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ON KIDNEY TUMOURS DERIVED FROM SUPRARENAL "RESTS."*

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MY attention was first called to the subject by the examination of a tumour of this kind, which my colleague Mr. Coppinger successfully removed by nephrectomy in March, 1892. Another such case having been operated on at the Mater Misericordiae by my colleague Mr. Lentaigne in September, 1895, I resolved to publish both in detail, and at the same time to collect from various sources our knowledge of this class of tumour, which, so far as I can ascertain, does not seem to have received from British pathologists the attention which its well-marked characters undoubtedly deserve.

CASE I.—Mrs. B., a thin delicate-looking woman, aged 53, mother of seven children, had suffered for nine months from night sweats, vomiting, and abdominal pain. She had been operated on by Mr. Reeves at the Soho Hospital for movable kidney. Further operation for the removal of the organ was proposed and declined. There was now a tumour on the left side of the abdomen; no hæmaturia. On March 4th, 1892, abdominal section was performed by Mr. Coppinger, and a smooth tumour as big as a large melon exposed in the situation of the left kidney. It fluctuated, and after an unsuccessful attempt to aspirate its contents it was slit open, and a bowlful of brain-like hæmorrhagic material evacuated; Mr. Coppinger remarking that all previously reported cases of soft sarcoma of the kidney which had been opened had proved fatal by hæmorrhage. The cavity at once filled with blood, but the hæmorrhage was successfully dealt with and the tumour removed. The patient, who recovered without a bad symptom, is still alive and well.

Naked-eye Appearances.—The specimen consists of three-fourths of a left kidney, the lower fourth being merged into the walls of a sort of cyst, the inner side of which is covered with pultaceous and hæmorrhagic shreds of tumour substance. There is a distinct fibrous partition between kidney and cyst.

Microscopic Characters will be dealt with together with those of the second case.

CASE II.—Patient, female, aged 38, admitted in September, 1895, to the Mater, under the care of Mr. Lentaigne. Had been suffering for six months from abdominal pain and a tumour in left side of abdomen. No disorders of micturition. Patient looked cachectic and emaciated. Laparotomy revealed a large lobulated tumour of the left kidney extending to the middle line. The size and connections of the growth rendered the operation very difficult and prolonged. Death followed in nine hours from shock. Necropsy refused.

Naked-eye Appearances.—The mass weighed 1,100 grammes, and consisted of a mass of confluent encapsulated nodules, from the upper part of which projected the tip of the left kidney. The colour and consistence of the nodules were not unlike those of kidney cortex. The dimensions were 21 cm. × 16 × 8.6. The diameter of the largest nodule was 9 cm. The centre of each of the larger nodules was occupied by a necrosed cheesy-looking mass as big as a filbert, and here and there were yellowish degenerate patches as big as a pea. Elsewhere the tissue looked free from retrogressive change, and there were no cysts. The encapsulation of each nodule was perfect and definite.

Microscopic Characters.—To avoid repetition, the two cases will be described together. The structure of both was the same, and consisted of (a) rows and (b) groups of large (7 to

12 μ wide by 12 to 20 μ high) columnar or cubical cells of obviously epithelial character with clear, sometimes reticulated protoplasm and a relatively small, round, not very deeply staining nucleus, in which a distinct nucleolus was generally visible. Their general appearance was like that of liver cells

Fig. 1.—Low power view showing capsule with tumour tissue below and right, and kidney above and to the left.

The rows in which they were arranged were usually two cells deep, and there was usually no trace of a lumen. On each side of the rows was a line of delicate endothelial nuclei evidently forming the wall of capillaries in which remains of blood could still here and there be traced. Elsewhere the

Fig. 2.—Typical high power view; "fasciculate" arrangement of cells. capillaries were collapsed, and then the adjacent cell rows came into contact with each other. Between the epithelial cells comprising these rows there entered no stroma what

* Extracts from a paper read before the Royal Academy of Medicine in Ireland, Section of Pathology, November 29th 1895.

ever. In fact, no stroma existed, the tumour cells being placed directly on the endothelium of the capillaries. Distinct fibrous trabeculae divided the tumour substance into lobules, and supported the larger vessels. All transitions could be traced from lengthy rows or double columns to circular groups of cells (see Figs. 2 and 3).

Towards the degenerate parts, many of these groups contained a central space or pseudo-lumen, as I propose to term it, and might readily be mistaken for gland tubules. The cells, however, in these situations are flattened or cubical rather than high-columnar, the nucleus lies close to or may actually project into the "lumen," the latter is irregular in outline, running out, so to speak, into gaps formed by the partial disappearance of one or more of the surrounding cells; and lastly, serial sections show that the "lumen" ends blindly in the continuity of a cell column, or seems to twist out between the cells. For the four reasons just given, I consider that these central spaces are due to degenerative or metaplastic change, and are not to be regarded as the lumina of gland tubules. As we advance further into the degenerate regions, we find the cell groups becoming smaller, the protoplasm more swollen-up and reticular, the nucleus poorer in chromatin, and showing signs of impending fragmentation (karyorrhexis of Klebs), until in some fields we see only a few enormous cells imbedded singly, or in twos or threes, at wide intervals in structureless, hyaline, or hæmorrhagic ground substance.

Fig. 3.—Showing rounded cell-groups abutting on degenerate tissue.

The tissue that filled the cyst in Case I differed from the type just described in the fact that the extensive hæmorrhagic and fatty changes of which it had been the subject somewhat obscured the structure. Extensive deposition of glycogen, in the form of intracellular granules and largish extracellular masses had occurred in Case I. Case II showed no trace of glycogen; fat globules, however, occurred in many cells, and in the paraffin preparations were represented by large vacuoles.

The neighbouring kidney tissue showed atrophied or dilated tubules lined with flattened, confluent, badly-stained epithelium, shrunken or hyaline glomeruli, blood vessels with thickened walls, and, between these, tracts of connective tissue crammed with nuclei. The septum which everywhere intervened between kidney and tumour tissue (see Fig. 1) consisted, on the tumour side, of dense laminated connective tissue rather rich in nuclei, and, on the kidney side, of atrophied and compressed renal structures. Nowhere could a transition from urinary tubules to tumour tissue be traced.

Diagnosis.—The resemblance of the sections to the tissue of the suprarenal cortex was evident and unmistakable. Zona fasciculata and glomerulosa were both represented—see arrangements (a) and (b) above. I consider that these tumours are really of suprarenal origin, for the following reasons:

1. The appearance of the cells, their arrangement in rows and groups, and their relation to the capillary wall, agrees with that of the suprarenal, and differs altogether from the kidney.

2. The presence of large fat globules in many of the cells, coupled with the absence of indication of degenerative change. This fatty infiltration is a normal condition in the adult suprarenal, and here, as in the tumour, is associated with abundant vascular supply.

3. The fact that aberrant nodules of adrenal tissue have been described by Klebs,¹ Schmorl,² Newton Pitt,³ and Rolleston,⁴ as occurring imbedded in the kidney, or flattened against its capsule.

4. The fact that tumours of precisely similar structure not infrequently originate from the suprarenal capsule, and growing downwards into the kidney cause its destruction (Morris⁵).

Granting that these tumours are really so derived, we have next to consider the question of nomenclature. Are they sarcomata, carcinomata, adenomata, teratomata, or what? The term angiosarcoma actually applied by de Paoli⁶ to a

Fig. 4.—Showing dilatation of some of the capillary spaces partly due to distension and partly to degenerative change.

tumour of this class might to some seem applicable. Driessen⁷ deliberately rejects (on manifestly inadequate grounds) the suprarenal origin of two growths, which from his illustration and description clearly belong here, and calls them endotheliomata. He regards them as originating from the endothelium of lymph-clefts. Sudeck,⁸ by an elaborate chain of argumentation, in the course of which he claims to have traced the transition from urinary tubules to tumour tissue as above described, seeks to class them with renal adenoma. The consideration of these views must be reserved for another place.

The following characters seem to point to carcinoma: 1. The cells are obviously "epithelial." 2. The stroma does not penetrate between them, but divides the cell groups into lengthy or circular alveoli.

I take the "stroma" of these tumours to consist merely of capillary blood vessels—a stroma "reduced to its lowest terms." Now since the adoption of Waldeyer's⁹ and Thiersch's¹⁰ views we must, in diagnosing carcinoma, take into

account the development of the tissue from which the tumour originates. If mesoblastic, sarcoma; if epiblastic or hypoblastic, then adenoma or carcinoma. Balfour and Mitsukuri¹¹ and Braun¹² derive the adrenal from accumulations of connective tissue cells which are formed at the anterior part of the primitive kidney (Wolffian body) along the inferior cava and cardinal veins. Janosik,¹³ Weldon,¹⁴ and Mihalkovics¹⁵ regard these formative cells as derived from the epithelium of the body cavity.

Concerning the exact point of origin, however, two distinct views are held. Janosik and Mihalkovics divide the suprarenal from the germinal epithelium in the anterior part of the genital ridge. Weldon, on the other hand—and his view is the one favoured by Hertwig¹⁶—brings the suprarenal body into connection with the most anterior part of the primitive kidney. When the "sexual cords" at the head end of the primitive kidney sprout out of the epithelium of the Malpighian glomerules they divide into two branches, one of which turns ventrally into the fundament of the sexual gland, whilst the other turns dorsally, and spreads out in the vicinity of the vena cava. Hertwig goes on to point out how Marchand's¹⁷ observations of accessory suprarenal bodies at the margin of the broad ligaments are explained by this genesis; small portions of what is to be suprarenal cortex appear sometimes to detach themselves, and remain in the vicinity of the sexual organs, in the migrations of which they participate. Again, the researches of Semon¹⁸ place the adrenal in close developmental relation with the mesonephros or primitive kidney, which would to some extent account for the distribution of adrenal "rests" through the substance of its successor, the metanephros or permanent kidney. The coelomic "epithelium" being a mesoblastic structure, it follows that the suprarenal cortex is also mesoblastic. Hence, according to the received method of tumour, nomenclature, malignant neoplasms originating therefrom would be classed as sarcomata. But Waldeyer himself, the originator with Thiersch of this system, defines¹⁹ epithelium—for tumour classification purposes—as comprising all those cells "which arise from the epiblast or hypoblast, or from the so-called germ epithelium."

Fig. 5.—"Carcinomatous" appearance of part of a section.

Now, the germ epithelium is part of the coelomic epithelium, from which competent embryologists (*vide supra*) derive the connective tissue cells (Hertwig) or formative cells which (*vide supra*) give rise to the suprarenal body. Therefore, the cells comprising the suprarenal come to be epithelial in Waldeyer's meaning, and tumours arising from them are adenomata or carcinomata. Again, Graf Spee²⁰

claims to have traced epiblast into the primitive kidney, and if this view be accepted in connection with Semon's results, the growths in question might be classed as carcinoma *sensu stricto*. As a matter of fact, many parts of Case II diverge more or less markedly from the suprarenal type, and tend to take on a carcinomatous structure (see Fig. 5). A glandular appearance and arrangement of the cells in the normally-situated suprarenal cortex has been described by Creighton,²¹ Pfäundler,²² Marchand,²³ and others, and may be brought into an interesting parallelism with Pflüger's tubules in the ovary, which are also derivatives from the coelomic epithelium. To sum up, we have to deal with cells mesoblastic in origin and nevertheless epithelial both in appearance and arrangement—a striking example of the way in which the two criteria accepted nowadays for tumour classification may clash with one another. Developmentally these growths are mesoblastic; morphologically they are epithelial. Precisely the same difficulty applies to other kidney tumours. Those who speak of "carcinoma" and "adenoma" of the kidney tacitly drop the developmental and adhere solely to the morphological criterion—a procedure which would, if logically pursued, place the alveolar sarcomata and the endotheliomata amongst the carcinomata, as Hansemann actually proposes.²⁴ In view of their widely different clinical aspect, such a course might, as Lubarsch²⁵ points out, be inadvisable. Until, therefore, tumour classification finds its way out of the *impasse*, in which the attempts to combine histogenetic with morphological criteria have landed it, we must hesitate to rank the neoplasms now under discussion with either the sarcomata or the carcinomata. For the present I prefer to call them "kidney tumours derived from suprarenal 'rests,'" discarding Grawitz's name, *strumæ lipomatodes aberratæ renis*, as equally cumbersome, more obscure (*struma*) and not, always (*lipomatodes*) applicable.

HISTORY OF THE SUBJECT.

Grawitz²⁶ was the first to derive renal tumours from suprarenal "rests." He worked out his views in the first instance on some specimens preserved in the Berlin collection under the name of renal lipomata, and describes in detail two cases of large tumours, one of which had formed metastases in the lung, and the structure of which is identical with those now under consideration. He proposes to call them "*strumæ lipomatodes aberratæ renis*," basing his nomenclature on the fact that Virchow, comparing localised enlargements of the suprarenal with those of the thyroid, calls the former adrenal "goitres" (*strumæ*). Strübing,²⁷ Löwenhardt,²⁸ Beneke,²⁹ Ambrosius,³⁰ and Horn³¹ take the same view, and add fresh cases. The latter generalises on Grawitz's position, and classes Klebs's³² and Sturm's³³ adenomata of the kidney, Weichselbaum and Greenish's³⁴ "papillary and alveolar adenomata," and Sabourin's³⁵ *épiléliomes métatypiques*, as well as de Paoli's³⁶ primary angiosarcoma of the kidney in the same category. Askanazy³⁷ adds a first-rate case, and accepts Grawitz's explanation. Meanwhile Driessen³⁸ and Sudeck³⁹ describe cases which clearly belong here, but, as above stated, reject the suprarenal origin. Lastly, the whole question receives a masterly discussion at the hands of Lubarsch, who concludes in favour of Grawitz's opinion.

GENERAL CLINICAL CHARACTERS.

I will now briefly summarise the main points of arguments offered by the thirty cases collected last year by Lubarsch, and point out in what respects our Mater cases agree or differ from the other.

Sex.—Out of 29 cases cited by Lubarsch 20 were those of males. Both our Mater patients were females.

Age.—Out of 29 cases, 21 were between 40 and 79; 8 between 2½ and 39. One of our cases was 53, the other 38.

Side.—The right kidney was affected 12 times, the left 11. In four of our cases the left was the seat of the disease.

Duration.—This is usually long, two, six, and even ten years elapsing from the first clinical symptoms. Askanazy's patient felt the tumour when very young. It disappeared for a time, and returned fatally when he was 53. They grow slowly at first, and then seem suddenly to produce cachexia and prove fatal.

State of Urine.—This seldom yields positive evidence of the

existence of the tumour. It did so, however, in Grawitz's first case, though the indications were susceptible of misinterpretation.

Result of Operation.—This is unusually fatal. Madelung's 3 cases reported by Lubarsch died, without uræmia or peritonitis to account for the fatal termination. Askanazy's case died from recurrence. One of our Mater cases (Mr. Coppinger's) is still alive, three years and a-half after operation, and is one of the very few recorded cases in which the patient was cured by the operation.

Metastases.—These were found 20 times out of 29, a fact which proves the malignant tendency of these suprarenal neoplasms. One of our cases having recovered, and the necropsy of the other having been refused, I am not in a position to say anything on this head. Generalisation is usually ushered in by rupture of a tumour mass into the renal vein. The lung is a favourite seat of the secondary growths. They have also occurred in the liver, pancreas, heart, thyroid, etc.

British Cases and Literature.—In the debate¹¹ on the case of a kidney tumour, which seems to belong to this class, and which was operated on by Mr. Walsham, Dr. Newton Pitt expressed the opinion that some renal tumours were possibly related to aberrant suprarenal bodies. The patient in this instance was a child aged 9 months. If my suspicion as to the true nature of this malignant growth, which recurred and caused the patient's death eleven months after Mr. Walsham's successful operation, prove correct, this will be, perhaps, the earliest known instance in point of age. On the same occasion, Dr. Snow spoke of a collection of 60 tumours derived from the Wolffian bodies having been made by Mr. Windle. I do not know where the account of this collection is to be found. Mr. Shattock¹² suggests the Wolffian origin of many kidney growths. Hamilton¹³ calls tumours of this kind "hæmorrhagic sarcoma." Cases recorded by Morris,¹⁴ Sharkey,¹⁵ Paul,¹⁶ and others may possibly prove to belong to this category, as most certainly does Bell and Johnston's case.¹⁷ In Mr. Bland Sutton's work on tumours, there is no mention made of the relation of epithelial kidney tumours to suprarenal "rests." I heartily agree with the author when he says (p. 257) that "it is impossible to write an account of carcinoma of the kidney until surgeons are more alive to the interest of the question, and take steps to place malignant tumours of the kidney whilst still fresh in the hands of experienced pathological histologists." Enough has been said to show that the English literature of surgical pathology is almost a blank on this important and interesting subject; and the object of this paper is to attract the attention of British pathologists to these little known tumours, and to do something towards placing our knowledge of them on the same level as that of most other neoplasms. My best thanks are due to my colleagues at the Mater, Messrs. Coppinger and Lentaigue, for kind permission to utilise their specimens and clinical notes.

[The paper was illustrated with microscopic preparations and lantern slides by the author and Mr. A. Pringle.]

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THE PATHOLOGY OF PERNICIOUS ANÆMIA.¹

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IN undertaking the duty imposed upon me by our Secretaries of opening this discussion I deem the moment not inopportune to review our present position with regard to this subject. Personally I welcome this opportunity because, since the publication of my first investigation, now seven years ago, my own published work has been confined almost exclusively to special observations, for example, excretion of urinary pigment, of iron, of blood pigment, of aromatic sulphates, and of ptomaines—fitted to throw any light on the nature of the disease.

Avoiding then going into details, I propose, on the present occasion, to confine my attention to discussion of the broad question, the relation of pernicious anæmia with other forms of anæmia.

THE RELATION OF PERNICIOUS ANÆMIA WITH OTHER FORMS OF ANÆMIA.

Thanks to the many valuable contributions made within recent years by a number of observers—Russell, Mott, Garrod, MacMunn, Hale White, Gowland Hopkins, Stockman, and others—the material available for such a discussion has been greatly increased. So far as my own view is concerned I see no reason to change the opinion I expressed seven years ago—namely, that there are very strong pathological grounds for regarding this form of anæmia as a special variety of anæmia, if indeed, it be not a special disease. In particular from no form of anæmia is it, in my view, more easily distinguishable by its pathological characters than from anæmia resulting from loss of blood or from the anæmia of wasting disease. The grounds on which I base this conclusion are, as determined in my earlier work, briefly as follows:

HÆMOLYTIC NATURE OF PERNICIOUS ANÆMIA.

1. The extreme degree of blood change which pernicious anæmia invariably presents (and which I may add is not at all invariable in the case of many conditions whose anæmia is regarded as identical with pernicious anæmia) is always marked by certain pathological changes, characteristic either as regards their nature, their degree, or their peculiar association. These changes are constantly met with in the liver, and not infrequently in the kidneys and spleen.

2. These changes according to my observations are characteristically absent in traumatic anæmia and in wasting anæmia.

3. They consist for the most part of deposits of blood pigment, with corresponding increased richness in iron in the liver, preferably in the liver cells of the outer two-thirds of the hepatic lobule, frequently also the capillaries of the liver, and within the cells of the convoluted tubules of the kidneys.

4. This pigment is not the result of extravasation, and is distinguishable from such by important differences affecting both its character and its distribution.

5. From its character and its amount it denotes an excessive destruction of blood as the prominent and most constant and characteristic feature of the disease.

SPECIAL CHARACTER OF THE HÆMOLYSIS.

As regards the nature of this destruction I concluded from my experiments further, (1) that it differs in important respects from, and is no mere exaggeration of, the ordinary blood destruction of health (*vide postea*).

¹ Read in the Section of Pathology at the annual meeting of the British Medical Association, held in London, July-August, 1895.