, like myxœdema. On section, the subcutaneous tissue appeared of a light yellow colour and infiltrated with a homogeneous, semi-solid mucoid material.

Watson-Williams⁶ described a similar case in December, 1895. Mackenzie,⁷ in 1897, recorded the occurrence of a non-pitting swelling resembling that of myxœdema, affecting the lower extremities, the feet excepted, of two patients with Graves' disease. Morrow⁸ reported an example of the disease in 1899 and, like Sollier,³ commented upon the symmetrical distribution of the lesions as well as their resemblance to elephantiasis. Dore,⁹ in 1900, also referred to a non-pitting swelling of the lower extremities, similar to myxœdema, in a patient with Graves' disease. Thereafter, interest in the disorder lapsed, evidently, to be revived in 1927 by Richter,¹⁰ although certain cases variously described during the intervening period as circumscribed scleroderma¹¹ and trophœdema,¹² involving the legs of patients with exophthalmic goitre, were doubtless examples of the same condition.

During the past 18 years a number of cases of localized (pretibial) myxœdema have been reported, mainly in the dermatological literature, which probably accounts for the failure of the disease to gain recognition in textbooks on medicine. Comprehensive reviews of the subject have been given by Pillsbury and Stokes,¹³ Carol¹⁴ and Trotter and Eden.¹⁵ The last-named writers were able to collect 45 published papers containing references to 73 recorded cases of localized pretibial myxœdema to which they added four cases.

Even although fewer than 80 cases of this particular type of atypical myxœdema are on record, the disease may be more common than is generally realized. In fact, Trotter and Eden¹⁵ found it in 3% of thyrotoxic patients when they looked especially for it.

Clinically, this peculiar form of solid œdema, which has been described as occurring only in

persons with present or past thyrotoxicosis, involves the lower portions of the legs, bilaterally, with extension at times to the dorsum of the feet or upward toward the knees. The lesions are variable, ranging from plaque-like nodules to diffuse irregular swellings involving the whole circumference of the leg. The affected areas of skin feel thick, coarse and dry to the touch and have an uneven contour. There is often an associated excessive growth of unusually coarse hair. The sites of the emergence of the hairs from the skin create a characteristic dimpled or "pigskin" effect. Pink or brownish discoloration may be present and the surface temperature of the affected parts may be several degrees cooler than that of the adjacent normal skin. In some cases, the skin is raised in irregular folds and any scars which may be present show hypertrophy. In many instances, the development of the circumscribed myxœdema has been preceded by pitting œdema of cardiac origin. According to the data reviewed by Trotter and Eden,¹⁵ about one-half the number of cases of pretibial myxœdema developed during the active stage of toxic thyroid disease, before treatment had been undertaken. In the remainder, the cutaneous lesions followed thyroidectomy but, in a considerable proportion of these cases, residual or recurrent thyrotoxicosis existed.

The characteristic histological features consist of the presence of so-called mucin or a mucin-like substance demonstrable by special staining techniques and an associated splitting apart of the connective tissue fibres. Hyperkeratosis is often present. There are no signs of inflammation or lymphatic stasis.

Knowledge regarding the biochemistry of the skin in health and disease is remarkably deficient. The bulk of the information concerning the nature of the changes in the skin in myxœdema has been acquired by histochemical methods. Apparently the only report of an attempt at the chemical analysis of the skin in this atypical myxœdema is that of Carol,¹⁴ who extracted a mucin-like substance which, after hydrolysis with hydrochloric acid, caused a slight reduction of Fehling's solution.

Opportunity has been provided to study two cases of this little understood type of myxœdema which is associated with Graves' disease. The observations are presented below.

CASE 1

Miss R.M., aged 19, with non-contributory family and past histories, became aware of fatigability, cardiac palpitation, tachycardia, nervousness and emotional instability in November, 1943. A soft, pitting œdema of both ankles, present only at the end of the day, existed for about one week and was followed by a persistent, irregular, solid swelling involving the lower third of the legs above the ankles.

Clinical investigation in February, 1944, revealed definite manifestations of thyrotoxicosis without obvious weight loss. The patient was apprehensive, tense and restless. The eyes had a distinct stare. The palms were moist and a fine tremor of the outstretched fingers was present. The thyroid gland showed moderate diffuse enlargement with a palpable nodule in the right lobe. The basal metabolic rate was +46%, with a resting pulse rate persistently faster than 100 beats per minute; weight 130 lb. There were no clinical signs of cardiac failure. The blood pressure was 140/60 mm. Hg.

Both legs between the ankles and the knees were definitely enlarged due to obvious thickening of the skin. The process was quite sharply demarcated below, forming a distinct ledge above the ankles; but it merged gradually into normal skin below the knees (Figs. 1 and 2). The involved parts had an irregular contour particularly noticeable on running the hand over the surface. The skin was quite dry in contrast to the moistness of other parts of the body surface. The elevated areas presented a pinkish, blotchy discoloration and there was a heavy growth of coarse dark hair over the anterior surface of the legs. The dimpling of the skin gave it an orange-peel appearance. This solid, non-pitting œdema involved the whole circumference of the legs which measured 16 inches at the calves and 12½ inches above the ankles. The skin temperature was 1 to 2 degrees lower than that of unaffected parts. The ankles and feet were normal in size and appearance. There was no sign of active inflammation and no similar lesions were present elsewhere on the body. A recently produced traumatic break in the skin surface on the anterior aspect of the right leg permitted the escape of a glairy fluid.

No albuminuria was present on repeated examinations. The non-protein nitrogen of the blood was 37.0 mgm. %. The blood sugar was normal. The total plasma proteins were 6.3%, consisting of albumin 3.6%, globulin 2.7% with an A:G ratio 1.3:1. A moderate hypochromic anemia existed. With the exception of a slight relative lymphocytosis, the white blood cells were normal. The Wassermann reaction was negative.

A biopsy specimen of skin and subcutaneous tissue was obtained from an affected area with the patient under gas anesthesia. During this operation, a layer of semi-solid, lobulated, yellowish material about one inch thick was observed between the epidermis and the fascia covering the muscle. A glairy, gelatinous substance oozed from the cut surfaces. A portion of the tissue so obtained was placed in absolute ethyl alcohol for histological study and the remainder was used for chemical analysis, as described below.

Histologically, the epidermis was essentially normal. The papillary and subpapillary layers of the corium showed hyaline degeneration of the fibrous connective tissue. The remainder of the corium in its entirety exhibited a wide separation of the connective tissue cells and the strands of connective tissue, by the presence of a homogeneous, finely reticulated substance in the interstitial spaces. Scattered foci of chronic inflammatory cells, lymphocytes and plasma cells, were observed about the small blood vessels, the sweat glands and the hair follicles (Figs. 3 and 4). The material in the interstitial spaces had the appearance and the staining characteristics of "mucoid".

When stained with hæmatoxylin and eosin, this took up the basophilic hæmatoxylin. With mucicarmine, it stained a bright to dark red colour and with thionin, it showed a metachromatic staining reaction varying from blue to purplish red.

This patient was treated with thiouracil with gratifying results insofar as the general thyrotoxic manifestations were concerned but without appreciable change in the condition of the legs.

CASE 2

Mrs. E.P., aged 55, developed symptoms due to thyrotoxicosis in 1938, including palpitation, tachycardia, loss of weight, exophthalmos, tremor and heat intolerance. Prior to a subtotal thyroidectomy in 1940, the basal metabolic rate was +60%. The thyroid tissue revealed epithelial hyperplasia typical of that occurring in Graves' disease. For about one year preceding the operation, ankle œdema had been noticed at night with its disappearance in the morning. While convalescing from the thyroidectomy, the patient became aware of the development of a different type of swelling which involved her legs. The skin became much firmer, coarser in texture and darker in colour than previously. The condition was not painful but an aching sensation would ensue if she were on her feet for any length of time.

Originally, this solid œdema was limited to the regions above the ankles, with an irregular distribution. Later, the feet became affected. The size of the extremities gradually increased and eventually assumed massive proportions which precluded her wearing shoes or moving about. Subsequently, deep furrows and ridges appeared on the feet and lower parts of the legs.

On examination, in March, 1945, apart from the extreme abnormality of the lower extremities noted above, the patient presented no remarkable physical or mental peculiarities, with the exception of obvious residual exophthalmos. There were, however, no manifestations of active hyperthyroidism or of hypothyroidism. The basal metabolic rate was +9%. Clinical and laboratory investigations failed to reveal evidence of cardiac or renal functional impairment. Hypochromic anemia of moderate severity existed. The blood pressure was 154/86 mm. Hg.

The skin of the body, with the exception of the legs below the knees, was smooth and of fine texture, but from about eight inches below the knees downward the skin gradually became thick and hard; over the ankles, the dorsum of the feet and toes it was piled up in folds. The scars remaining from previous plastic operations showed hypertrophy and keloid formation (Figs. 5 and 6). No suggestion of such change was visible in the only other superficial scar which she had, namely, that resulting from the thyroidectomy. A growth of coarse black hair was present over the upper parts of the legs anteriorly.

In an attempt to provide the patient with some measure of relief from her physical disability, a series of modified Kondoleon operations had been performed. The material which was excised at these operations consisted of a grossly thickened epidermis, beneath which was a thick, heavy layer of greyish-white, tough, fibrous-like tissue from the cut surfaces of which exuded a slimy, stringy, gelatinous material.

Histologically, the surface of the epidermis showed marked hyperkeratosis, with atrophy and loss of the rete cones (Fig. 7). The papillary, subpapillary and deeper layers of the corium contained much mucoid substance which was laid down as a finely reticulated basophilic material in the interstitial spaces. Also, the deeper layers of the corium and subcutaneous tissue showed marked fibrosis, the appearance being that of dense hyalinized collagenous fibrous connective tissue, free from inflammatory cell infiltration (Fig. 8).

CHEMICAL DATA*

Considerable confusion has existed with regard to the terminology and classification in respect to mucins and mucoids. According to Meyer,¹⁶ mucin is a chemically meaningless term which should be used only to describe a slimy secretion. The mucins and mucoids belong to a class of substances called glyco-proteins, consisting of a combination of carbohydrate and protein. Meyer¹⁶ has undertaken a classification of these compounds, based upon the nature of the carbohydrate radicals which are, ap-

while Chain and Duthie²⁰ demonstrated hyaluronic acid, or a substance closely resembling it, in rabbit skin. A search in the literature for a description of the isolation of these mucopolysaccharides from human skin was unsuccessful, although Chain and Duthie,²⁰ without presenting any evidence, stated that there seemed to be an accumulation of hyaluronic acid in the skin of myxœdematous subjects. Trotter and Eden¹⁵ suggested that hyaluronic acid might be a constituent of the substance causing the swelling in localized pretibial myxœdema.

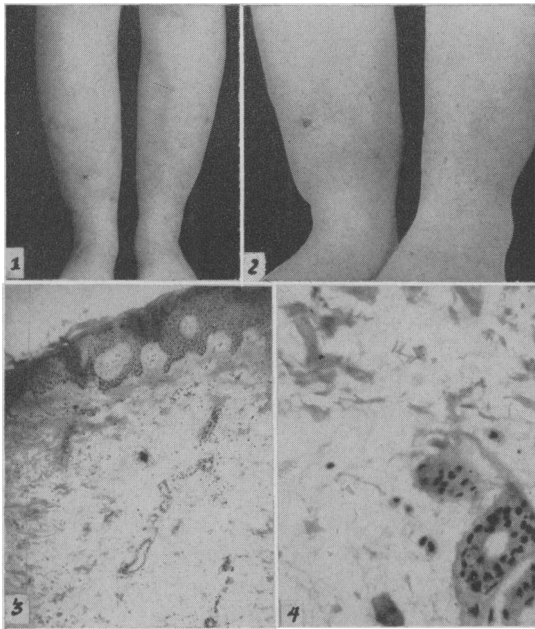
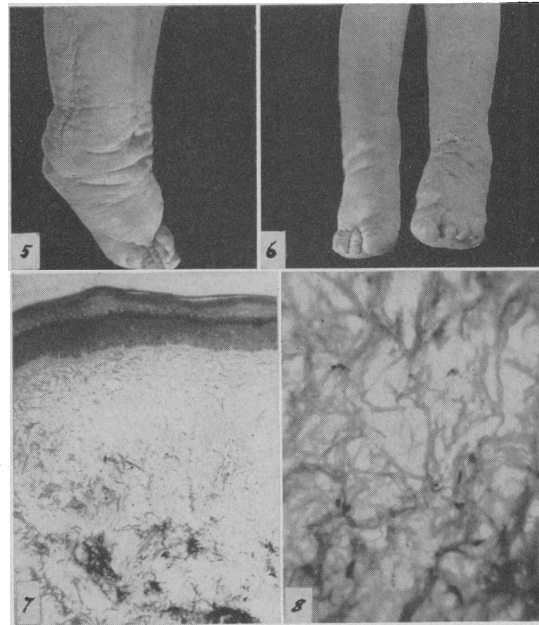


Fig. 1.—The clinical appearance of the lesions in Case 1, showing the general contour of the legs. Fig. 2.—The clinical appearance of the lesions in Case 1, showing the ledge-like demarcation above the ankles. Fig. 3.—Low-power photomicrograph of the skin biopsy from Case 1. Fig. 4.—High-power photomicrograph of the skin biopsy from Case 1.

parently, the essential components; and recent investigations have disclosed in a large measure the true nature of the substances. For example, Meyer and Palmer¹⁷ isolated from the gelatinous material in the vitreous humour of the eyes of cattle and from Wharton's jelly of umbilical cords a protein-free polysaccharide acid which they called hyaluronic acid. Meyer, Smyth and Dawson¹⁸ demonstrated a substance with identical properties in synovial fluid. Subsequently, Meyer and Chaffee¹⁹ separated hyaluronic acid and chondroitin sulphuric acid from pig skin,

* The chemical analyses of the specimens of human skin referred to in this section of the paper were made by Dr. H. L. Williams, Senior Research Fellow in Pathological Chemistry and Mr. R. H. Pearce, Research Assistant.



Figs. 5 and 6.—The clinical appearance of the lesions in Case 2, showing their elephantiasis-like character. Fig. 7.—Low-power photomicrograph of the affected skin from Case 2. Fig. 8.—High-power photomicrograph of the affected skin from Case 2.

In an attempt to investigate the chemical nature of the mucinous material which was present in the specimens of skin removed from the legs of the two patients referred to in this report, the skin was treated in essentially the same manner as that employed by Meyer and Palmer¹⁷ for the isolation of polysaccharides from vitreous humour and umbilical cords. This technique was considered to yield the hyaluronic acid fraction. Treatment with alkali, according to the procedure used by Levene,^{21, 22} for the separation of the mucoid of sclerae, gave the chondroitin sulphuric acid fraction. For the purpose of comparison, samples of skin obtained from surgically amputated legs were analyzed in a like manner.

All of the samples, after treatment as above, were subjected to hydrolysis by means of a solu-

tion of an active hyaluronidase preparation contained in an extract of bovine testes, made according to a method described by Madinaveitia.²³ This resulted in the liberation of reducing substances which consisted of hexosamine, estimated by the method of Palmer, Smyth and Meyer²⁴ and glucuronic acid, estimated according to the method of Maughan, Evelyn and Browne.²⁵ These two polysaccharides were found to be present in the hydrolysate in approximately equimolecular amounts.

It is of interest to note that of the substances capable of being hydrolyzed by hyaluronidase, only hyaluronic acid, chondroitin sulphuric acid and mucoitin sulphuric acid contain hexosamine and glucuronic acid in equimolecular ratios. Therefore, in view of the findings mentioned above, it must be assumed that mucopolysaccharides of this nature are constituents of human skin. The analyses revealed, moreover, that both hyaluronic acid and chondroitin sulphuric acid were present in much greater quantities in the affected skin of the patients with pretibial myxœdema than in the control samples of skin. The results of these investigations will appear in greater detail in a succeeding report.

DISCUSSION

The relationship of so-called pretibial myxœdema to thyroid dysfunction has not been explained. Doubt has been expressed as to the applicability of the word myxœdema in reference to the pathological condition in question. For example, O'Leary²⁶ preferred to avoid the expression "localized myxœdema" on the ground that the term myxœdema should be reserved for use in connection with the more classical clinical manifestations which develop as a result of the hypofunctioning of the thyroid gland. On the other hand, Pillsbury and Stokes¹³ favoured the descriptive term "circumscribed myxœdema", pointing out that myxœdema (mucin œdema) connotes but one feature of the myxœdematous process, while the word circumscribed serves to differentiate the particular disorder from conditions of general constitutional character.

That the pathological condition of the skin under discussion is myxomatous in nature seems certain. The presence of so-called mucin in the skin is a rather constant observation in myxœdema.²⁷ Carol¹⁴ demonstrated a mucin-like substance in the skin of a thyrotoxic patient with pretibial myxœdema, and Trotter and

Eden¹⁵ suggested that hyaluronic acid, a constituent of mucin, may be present in the affected skin of patients with this condition. The results of the chemical analyses referred to in the present paper lend support to that suggestion.

The existence of the mucopolysaccharide, hyaluronic acid, in excessive amount in the connective tissue of the cutis might be explainable in three ways: (1) its transportation to and deposition in the affected parts; (2) its formation in abnormal amount from connective tissue cells; or (3) as a result of a local disturbance of hyaluronic acid metabolism. The first possibility, *i.e.*, mucinous infiltration from without the affected sites, is extremely unlikely. Connective tissue cells possess the property of secreting a mucinous substance, but whether the accumulation of this material in excess, under certain circumstances, is a manifestation of cellular over-stimulation, degeneration, nutritional defect on a basis of gravitational œdema, a reversion to an embryonal state, or the result of an enzyme deficiency is undecided. However, it may be of significance in regard to the last-mentioned possibility that the enzyme hyaluronidase which causes hydrolysis of hyaluronic acid and reduces its viscosity has been demonstrated in rabbit skin in rather large amount.²⁸ The rôle, if any, of this enzyme in the pathogenesis of myxœdema is purely speculative at the present time. However, its possible significance in this regard is under investigation. Nevertheless, it is of interest to note that, according to the data of Meyer and Chaffee¹⁹ and Chain and Duthie,²⁰ hyaluronidase is identical with the "spreading factor" of Duran-Reynals²⁹ and McClean³⁰ which is of importance apparently in respect to the invasive properties of certain micro-organisms and possibly to capillary permeability as well.

The treatment of pretibial myxœdema is not encouraging. The condition has not responded to thyroid or other forms of medication. Excision of the affected areas, especially when localized, has been accomplished in some cases and the spontaneous disappearance of the lesions has been reported.

SUMMARY

Two examples of pretibial myxœdema associated with Graves' disease are described. In one case the myxœdema developed early in the course of the thyrotoxic disease, while in the other it followed a subtotal thyroidectomy in the absence

of obvious hypothyroidism. The clinical features of the condition, including its possible resemblance to elephantiasis due to lymphatic obstruction, are reviewed. In both instances, the affected skin showed a higher content of the mucopolysaccharides, hyaluronic acid and chondroitin sulphuric acid, than was found in the skin from the legs of other patients. The significance of these chemical substances in relation to the etiology of the cutaneous complications of thyroid disease is undecided.

The author wishes to express his appreciation to Dr. J. H. Fisher, Professor of Pathology, for the preparation and the interpretation of the histological specimens, and to Dr. H. O. Foucar for permission to include the record of the patient referred to as Case 2.

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THE CAUSE OF OLD AGE.—“As the World waxeth old, Men grow old with it: not by reason of the Age of the World, but because of the great Increase of living Creatures which infect the very air, that every way encompasseth us, and Through our Negligence in ordering our lives and that great Ignorance of the Properties which are in things conducing to Health, which might help a disordered way of Living, and might supply the defect of due Government.”—Roger Bacon: *The Cure of old Age and the Preservation of Youth*.

METASTATIC TUMOURS OF BRAIN*

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THIS is a review of 82 cases of metastatic tumour in the brain. We have excluded the cases in which the metastases were confined to the skull or dura mater, and the cases in which the metastatic tumours were causing compression of the spinal cord or spinal nerve roots.

As would be expected, the majority of the tumours occurred in patients between the ages of 30 and 70, the sixth decade containing the largest number (Table I). About 60% of the tumours were in males.

TABLE I.
AGE INCIDENCE

Age	Male	Female	Total
1 - 9.....	0	0	0
10 - 19.....	1	0	1
20 - 29.....	2	0	2
30 - 39.....	4	7	11
40 - 49.....	10	8	18
50 - 59.....	18	11	29
60 - 69.....	9	5	14
70 - 79.....	2	0	2
Unknown.....	3	2	5
	49	33	82

The most common primary site, as shown in Table II, was the lung, and the large preponderance of males in this group is noteworthy. The breast came second in frequency as the site of the primary tumour. The primary in the breast was almost invariably recognized before symptoms of cerebral metastases were observed. This was not true of the primaries in lung. Metastases from large intestine and malignant melanomas formed the only other large groups.

Table III gives the cerebral sites of the metastatic deposits and the proportion of multiple to single metastases. It is interesting to note the numerous metastatic deposits in the pituitary gland and in the subarachnoid space. Only once in this whole series was a metastasis seen in the choroid plexus. The figure given in the table for single metastases is probably too high, as 18 of these 41 were operative cases which did not come to post mortem. In these cases we cannot be sure that additional cerebral metastases were not present.

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