

SOME RARE CASES OF SARCOMA OF THE THYROID.¹

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THE subject of this paper might appear on superficial consideration to be rather of academic than of practical interest, but the subject of malignant disease in any shape and form is essentially practical and if by calling attention to it the early diagnosis of malignant disease of the thyroid will be facilitated and radical treatment thereby obtained a great amount of suffering and a terrible termination to life may be averted, if permanent cure do not result.

Berry, in his excellent work on the diseases of the thyroid body, suggests that although sarcomata may appear to be equally common as carcinomata of the thyroid, yet it is probable that more cases of sarcoma are recorded in literature or placed in museums on account of their greater rapidity of growth rendering them a more striking affection and that consequently carcinoma may be really the more frequent. In Charing Cross Hospital during the past six years we have on record one case of carcinoma, one of malignant adenoma, and four cases of sarcoma of the thyroid.

The four cases that I wish to record this evening confirm the statement that most cases of malignant thyroid are unfortunately seen at too late a stage for radical treatment. Extirpation was possible in one only and this case indicates clearly the uncertainty of diagnosis and prognosis and the difficulty of removing the disease once it has become extra-capsular. In one case tracheotomy was performed. Malignant disease of the thyroid is said to be more common in glands which have been the seats of previous non-malignant growths. This may be correct generally but there is no definite history in either of these cases to suggest the presence of any form of simple growth and in only one of the four cases was there a probability of any previous disease of the thyroid and this was not of the nature of a growth. In this case a preceding pathological condition may be assumed, inasmuch as there is a possibility that the patient suffered to a slight extent from myxœdema for some time before the malignant disease was observed. This, however, is a moot point, as it is not improbable that a diffuse form of sarcoma may have existed for some time, resulting in the destruction of the essential elements of the thyroid and loss of function, with myxœdema following as a logical sequence. The disease generally affects males and females equally and the proportion is retained in this instance, two of the patients being males and two females. It is more common in districts where goitre is endemic. During the later years of their lives these four patients lived at Barkfield in Kent, Lewisham, Greenwich, and Wandsworth respectively, none of which districts are, I believe, goitrous. The onset of malignant disease of the thyroid is late in life. Berry, in his investigations, limits practically its earliest appearance to 40 years of age. In these four cases the ages were respectively 57, 59, 60, and 69 years. The two younger patients were males, the two older were females. The patient who was 60 years of age had the symptoms of myxœdema and the one who was aged 69 years had the affected lobe extirpated. The histological varieties of sarcoma found in the thyroid are either spindle- or round-celled; in three of the following cases the cells were round and of medium size. In the fourth the structure was that of a giant-celled sarcoma. The duration of life in malignant thyroid is variable, from nine weeks to two and a half years being the limits, although in those cases grafted on to pre-existing simple growths the date of origin of malignancy is uncertain and its duration may be considerably longer. These four cases terminated fatally in eight, nine, 12, and 17 months respectively from the period of earliest observation of the growth, and being primarily malignant the history is fairly accurate. The immediate cause of death in each case is recorded as follows. The first patient died suddenly from heart and respiratory failure five or six hours after tracheotomy; the

second from syncope on the day upon which he was prepared for tracheotomy; the third five days after extirpation, from exhaustion; and the fourth from general suppurative peritonitis, pleurisy, and pericarditis. The sarcomata grow more rapidly than do the carcinomata.

The seat of origin of sarcoma.—Whether one lobe is more prone to involvement than the other I cannot say, but the isthmus is the least frequent site of origin. Sarcoma generally is more prone to involve one lobe and to grow rapidly; carcinoma early to involve the second lobe and to grow more slowly. Of these four cases three were primarily in the right lobe; of these one appeared in the mid-line but was clinically, and at the operation obviously, a growth of the right lobe. In the fourth case the growth involved both lobes simultaneously but grew more rapidly in the right lobe, so that in all four cases the right lobe appeared to be selected by preference. Involvement of lymphatic glands is variable and is too late to be of diagnostic value; in three cases the cervical glands were involved and palpable, but when they became the seat of new growth it is impossible to say. In the fourth case—the (?) giant-cell sarcoma—no secondary glands were found.

Secondary growths.—In the earliest case, although the primary growth was most extensive and involved the walls of veins, the fasciæ, and the pleura, no embolic deposits were found. In the second case extensive secondary growths were found involving the dorsal and lumbar vertebrae, both kidneys, both suprarenals, the coeliac and cervical lymphatic glands, and the stomach. The last will be referred to later. In the extirpated case secondary growths were found in both kidneys and the cervical and thoracic glands were involved. In the fourth case, that with co-existing myxœdema, there were malignant ulcers of the stomach and intestine, malignant infiltration of the pancreas, and the cervical glands were involved.

Deviation of the trachea.—In three of these cases deviation was not marked, such slight deviation being the usual condition found in malignant disease. The greatest was one inch. In the fourth case—the (?) giant-cell sarcoma—the deviation of the trachea from the mid-line was two inches. Pain was not a prominent sign in either of these cases; two patients complained of slight neuralgic pain situated in the neck and radiating up towards the ear and down towards the chest. Dysphagia and dyspnoea were present in three cases.

Ingrowth into the trachea.—This is comparatively common and takes place usually from one-half to an inch below the cricoid cartilage. In the second of these cases the larynx had been invaded and the mucous membrane was ulcerated. In the fourth (the myxœdematous) case there was distinct infiltration of the submucous tissue of the larynx and the trachea. This extended for a distance of one and a half inches and resulted in a fusiform elevation; it extended above and below the cricoid and seemed to have enveloped, if not to have destroyed, the cartilage. There was no obvious loss of tissue—i.e., ulceration—over it.

The consistence of sarcoma generally is softer than is that of carcinoma of the thyroid. One of these cases was described as stonily hard, one as firm and elastic, and the other two as hard.

Complete fixation of the mass to deep structures was found in three cases.

The carotids.—In two cases the carotids were embedded in the growth. In the third case the vessel lay at the posterior border. In the fourth case the vessel lay at the outer border, below the growth.

CASE 1.—The patient, a man, aged 57 years, who was admitted to hospital on Oct. 25th, 1895, suffering from a tumour in the neck and was operated upon on the following day, died suddenly on the day of operation. The history of the case showed that during the winter of 1894, not more than 12 months previously, the patient noticed a lump of the size of a small marble which was situated behind the right sterno-mastoid at the junction of the lower and middle thirds. This disappeared in March, 1895 (at about the fifth month), and it returned in April, since when it had gradually increased in size. It had been painless and free from tenderness. In May (the seventh month) the patient began to have dysphagia for fluids; there was no difficulty in swallowing solids. In August (the tenth month) solids were taken with difficulty and this was accompanied by the onset of hoarseness. The dysphagia gradually increased, the hoarseness remaining more or less the same. Two weeks before admission the patient began to regurgitate food

¹ A paper read before the Harveian Society of London on March 6th, 1902.

shortly after taking it, but he did not feel nausea. He had lost flesh during the last six months. The patient had to recline or to sit up in bed, being prevented from lying down by a sense of threatened asphyxia. His expression was painful and distressed. He coughed frequently. The respirations, which were of a sighing, laboured character, were 28 and the rate of the pulse, which was small and weak, was 133. The patient was given two or three teaspoonfuls of beef-tea which were disposed of with great effort. About three minutes later, without difficulty or nausea, he regurgitated the beef-tea unchanged. This was repeated several times and on each successive occasion the beef-tea became increasingly mixed with mucus. The fifth time mucus composed the greater part of the regurgitated fluid and was markedly acid. On examination the abdominal wall was found to be emaciated and retracted. No tumour was felt and the liver was not enlarged. Pulsation was felt along the whole course of the abdominal aorta. A large mass was seen on the right side of the neck, measuring from four to five inches vertically and from five to six inches transversely. It extended from an inch to the left of the mid-line in front to within two and a half inches of the mid-line posteriorly. Above it reached as high as the base of the lower jaw; below it reached the clavicle and it projected about two inches above the normal surface of the neck. Numerous large veins ramified in the skin over the growth, but otherwise this was not obviously changed. On palpation the skin was found to be not hotter over the tumour than elsewhere but it appeared to be markedly thin and more or less adherent over the growth. The mass was absolutely fixed to deep structures and was stonily hard in all parts. There were no soft spots nor was fluctuation found anywhere. The thyroid notch was felt two and a half inches to the left of the mid-line; the trachea was consequently considerably deviated but was difficult to palpate (obscured by growth), and it appeared to lie near the mid-line, just above the supra-sternal notch. Mr. Boyd decided on immediate tracheotomy and the operation was performed at 3 P.M. on Oct. 26th. A 5 per cent. solution of cocaine was freely injected in all directions over the position of the trachea. An incision two and a half inches long was made from the lower border of the thyroid cartilage in a position two inches to the left of the mid-line, several bleeding points were secured, the fascia over the trachea was divided and the latter exposed, and three rings were cut. A bi-valve tracheotomy tube was inserted by means of a gum-elastic catheter used as a stylet. The patient felt no pain; the injection of cocaine was repeated several times during the operation. He was considerably relieved, the dyspnoea was markedly diminished, and he was comfortable. The patient died suddenly during the night from respiratory paralysis.

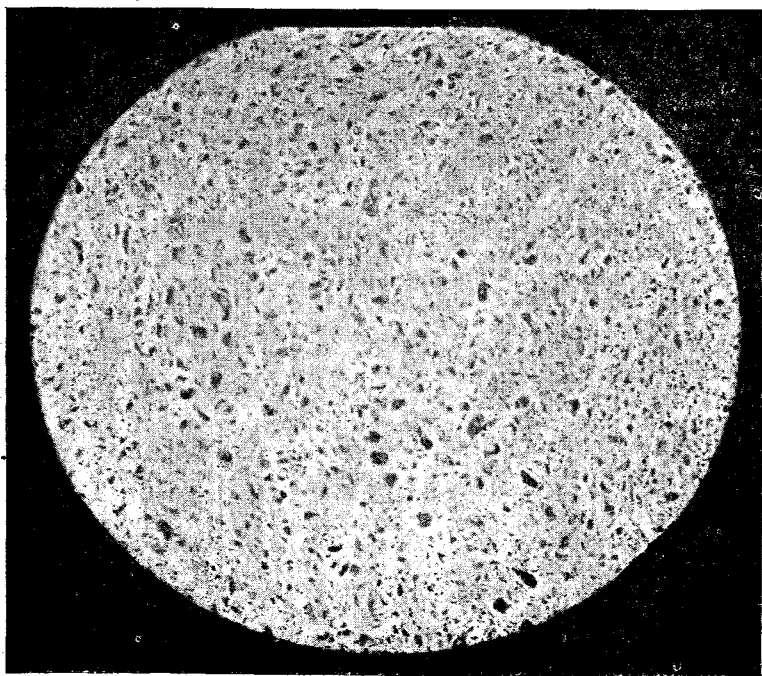
At the post-mortem examination the patient was found to be sparsely developed and emaciated. There was a large growth in the neck especially involving the right side; it weighed 15½ ounces. The growth extended from the first rib upwards for five and a half inches, its depth below the first rib was four inches, its breadth was two inches, and its antero-posterior diameter was three inches. It was lobulated, convex anteriorly and posteriorly where it was attached to the spine. It blocked completely the right inlet of the thorax and was pale in colour, soft and brain-like in consistence, and had the appearance of a sarcoma. It was firmly adherent to the anterior aspect of the lower cervical vertebræ behind the œsophagus. It involved the right lobe and isthmus, extending well over to the left side of the trachea without implicating the left lobe of the thyroid. The trachea had been greatly pushed over to the left side and in order to reach it the portion of growth in front of the trachea had to be cut through. The growth was closely attached to the trachea. The œsophagus lay between the tumour and the trachea; both the œsophagus and the pharynx were involved in the growth, especially the latter, the wall of which was atrophied. The œsophagus must have been greatly pressed upon throughout the entire length of the growth. Inferiorly the mass extended into the upper division of the thorax four inches below the level of the first rib. It lay in concert with the apex of the lung but did not involve its substance. It involved the right subclavian vein

in its course from the first rib to the innominate. It extended downwards over the arch of the aorta, involving the innominate and carotid vessels. The left vagus was deeply embedded in the growth. With regard to the heart there was no coarse lesion except one or two points of atheroma at the base of the aorta. There was no other disease of the viscera. The patient had an ununited fractured patella. On looking at the cut surface of the growth a central circular area was seen which presented the appearance of carcinoma, while the greater portion of the periphery showed the solid homogeneous appearance of sarcoma.

The following are points of interest in the case.

1. As to the histological appearances, sections showed under the low power an arrangement of cells which in parts immediately suggested sarcoma, there being little or no stroma and the cells were closely approximated and of fairly uniform size, but in other parts one would be led to diagnose carcinoma. Here there was a stroma consisting of degenerating fibrous tissue and round cells of a sarcomatous nature, throughout which were scattered, but not uniformly, a large number of what might be called giant cells (Fig. 1); these were of irregular shape and size, and were more or less angular and showed evidence of nuclear proliferation, vacuolation, and cell-inclusion (Fig. 2). In a small minority only of the cells the nuclei were multiple and discrete (Fig. 3); the majority presented imperfect nuclear proliferation. Were these cells of that variety which is generally called giant cells of new formation? Or were they simply clusters of thyroid epithelium aggregated and compressed so that the protoplasm surrounding the nuclei appeared to form one mass? The great variety in size, shape, and distribution of the cells and the character of the nuclei suggested the latter possibility. On the other hand, comparison with the imperfect giant cells of a growth removed by Mr. Morgan from the subcutaneous tissue of the forearm of a youth in November, 1900, where no such epithelial cells could possibly exist, rendered it possible that they were not of thyroid origin. Multi-nucleated giant-celled tumours growing in structures unassociated with bone have been recorded on numerous occasions. Some of these have been described as carcinoma but the great majority as sarcoma. Waring² has described a tumour which grew in the subcutaneous tissue of the neck which contained cartilage cells and showed cell inclusions but was probably, as he suggested, derived from some displaced embryonic osteo-genetic tissue associated with the clavicle. H. Snow, Targett, and others have recorded giant-celled tumours which have grown in the subcutaneous tissue

FIG. 1.



Case 1. Low power. Showing the giant cells interspersed in the fibrous and round-celled stroma.

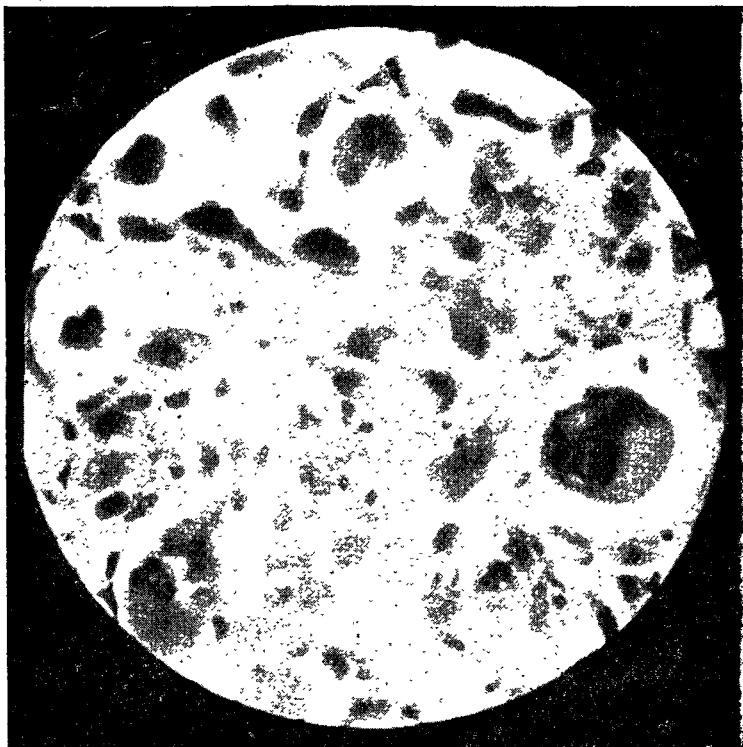
of the integuments and in the breast. I show a section of the growth removed by Mr. Morgan, also one of a giant-celled sarcoma recently removed by Mr. Stanley Boyd from the breast of an elderly woman, aged 60 years, in which the giant cells show distinct multiple nuclei. This patient (Case 1) was 57 years of age and most of Targett's cases were elderly subjects. He says that giant cells are seen in malignant tumours which have grown rapidly and are soft in structure. This thyroid tumour clinically was very hard but post mortem it was described as being soft and brain-like. It is probable that, as in the case of cysts, the hardness was due to tension, and as the tumour was of rapid growth and Mr. Boyd's "breast case" also showed recent very rapid increase in size Targett's statement is not negated by these cases. Mr. Morgan's patient was a youth. At the meeting of the Clinical Society of London on Feb. 28th, 1902, Mr. G. R. Turner showed giant-celled sarcoma growing from the synovial membrane of the ankle-joint, and at the same time I had the opportunity of seeing a section from a case recorded by Mr. Howard Marsh of a pedunculated sarcoma growing from the under aspect of the patella. In both these cases the cells were perfect myeloids, but their origin is closely associated with bone-forming tissues.

2. What was the cause of the dysphagia for fluids which set in first and which was not accompanied by signs of nerve involvement such as aphonia? The dysphagia for solids which occurred three months later was accompanied by hoarseness, showing probably direct involvement at the latter period of one recurrent laryngeal nerve. Post mortem there was a note that the left vagus was deeply embedded in the growth; it was obvious from the specimen that the right vagus and recurrent laryngeal nerves were involved. It is possible that the early dysphagia for fluids was mechanical, the fixation of the pharynx and larynx preventing the necessary movements, while the later dysphagia for solids was due to mechanical obstruction by pressure upon the œsophagus, aided perhaps by paresis of the muscles due to increasing involvement of the vagi and recurrent laryngeal nerves. Or was the early dysphagia of nervous origin and the later of superadded mechanical origin? That this sequence is probable is shown by the fact that towards the end persistent and rapid regurgitation of both solid and fluid food occurred.

3. It is questionable whether the small tumour first seen and which disappeared for about a month was not an adenoma which moved about freely.

CASE 2.—The patient, a married man, aged 59 years, was admitted to hospital on Feb. 28th, 1898, and he died on March 10th. It was ascertained that a sister of the patient had died from cancer, the site of which was not known. Eight months previously to admission the patient first noticed two hard lumps, one on either side in the region of the thyroid lobes. He rubbed them with hartshorn and thought that for about three weeks they got smaller. After this they began to increase in size; the right side had always been bigger than the left. There had been only slight neuralgic pain in the neck. The swelling on both sides had grown in a backward direction. Since the onset of the swelling the patient noticed a considerable accumulation of mucus in the throat. During the last fortnight the growth became half as big again as it was before. On admission the patient, who was a big powerful man, complained that he had lost flesh lately. His breathing was very audible and tubular. He could not swallow solids and his voice was slightly husky. There was an enormous swelling in the neck occupying the right side, the centre, and to a less extent the left side, of the neck, and extending from the jaw to the sternum. It involved both triangles. The consistence of that portion of the swelling on the right side was uniformly elastic but it did not fluctuate. Fixation to the adjacent parts was absolute. The skin on the right side was hot and congested but it was not tender or œdematous. The skin on the front of the neck and on the left side was unaltered. Along the posterior border of the sterno-mastoid was a chain of enlarged glands. The left border of the mass corresponded to the posterior border of the left sterno-mastoid, but the swelling on this side was far smaller than was that on the right side. Swallowing even of sops and fluids was difficult, but this varied. In an ophthalmological

FIG. 2.

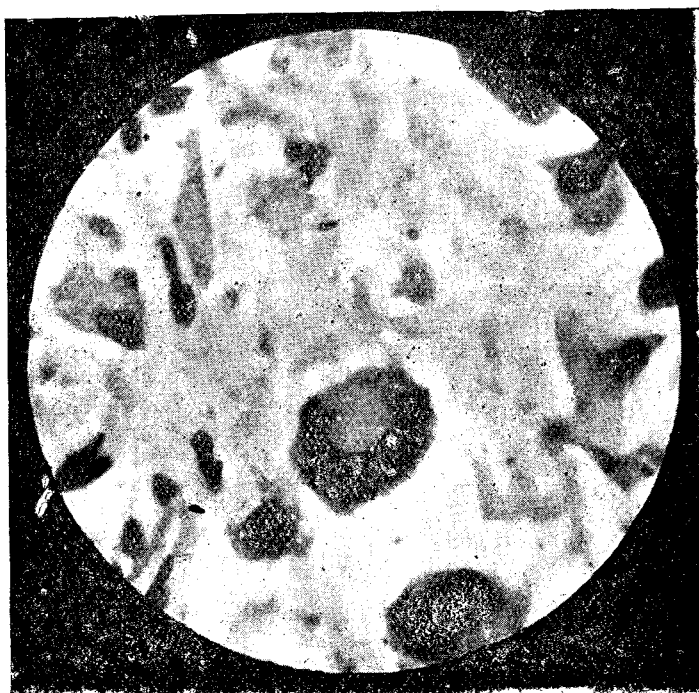


Case 1. High power. Showing a giant cell with vacuolation and cell inclusion.

examination by Dr. W. C. Bosanquet nothing pathological was found. Laryngological examination was carried out by Dr. F. Willcocks. The patient did not elevate his epiglottis in phonation; there was much swelling of the epiglottis and the arytenoids. The vocal cords were not visible. The superior orifice of the larynx was compressed laterally. Mr. Morgan did not consider the patient sufficiently distressed to need tracheotomy for some time after admission. Dyspnoea and dysphagia increasing, however, the patient was prepared for operation but he died suddenly from syncope.

That tracheotomy should be delayed until the dyspnoea has become a source of considerable distress to the patient is the teaching of those who have had experience of these cases, as once the incision is made septic changes in the

FIG. 3.



Case 1. High power. Showing a giant cell with nuclei arranged circumferentially.

growth and the complications following tracheotomy are very prone to occur. Palliative operations such as partial excision for relief of pressure symptoms should be undertaken only when there is great probability that the skin incision will completely heal or when the symptoms of distress are great. Tracheotomy may be performed early when there is danger of oedema of the glottis occurring or when the growth is slow and the tumour can be avoided in reaching the trachea. (*Vide Semon's case.*)

At the post-mortem examination the left pupil was seen to be larger than the right. The neck, which was greatly thickened by growth, was 21 inches in circumference. The growth was adherent to the skin on the right side; it extended up under the angle of the jaw and was firmly adherent to the cervical fascia. On the left side the line of cervical glands, much enlarged, could be distinguished separately. The thyroid growth involved the isthmus and both lobes. The right lobe and isthmus could not be distinguished as such, the left lobe on section retained its shape, though it was much enlarged. There was slight ulceration of the laryngeal mucous membrane. The growth did not extend into the mediastinum and the glands in the thorax were normal. There was no pressure on the veins. The left carotid, with the nerves, was embedded in its sheath; in the growth near the bifurcation the vagus nerve was tightly involved and compressed. The right carotid was lost in the growth. In the lower dorsal region a large secondary growth springing from the vertebræ projected forwards and partly surrounded, without involving, the aorta. It extended between the laminae backwards and several secondary nodules were found in the muscles behind. The spinal cord was not affected although the growth was very near it. There was a large mass of growth in the glands behind the cardiac end of the stomach; this was adherent to, and growing through, the stomach wall near its cardiac orifice and was fungating in the cavity. The growth involved half the circumference of the wall of the stomach near the cardiac orifice; part of it had ulcerated and it presented a hæmorrhagic appearance. About the middle of the stomach was a small ulcer with raised firm margins of the size of a sixpenny-piece. Both kidneys contained new growths. The largest, which weighed eight and a half ounces, was in the left kidney; that in the right weighed seven and a half ounces. Both suprarenals were involved by solitary growths, the largest occupying the whole of the left capsule. The liver and spleen were congested but there were no new growths. The lungs were not diseased.

The points of greatest interest in the case are the following. 1. The association of ulceration of the stomach and intestine in sarcoma of the thyroid in this case and in Case 4. The condition of the stomach I will refer to in discussing Case 4. 2. The signs of hyperæmia and the post-mortem evidence of attachment to the skin show how closely the latter may be involved and yet resist perforation. It is possible that the heat and redness of the skin might be due to involvement of the sympathetic, as suggested by Agnew; the rapid increase in size, however, towards the end, suggests that some inflammatory reaction was set up. The increase certainly was not due to hæmorrhage or to cystic degeneration. Clinically no note was made of eye changes, yet probably such existed, as an ophthalmological examination was made and the left pupil post mortem was stated to be more dilated than the right; probably the left sympathetic was becoming involved. 3. The secondary growths were exceedingly large and numerous; they were also median or symmetrical. Rolleston states that the vascular medulla of the suprarenals is more often affected by secondary deposits of sarcoma than of carcinoma.

Were the lumps first noticed simple growths irritated by the vigorous application of hartshorn and undergoing sarcomatous change in consequence? This is extremely improbable. On the other hand, spontaneous disappearance of malignant growths has been not infrequently noticed and in Case 1 also we have the statement that the first growth seemed to disappear. Thyroid sarcomata have shown great decrease in size following tracheotomy. The very notable case recorded by Sir Felix Semon³ and that recorded by Mr. G. R. Turner⁴ are cases in point.

CASE 3.—The patient, a widow, aged 69 years, who was admitted to hospital for swelling of the neck on Feb. 1st,

1900, was operated upon on the 3rd. Death took place on the 8th. The patient had had no children and had been a widow for four years. She had suffered from chronic bronchitis. Nine months previously her attention was drawn to the swelling by a shooting pain extending into the top of the left breast and up to the right side of the neck into her ear. The swelling was in the mid-line of the neck low down and had extended upwards gradually. It had grown more rapidly during the last few months. The swelling itself was painless. For some time she had had a "funny" sore-throat and complained that it hurt her to swallow her spittle but not food. She did not complain of unusual dyspnoea but obviously her breathing was not easy and natural even while she was at rest. On admission the patient was found to be a fairly healthy-looking woman for her age and had a good colour but was rather thin. The urine contained a little albumin. Occupying the lower part of the neck and extending from the sternal notch below, upwards to the level of the thyroid notch in the mid-line was an oval swelling of the size of a goose's egg. It lay obliquely and occupied chiefly the right side but it extended well beyond the mid-line into the left anterior triangle. The skin and veins over it appeared to be normal. On palpation the swelling was found to have a smooth surface except at its upper right lateral angle; here it terminated in a blunt point like the lateral lobe of the thyroid. On this were small masses, probably enlarged glands which caused it to be irregular at this part (? glands pushed into prominence). The growth did not appear to affect the isthmus and the left lobe was normal. In consistence it was firm and elastic, like a deep-seated thick-walled cyst. The right sterno-mastoid was stretched over the swelling but the inner edge of the muscle stood up clearly on bringing it into action. The infra-hyoid muscles could not be demonstrated. The trachea was pushed towards the left side from three-quarters of an inch to an inch beyond the mid-line. The right carotid artery was pushed backwards into the posterior triangle and could be easily felt pulsating behind the sterno-mastoid. The growth was not freely moveable but did not give the impression of being very fixed to surrounding parts, but it was firmly fixed to the trachea and moved with it on deglutition. The larynx was normal and the cords moved perfectly; the voice was unaltered. The patient did not complain of dyspnoea but she certainly breathed rapidly and with obvious effort. Dysphagia was not present except when the patient wished to swallow her spittle. She had coughed considerably since admission but she attributed this to chronic bronchitis. There was not much expectoration. Under the anæsthetic Mr. Stanley Boyd revised his diagnosis thus: "The evidence of deep cyst is very doubtful. Against malignancy is the smooth circumscribed surface and outline, the absence of dysphagia and of interference with the recurrent laryngeal nerve. In favour of malignancy is the short history, the patient's age, the fixation to the trachea, and the prominence of glands at the upper angle." Yet after Kocher's angular incision was made and the growth bared it appeared "as a pale, slightly bossy, circumscribed, encapsulated mass, it looked like an adenoma and I endeavoured to enucleate it, but could find no inner capsule of thyroid tissue so determined to extirpate it." Great difficulty was experienced in removing the growth which extended deeply into the thorax. A continuous chain of glands was seen. Into the cavity which was left in the thorax after the removal of the growth air was being freely sucked. A doubtful nodule of growth was observed in the cut surface of the portion of isthmus left. The wound was drained. The prognosis was grave. After the operation the patient was in a very precarious condition. Next day surgical emphysema developed and the patient appeared almost comatose until she was given a brisk purge (on the assumption that the condition was uræmic), which entirely dissipated the symptoms. She did not pick up at all after the operation and died on the fifth day.

I think the interest in this case lies in the following points. 1. The deceptive clinical appearance and signs. The growth appeared to be encapsuled, oval in shape, and in consistence it appeared even to such an experienced surgeon as Mr. Stanley Boyd to suggest the probability of a deep-seated thick-walled cyst, and it was moveable on deglutition. The carotid artery, instead of being overlapped and surrounded, as is usually the case in malignant thyroids, was pushed backwards and could be felt easily at the posterior border of the growth. The patient appeared to be in good general health and her signs and symptoms might all be

³ Transactions of the Royal Medical and Chirurgical Society, 1893.

⁴ Transactions of the Clinical Society of London, 1890.

attributed to chronic bronchitis. Under the anæsthetic a revision of the diagnosis was made, yet after incision the growth on its anterior aspect showed a pale, slightly bossy, circumscribed, and encapsuled tumour. It appeared to have traversed its capsule on the posterior aspect which is probably accounted for by the fascial arrangements. That malignant growths of the thyroid tend to extend backwards in a marked manner has been clearly indicated by the cases which I have seen. The extreme difficulty with which the growth was removed shows how great may be the fixation to surrounding parts and yet allow up-and-down movement with deglutition. I should, personally, in future, lay more stress on lateral movement with the trachea. 2. The drowsiness noticed after operation was similar to the condition in the case recorded by Mr. G. R. Turner, previously referred to, in which after the operation the patient was comatose until a brisk purgative had acted. This patient was albuminuric likewise. 3. The surgical emphysema. 4. It is interesting to note that in Case 2 both suprarenals and kidneys and in this case both kidneys were symmetrically involved in secondary growths.

CASE 4.—The patient, a married woman, 60 years of age, was admitted to hospital on April 24th, 1901, for tumour in the neck. She died on May 14th—the twentieth day. The urine had a specific gravity of 1015, was acid, but contained no albumin or sugar. The patient had suffered from bronchitis every winter and she also had asthma. There was no history of goitre, of cancer, or of myxœdema. She had been treated for dyspepsia and constipation during the past 12 or 15 months. In October, 1899—that is, 17 months before admission—the tumour was first noticed; it appeared to have commenced on the left side in the position of the left lobe of the thyroid. It then seemed to involve the right side and had increased greatest on the right side. The husband of the patient said that when the fulness of the throat was first noticed the patient's skin began to be very dry and she developed progressive weakness. Her speech was always slow and she was rather stout but not to the extent now observed. The consistence of the swelling was not noticed. Six months previously the right side began to increase rapidly in size and the growth steadily persisted. It was accompanied by an increase in stoutness. She was seen at this time by Dr. G. H. Charlesworth of Wandsworth who at once diagnosed myxœdema. When she was admitted on April 24th, 1901, the neck looked very thick—that is, it was broad, full, and "expressionless"; there were no elevations or depressions visible. This fulness was most marked on the right side. On palpation a large tumour was found to occupy the neck which was more prominent on the right than on the left side. It obscured the trachea and was hard and solid and had distinctly defined margins, but the fulness of the neck extended beyond these margins. The carotid on the right side seemed to lie posteriorly and deep to the swelling. On the left side it was palpable at the outer border. The skin was free from attachment and except for a dark pigmentation where the patient had been painted and blistered with iodine it seemed normal. The mass was adherent to the deep parts and was very fixed. It did not move on deglutition. The trachea was deflected a little to the left but palpation was difficult. It could be felt in the mid-line below. The thyroid cartilage was easily felt in the mid-line but was not visible, being obscured by fulness. The lymph glands were enlarged and of firm consistence and were easily felt on the left side but less easily on the right side above the level of the growth. The patient had the characteristic appearance of myxœdema—i.e., subcutaneous thickening, double chin, puffy eyes, and swollen hands. She was slow of comprehension and speech; the latter was drawled. All her movements were slow, the voice was peculiarly harsh, thick, and of deep tone. The skin was dry, harsh, and coarse. Her hair was scanty but the scalp was uniformly covered. She was placid if left alone but was easily irritated. It was said that her voice had become harsher during the previous six months and that her breathing had become shorter; she complained of the latter considerably, but there was no obvious dyspnoea when she was at rest. Her temperature on admission was about normal. During the night she had some dyspnoea. She was put on Burroughs and Wellcome's thyroid tabloids which were gradually increased to five or more tabloids a day. She was being kept under observation to see the result of thyroid feeding and was considered to be inoperable. On April 28th her breathing had been variable in frequency and ease. She had considerable expectoration and so was given an expectorant mixture.

Her temperature was 98° F. On the 29th the cough was worse. She was more cyanosed, complained of difficulty in drawing her breath, and was much less comfortable. The pulse was rapid and feeble and she had some sibilant rhonchi. On the 30th after a distressed, restless night she complained of pain in her throat of a shooting character and was given chloral. When seen on May 6th it was ascertained that the patient had felt and shown no ill effects of the thyroid extract. There was less œdema of the fingers and hands, the nose was less swollen, the face had improved, and the speech was clearer and more rapid. The dyspnoea, on the whole, was getting worse and especially affected her at night, so she slept badly. There was little or no cyanosis. The pain in the throat occurred now and again. The cough was variable. Examination of the larynx revealed no evidence of paralysis of the vocal cords and the breathing was not stridulous. The expectoration was less and the temperature continued about normal. On the 9th the dyspnoea was still well marked. The patient was restless and she felt more comfortable when lying on her right side. Speech and intellect were better, the puffiness about the eyes was less, the face was thinner and more natural, and the neck was probably slightly smaller, especially about the left lobe. On the 11th—the seventeenth day after admission—suddenly, without obvious cause and without a rigor, the temperature rose to 102° and subsequently to 104°. The patient had slight diarrhoea, the dyspnoea became well marked, and the skin pallid. She felt very ill but could not say how. She completely lost her appetite and although considerable improvement had been made as regards the myxœdema she rapidly got worse. The thyroid extract was discontinued. The temperature continued at 104° and then gradually fell. The pulse became thin and feeble ranging from 130 to 160. Slight delirium developed at night. A marked shrinking occurred in the size of the tumour. The neck became quite slim and except for a localised swelling on the right side the growth seemed to disappear. She occasionally complained of pain in the abdomen and always persisted in lying on her right side, slightly propped up. She did not vomit and after the first day of fever her bowels did not act. Her condition for the last three days of life may be summed up as follows. The temperature was 104°, falling to 101°; there were intense restlessness, marked dyspnoea with pallor and cyanosis, a thin, thready pulse, varying from 130 to 160, and slight pain in the abdomen; there was no vomiting; she was constipated; she was conscious but was too distressed to speak much about herself and at night she became a little delirious; most of the subcutaneous thickening and the thyroid fulness seemed to disappear suddenly; there was no suspicion of pelvic trouble and no signs of secondary growths were observed. She died on the twentieth day after admission.

Post-mortem examination showed the right lobe of the thyroid to be involved in a mass of new growth but the left lobe appeared to be normal. The trachea was narrowed by the growth and was pushed to the left side. The growth extended above to beyond the hyoid bone and below to within one and a half inches of the bifurcation of the trachea and measured four inches vertically. Anteriorly the isthmus was thickened and was continuous with the new growth in the right lobe. The right carotid and jugular were almost completely surrounded by new growth at the postero-external angle, the vein lying external. The bifurcation of the common carotid was involved in new growth. The subclavian could be separated from the growth but the lower end of the carotid was very adherent. The right half of the cricoid cartilage was embedded in new growth which had extended into the submucous tissue, forming an elevation of a fusiform shape one and a half inches in extent reaching above and below the level of the cricoid. There was no evidence of ulceration over the swelling. The growth lay in a retro-tracheal position, extending from the level of the tip of the epiglottis to the subclavian artery. The larynx was compressed from the right side and behind. The left lobe was firm and looked very fibrous, there was a mass of pigmented glands at the bifurcation of the trachea, and considerable tracheitis was present. Examination of the thorax showed purulent pleurisy on the right side and serous pleurisy with flakes of lymph on the left side. In the cavity of the pericardium there were flakes of lymph. The heart was normal. The lungs were compressed but were otherwise normal. The cavity of the abdomen was full of greenish-yellow, turbid, purulent fluid.

The stomach.—An ulcer twice the size of a florin lay near the cardiac orifice of the stomach and near it were

two smaller recent ulcers with raised thickened edges. There was no thickening of the wall of the organ. Near the pyloric end was another recent ulcer of the size of a sixpenny-piece, also two large chronic shallow ulcers, one of the size of a five-shilling-piece.

Intestines.—Two or three small sharply cut ulcers existed in the middle of the ileum. The mucous membrane of the lower part of the small intestine was stippled with dark dots throughout. In the neighbourhood of the cæcum and throughout the colon the mucous membrane was almost black with closely set points of pigment. The ureters contained much muco-purulent fluid. In the Fallopian tubes was a small amount of pus. The kidneys were slightly granular. The spleen was normal. The mucosa of the intestine examined microscopically showed masses of brownish pigment deposited between the glands; there were no hæmatoidin or hæmatin crystals. Microscopically the pancreas showed infiltration by new growth.

The points of interest in the case are (1) the direct association of myxœdema with sarcoma of the thyroid and (2) the ulceration of the stomach and intestine. The most interesting feature is the association of myxœdema with sarcoma of the thyroid.

Quoting Dr. G. R. Murray,⁵ "in only a few exceptional cases has the destructive lesion of the thyroid gland been traced to a definite cause. Kohler describes two cases, one of syphilis and the other of actinomycosis of the thyroid. Neudorfer gives one case of adenoma of the right lobe of the thyroid. In each of the three cases appropriate treatment of the exciting cause was followed by recovery of the functional activity of the thyroid gland and disappearance of the myxœdema." Assuming that Dr. Murray has collected all the cases bearing on this subject this case appears to be an exceptional one.

It is impossible to state whether the myxœdema, of which clinically there is no doubt, was due to sclerosis or to senile atrophy of the gland antecedent to the malignant change, or whether a diffuse sarcomatous infiltration was the immediate cause of the glandular destruction and consequently of the myxœdema. The history states definitely that the development of the symptoms of myxœdema, with one exception, that of slow speech, was coincident with an enlargement of the thyroid which became slowly progressive. When a marked increase in the size of the thyroid took place six months before death the symptoms of myxœdema also became more pronounced. Senile atrophy as a cause of myxœdema is rare. Clinically it was observed that thyroid treatment seemed to result in diminution in size of the left lobe. This may be best explained by assuming disappearance of the mucinoid deposit in the tissues about the thyroid, as microscopically there is no evidence of regular gland structure in any of the sections of the left lobe which I have examined; everywhere there is the diffuse infiltration with round cells; here and there may be seen remains of thyroid epithelium identical with the condition of the right lobe.

The condition of the stomach.—In this case marked ulceration of the stomach and slight ulceration of the small intestine with pigmentation of the latter were found. In Case 2, besides the massive involvement of the cardiac extremity of the stomach by the secondary growth in the coeliac glands, there was separate ulceration of the stomach near the pyloric extremity similar to that in Case 4. In a case not yet recorded of probably primary sarcoma of the larynx with bilateral growths in the thyroid there was found similar ulceration and new growth in the stomach. This association of ulceration of the stomach with thyroid sarcoma may be a coincidence but there are many points in favour of a direct relationship. Primary and secondary sarcoma of the stomach may be of four varieties: (1) round-celled, (2) spindle-celled, (3) myosarcoma, and (4) angio-sarcoma. Primary growths are much more common than are secondary ones except in the lympho-sarcomatous variety in which *secondary* involvement of the stomach is more common than is *primary* deposit (Hemmeter) and is most often found secondary to primary growths involving the neck, the pharynx, the gums, &c. Primary growths tend to be nodular and begin in the submucosa. Ulceration of the mucous membrane is late and signs and symptoms may be entirely absent, the post-mortem examination revealing the presence of growth for the first time.

In the two cases now recorded what is the nature of these

ulcers? In Case 2 the nature of the large ulcer was indubitable—viz., that of an ulcerating sarcoma. The smaller ulcer presented the same macroscopical characteristics as those in Case 4 and the small ulcer of the laryngeal case referred to. The latter is microscopically undoubtedly sarcomatous, so we may assume that the nature of the ulcers in Cases 2 and 4 is similar. Macroscopically those in Case 4 appear to be of two varieties, one having the appearance of acute ulcer, the other chronic with thickened edges. There was slight thickening with increased vascularity at the base of some of the ulcers but not of all. Microscopically the more acute ulcers showed a condition of erosion of mucous membrane surrounded by round-celled infiltration in the mucosa and submucosa impossible to distinguish from an inflammatory process. The area of ulceration appeared to be more vascular than did other portions of the stomach walls. If the brownish flocculent fungating portion of the new growth projecting into the stomach in Case 2 be brushed off the ulcer left is identical in appearance with the small ones seen in Cases 2 and 4. Probably at one time these had fungating growth adherent to their surface. The patient in Case 4 was for some time under treatment for dyspepsia and constipation, but her symptoms were not marked and there was no obtainable history of hæmatemesis. The duration of her symptoms seemed to have been coincident with the thyroid troubles. Extensive ulceration of the stomach may occur with few symptoms, yet it might be assumed from the condition of pigmentation of the intestine in this case, if due to blood absorption, that considerable hæmorrhage from the stomach had occurred from time to time, but the history did not support the assumption. Also the pigmentation was absent in the upper jejunum and was least marked in the lower jejunum and the upper ileum and most pronounced in the lower ileum and the colon. It is reasonable to assume that a great deal of the blood came from the intestinal ulcers, situated half-way down, one of which had probably ulcerated deeply and eventually perforated, causing general peritonitis.

The origin of the ulcers.—In Case 4 from the appearance and situation of the primary growth it is obvious that the pharyngeal muscles were involved by the new growth at their origin from the cricoid. In Case 2, from the extensive nature of the growth, a similar conclusion must be deduced. The larynx also was *ulcerated* slightly. In the unrecorded case of primary sarcoma of the larynx with ulceration of the stomach referred to the explanation which I beg to give of the origin of these ulcers suggests itself—namely, that it is probable that some of the sarcoma cells were swallowed and passing through the mucous membrane of the stomach and the intestine gave rise to secondary submucous growths. In my cases the pharyngeal mucous membrane need not have been perforated to permit this as cells of at least equal size constantly escape in the process of inflammation and probably under normal conditions also between the epithelium of mucous membranes. In addition in Case 4 there was involvement of the larynx which might be a possible source of sarcoma cells. Thursfield⁶ recorded a case of primary sarcoma of the stomach in which the infiltration was diffuse and ulceration was not present. In this case there was a mass in the region of the parotid and left thyroid. Was the stomach growth primary? The association of secondary lympho-sarcomatous growth in the stomach with primary lesions of the gums, the pharynx, and the neck, recorded on repeated occasions, suggests that some such simple explanation as I have suggested is probable.

In conclusion I will quote Kocher and Berry.

Kocher: "Every goitre in an adult and especially in an elderly person that enlarges without obvious cause, should raise a suspicion of malignancy, even though it should cause no pain or other trouble. If at the same time the goitre becomes harder and irregular and symptoms of increasing distress set in, then the diagnosis becomes almost certain. The prognosis as regards malignant goitre from the operating point of view is not worse than that of innocent goitre if performed while the growth is intracapsular. When the growth is still intracapsular there are no means by means of which we can make a certain diagnosis of malignant disease."

Berry: "When, however, in the thyroid gland of a person over 40, a tumour appears which is hard, which steadily and rapidly increases in size, and which is not of an inflammatory nature, the malignancy of such a tumour should be strongly suspected. If, moreover, the surface of the tumour is irregular and bossy and if there is likewise dysphagia and pain in the neck, shooting up to the side of the head or to the shoulders, then the diagnosis becomes almost a certainty."

My thanks are due to Mr. Morgan and to Mr. Stanley Boyd

⁵ Diseases of the Thyroid (1900), p. 33, on the Etiology of Myxœdema.

⁶ Transactions of the Pathological Society of London, vol. lli., 1901.

for permission to record these cases, to Dr. Bosanquet for much assistance and advice, and not least to Dr. Hunter for great assistance and permission to utilise the perfectly mounted specimens of the cases.

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ON THE ACETONE SERIES OF PRODUCTS IN CON- NEXION WITH DIABETIC COMA.

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(Continued from p. 66.)

THERE are two views of the pathogeny of diabetic coma which stand in a position to claim consideration. The one refers it to an acidosis or excessive production of acid and the other to the β -amidobutyric acid, an assumed precursor of the β -oxybutyric acid.

Excessive proteid disintegration is attended with excessive acid production. The sulphur and phosphorus of the proteid becoming oxidised give rise correspondingly to sulphuric and phosphoric acids. Under natural circumstances these acids encounter a sufficiency of fixed bases to neutralise them, but when developed in excess they have to attach themselves to a portion of the ammonia at the same time developed by the proteid disintegration and in this state they pass into the urine. Normally the amount of ammonia in the urine is very small, inasmuch as what is developed by downwards metabolism combines with the carbonic acid at the same time being produced and the combination becomes transmuted into urea. Combined with sulphuric or phosphoric acid the ammonia cannot pass into urea but escapes as the unaltered compound. Thus from simple increased tissue breaking down a source exists for the undue presence of ammonia in the urine and when the breaking down is attended with the formation of the additional acids, oxybutyric and diacetic, that have been receiving consideration, ammonia is appropriated and carried off by them into the urine, and thus the amount may rise from something under one gramme per diem to six or seven grammes or even more. The quantity of these acids that may be formed is such as to constitute a factor from more than one point of view of much significance. Estimations of diacetic acid are not given, for no satisfactory method of estimating it exists, but it must be reckoned that whatever diacetic acid is present means an addition to the troubled state otherwise induced. As regards oxybutyric acid it is not uncommon for from 50 to 70 grammes per diem to be eliminated. It is accepted that as much as 150 grammes per diem may be eliminated and considerably higher figures than these have been named (e.g., 226 grammes—approximately half a pound—by Külz), but doubt of the correctness of the extreme figures that have been given may be entertained. From the records supplied cases have occurred in which the oxybutyric acid has exceeded in amount the sugar. The waste occurring in these circumstances must be something enormous. The elimination of oxybutyric and diacetic acids constitutes an outgoing of material carrying with it unexpended energy and the same applies to the sugar. Hence with all three an immense sacrifice of potential energy is occurring.

"Acidosis" is the term which has been applied to the state resulting from the production of these acids. As they reach the blood they must obviously tend to decrease its alkalinity. The available fixed alkali, as already stated, is first appropriated for neutralisation and when the supply of fixed alkali fails the effete ammonia from proteid disintegration is taken and accompanies the acid into the urine. Notwithstanding these sources for neutralisation it has been found in cases when coma has supervened that the alkalinity of the blood has become reduced to a point standing much below the normal.

In the circumstances mentioned we have a sequence of events holding, it may be considered, a thoroughly established position. The existence of such a source of acidity cannot do otherwise than, by its influence on the constitution of the blood, act deleteriously. The altered constitution of the blood due, as in the "alimentary" type of diabetes, to the presence of sugar unaccompanied with any other condition interferes with nutrition and recognisably damages the

kidney. Experience shows that where sugar is allowed to be passing for a long time through the system a certain amount of albumin appears in the urine and granular and hyaline casts become discoverable. This condition may go on for a long time in, as it were, a quiescent form and without any of the classical phenomena of Bright's disease becoming developed, although sometimes, whether incidentally or derivatively, well-marked Bright's disease, with the concomitants belonging to the granular kidney type of it, becomes established. When the acidosis state is added to the other, kidney damage, indicated by moderate albuminuria with granular and hyaline casts, may with greater certainty and rapidity be looked for. Indeed, if marked acidosis exists I think it may be said that albumin and casts may be expected to be found in the urine.

I now come to the pathogeny of diabetic coma, and, as I have said, there are two views to which attention will be given. These are autotoxicosis from acidosis and from β -amidobutyric acid.

As far back as 1877 it was found by Walter¹ that when hydrochloric or phosphoric acid was given in repeated full doses to rabbits a state comparable to that existing in diabetic coma was induced. The heart's action became much increased in frequency, the breathing forced, deep, and more frequent, like what is appropriately termed the "air-hunger" breathing of diabetic coma, and the animal passed into a stupefied state. It was noted also that the carbonic acid in the blood dropped from about 24 to 2.5 and 3 per cent., a condition that has since been found to agree with that observable in connexion with diabetic coma. Further, when the rabbit was on the point of death in coma the injection of carbonate of soda restored it. At the time when these experiments were performed the acidosis associated with diabetes had not been recognised, but from its suggested existence it was looked for,² and in the course of a few years the presence of oxybutyric acid³ was discovered. It was in this way that the acidosis associated with diabetes was worked out, and whether it supplies the true explanation of diabetic coma or not it is found that with the supervention of coma the acids are present in the blood in such quantity as to be not far remote from covering its alkalinity. With this condition, as in the experimental acidosis, the amount of carbonic acid in the blood drops. Figures as low as 3.3 per cent. were noted by Minkowski⁴ in a case during the existence of coma. Three weeks previously in the same case they stood at 17 per cent. For comparison he mentions, quoting from the work of another authority, that 30.6 per cent. may be given as a representation of the normal amount present in arterial blood of the human subject.

By the advocates of the acidosis theory as an explanation of the production of diabetic coma it is considered that when the acids developed begin to fail to meet with bases to neutralise them a condition is reached productive of coma. The effect of the administration of carbonated alkali in the circumstances agrees with that observed in experimentally induced acidosis and soda has been frequently employed as a measure of treatment with, in some cases, temporary restoration from coma. Instances of the kind stand on record but the final issue has been disappointing. The bicarbonate of soda is the preparation that has been used, and very large doses have been found necessary to be given, so large, indeed, as to create a difficulty in putting the treatment into force. Magnus-Levy⁵ relates a case in which a boy, aged 13 years, was twice brought out of coma by the administration of 200 grammes (a little over seven ounces) of the bicarbonate of soda. In another case recorded by Magnus-Levy⁶ the patient, a girl, aged 12 years, recovered from fully-developed coma under the administration of 100 grammes per diem and showed no further signs of coma during the nine weeks she subsequently remained in hospital. Notwithstanding, however, that success may be thus for a while obtained, in the end coma supervenes which fails to be any longer susceptible of removal.⁷ This is not to be wondered at looking at the circumstances

¹ Walter: Archiv für experimentelle Pathologie und Pharmakologie, 1877, Band vii., p. 147.

² Stadelmann: Ibid., 1883, Band xvii., p. 419.

³ Minkowski: Ibid., 1884, Band xviii., p. 35. Külz: Zeitschrift für Biologie, 1884, Band xx., p. 165.

⁴ Mittheilungen aus der Königsberger medicinischen Klinik, 1888, p. 174.

⁵ Archiv für experimentelle Pathologie und Pharmakologie, 1899, Band xlii., p. 180.

⁶ Ibid., 1901, Band xlv., p. 399.

⁷ Naunyn: Diabetes Mellitus, p. 328.