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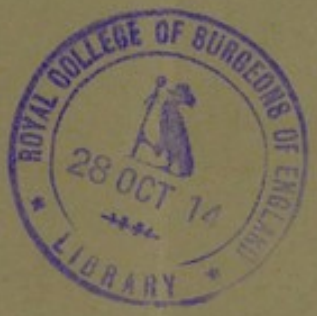
MULTIPLE MYELOMA (MYELOMATOSIS) WITH BENCE-JONES PROTEID IN THE URINE (MYELOPATHIC ALBUMOSURIA OF BRADSHAW, KAHLER'S DISEASE).

By F. PARKES WEBER, M.D., F.R.C.P.



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MULTIPLE MYELOMA (MYELOMATOSIS) WITH BENCE-JONES PROTEID IN THE URINE (MYELOPATHIC ALBUMOSURIA OF BRADSHAW, KAHLER'S DISEASE.)[1]

By F. Parkes Weber, M.D., F.R.C.P., *Physician to the German Hospital, Dalston, London.*

The patient, J. T., æt. 50, a stoker, came under my observation at the German Hospital in May 1900, but I did not make the diagnosis of multiple myeloma until the following July, when I happened to examine the urine by the ordinary methods. From May to July the Bence-Jones proteid[2] in the patient's urine had been frequently, at one time daily, measured by Esbach's albuminimeter, but had been entered in the notes as ordinary albumin. The daily amount of urine was found to be about 2000 c.c., and it contained about 7 per mille of the proteid.

The reactions, as afterwards ascertained, were quite typical, corresponding to those described by Bradshaw, Kühne, Bence-Jones, and others. The most characteristic are, I think, the following (that is, when the urine is acid[3]):—Coagulation of the proteid at a much lower temperature (about 58° C.) than ordinary albumin; more or less solution of the precipitate at a higher temperature (*e.g.* when the urine is boiled), and complete or almost complete solution on adding acetic acid to the boiling urine; after the precipitate has been partially redissolved by boiling, a characteristic reprecipitation should take place on allowing the urine to cool. What Dr. Bradshaw considered to be the spontaneous precipitation of the proteid in his case (noted also in some other cases) was likewise observed in the urine of the present case. Sometimes the urine was turbid with this precipitate when quite freshly passed, and on

[1] Based on a communication to the Royal Medical and Chirurgical Society of London, March 10, 1903.

[2] On account of the contention by A. Magnus-Levy (*Ztschr. f. physiol. Chem.*, Strassburg, 1900, Bd. xxx. S. 200) that the so-called Bence-Jones albumose is really an albumin, I have referred to it in this paper as Bence-Jones proteid. For the sake of brevity, however, I have sometimes spoken of "Bence-Jones albumosuria," when I meant to signify the presence of Bence-Jones proteid in the urine. It seems that precipitin experiments fail to solve this question of the nature of the Bence-Jones proteid. In fact, the so-called "biological method" fails to distinguish the Bence-Jones proteid from various other proteids of human origin. *Vide* Rostoski, "Zur Kenntniss der Präcipitine," *Verhandl. d. phys.-med. Gesellsch. zu Würzburg*, 1902, Bd. xxxv. S. 30–32.

[3] The urine is nearly always acid in Bence-Jones albumosuria cases.

these occasions, the reaction being always very acid, the turbidity could not be due to phosphates.

Summary of the Present Case.

The patient, æt. 50, a rather fat man, weighing 84¼ kilos (185½ lb.), complained of rheumatoid symptoms, commencing, so he thought, about the end of the year 1899. About February 1900 he began to suffer from pains in his loins and stiffness in the small joints of his hands. Soon afterwards the upper part of his back began to bend, so that he always stooped. Up to the time of this illness the patient had been strong, but as a young man he had gonorrhœa and a chancre on the penis. One of his sisters suffered from diabetes mellitus.

The urine of the patient contained Bence-Jones proteid. The daily amount of urine was about 2000 c.c., and it contained about 7 per mille of the proteid as measured by Esbach's albuminimeter. By a more exact method (precipitation with alcohol, drying and weighing), Dr. R. Hutchison found that about 15 grammes of the proteid was excreted daily.

For some time the patient's condition remained fairly stationary, and at first, by the use of local hot baths, massage, etc., the power of bending his fingers was improved. Afterwards, however, the general weakness, cachexia, and anæmia, progressed rapidly, and gummatous disease of the tongue and over one rib made its appearance. Examination of the blood showed great anæmia and slight leucocytosis. On 25th January the patient died after copious hæmorrhage from the intestines, which post-mortem examination showed to be due to chronic ulceration of the duodenum. The Bence-Jones albumosuria persisted to the last.

At the necropsy the bone marrow of all the bones examined was found to be more or less affected by a diffuse sarcoma-like growth of rounded or polyhedral mononuclear cells—a form of "multiple myeloma" or "myelomatosis." There were no localised outgrowths projecting from the bones, such as have been noted in some cases of multiple myeloma, and no other parts of the body were invaded. In fact, as the neoplasm was strictly limited to the osseous system, it could never be regarded as metastatic. The presence in the tumour-cells of certain granules and globules of various sizes constitute a striking histological feature in the present case. Professor R. Muir, of Glasgow, who kindly made a careful microscopic examination of the growth, considers—"That the tumour is formed by a special and characteristic type of cell, which is probably derived either from the neutrophile myelocyte or its predecessor; that this cell produces in its protoplasm, in a granular form, a substance which is closely allied to, though not quite identical with, the substance of the neutrophile granules; and that this substance is formed in excess, and may form larger granules by confluence of the smaller, the larger globules sometimes becoming free."

At the end of his report Professor Muir suggested a possible relationship between the granule and globule formation in the tumour cells and the excretion of Bence-Jones proteid in the urine. The view that the globules may represent a stage in the formation of the proteid in question is supported by the consideration, that during the life of the patient these globules were probably being produced in *all* the bones of his body. Further investigation in other cases will doubtless throw more light on the question. If, however, these globules are in any way connected with the Bence-Jones albumosuria, why have they not been discovered in the microscopical preparations from other

cases? It is perhaps worth mentioning, that in the present case the tissues were at once put into weak formalin, where some of them were kept for several months before sections were cut.[1]

R. Hutchison and J. J. R. Macleod made a careful chemical investigation of the bones, blood, and organs, but failed to find in any of these tissues and organs a body giving exactly the same reactions as those of the Bence-Jones proteid in the urine. From the vertebræ and ends of the femur, however, they obtained a proteid giving very similar reactions, differing somewhat in the temperature at which it coagulates and in not being redissolved on boiling. Moreover, by employing the same methods, no proteid, like the one they detected, could be derived from normal red-bone marrow. They argue that in the present case the bone marrow was probably the seat of production of the proteid excreted in the urine, and that this proteid is not a non-assimilated digestive proteid, as suggested by Magnus-Levy. Though the case was complicated with syphilitic gummata, chronic ulceration of the duodenum, and a generalised rheumatoid affection of the joints, it was a typical one of multiple myeloma with Bence-Jones proteid in the urine, the "myelopathic albumosuria" of Dr. T. R. Bradshaw, also called in Italy "Kahler's disease." When the diagnosis was first made it was probably the second case of the kind recognised during life in England, the first one being that of Dr. Bradshaw in 1898 (Case No. 10 in the Summary).

Remarks on Multiple Myeloma in General.

Multiple myeloma may be defined as a diffuse new growth primarily involving the bone marrow, especially that of the vertebræ, ribs, and sternum,[2] and affecting males as often or more often than females, and chiefly those past middle age. The disease nearly always remains limited to the osseous system, though by direct extension it may form localised outgrowths projecting from the bones. Owing to absorption of the hard osseous tissue the bones become softened or friable, and are easily broken. The vertebral column and sternum are sometimes much bent, and the spinal cord may be affected by pressure, due to the curvature of the spinal column or to the new growth bulging into the spinal canal. Owing to the destruction of bone marrow the formation of blood is impaired, and anæmia and progressive cachexia occur, doubtless, in some cases, favoured by the circulation of a toxic proteid.

[1] A 4 per cent. aqueous solution of formalin slowly precipitates the Bence-Jones proteid from the urine.

[2] In the present case, however, and in some other cases (Nos. 20 and 24 in the Summary), the bones of the limbs were likewise much affected. Doubtless if the whole skeleton had been examined, the long bones would have been found affected in some of the cases in which, from the clinical symptoms, the bone disease was supposed to be limited to the ribs, sternum, and vertebral column.

I cannot help drawing an analogy between the bone disease, myelomatosis (*i.e.* multiple myeloma) on the one hand, and the skin disease, mycosis fungoides on the other. In both cases the etiology, as well as the true nature of the new growth, is obscure. For both diseases an infection theory has been propounded, making the new growths allied to the class of infective granulomata; but at present the arguments in favour of any such infection theory are far from convincing. In myelomatosis there is a primary diffuse infiltration of the bone marrow of a great part of the skeleton, followed in some cases by the formation of definite localised tumours growing from the bones, whilst mycosis fungoides usually commences as a diffuse infiltration of the skin (premycotic stage), and the localised tumours, which give the disease its name, begin to sprout out later on. This analogy may perhaps turn out to be a very superficial one, but in the present uncertainty regarding both diseases it is worthy of mention. In one important point, indeed, the analogy is imperfect. The point is that, whilst mycosis fungoides seems to be a single definite disease (morbid entity), different kinds of neoplasm have apparently been included under the heading "multiple myeloma."

Multiple myeloma is a term which has been employed to include various diffuse new growths arising in the bone marrow (*i.e.* myelogenic), and not giving rise to definitely metastatic growths in other tissues.[1] After post-mortem investigations various names have been employed according to the histological features (and individual interpretations by observers) of the neoplasms, and particularly of the cell elements, of which the tumours are formed. The tumours have been regarded as simple overgrowth of the cell elements of the bone marrow, or as myelogenic sarcoma, endothelioma, perithelioma, plasmoma, etc. In my first case[2] of "multiple myeloma" I supposed that the tumour formation was an example of "general lymphadenomatosis of bones."

I have lately been able to re-examine the growth and get sections stained by special methods.

The following is a short abstract of the case:—

The patient, E. P., a man (æt. 61), was admitted to the German Hospital 17th October 1896, complaining of various pains, resembling those often described in rheumatoid arthritis. His illness was apparently of comparatively recent onset. He was rather emaciated, and looked older than he really was —more like a man of 80 than of 61 years. He walked very stiffly and carefully with the aid of a stick. There was considerable kyphosis, and this seemed to be progressive. No organic disease could be found in the viscera, and the urine, according to the single note entered, was free from albumin. The blood was unfortunately not examined. Various medicines were tried, including glycerophosphates, iodide of iron, and arsenic, but they had no obvious effect. The patient had a fair appetite, and was free from fever; yet he

[1] See later on in regard to the lymphatic glands becoming affected in some cases.

[2] "General Lymphadenomatosis of Bones, one form of 'Multiple Myeloma,'" *Trans. Path. Soc. London*, 1897, vol. xlviii. p. 169, and *Journ. Path. and Bacteriol.*, Edin. and London, 1898, vol. v. p. 59.

seemed to get weaker, and to complain more of the pains. The bilateral pains in the side of the abdomen, which were usually worse when the patient stood up, and the increasing lumbo-dorsal kyphosis made one think of the possibility of malignant disease of the spinal column, of vertebral caries, or of spondylitis deformans. The whole spinal column was kept rigidly fixed in one position. In December pneumonia developed, and this led to the patient's death on January 18, 1897.

The necropsy showed greyish consolidation of the bases of both lungs. The heart presented no abnormal appearance. The stomach was dilated. The spleen was slightly enlarged and soft, and its capsule was thickened. The liver, by macroscopical and microscopical examination, appeared normal. The kidneys had undergone a moderate degree of interstitial fibrosis, and in the cortex of one of them calcareous granules (microscopic calculi) were present, some of which were in close relation to minute adenomata.

All the ribs, the whole vertebral column, the clavicles, the sternum, and the bones of the calvarium were examined, and were all found to be the site of a very vascular pulpy neoplasm, growing from the interior outwards. The ribs were converted into delicate tubes formed of periosteum, with only a thin imperfect shell of bone; they were all stuffed full of the new growth. The slightest pressure sufficed to break them in any part. Many "spontaneous" fractures had occurred during life, and had already been thoroughly united by callus. Here and there the osseous tissue had been completely absorbed, so that the new growth lay directly under the periosteum, and in some places the periosteum and bony shell had been bulged out by the tumour so as to form nodular enlargements on the ribs. The clavicles were somewhat less affected than the ribs, sternum and vertebral column. There was a certain amount of new growth in the diploe of the cranial bones. Specimens of the new growth from the vertebræ, ribs, and diploe of the skull were microscopically examined, and consisted of rather small mononuclear cells, with none, or scarcely any, substance between them. Interspersed amongst the cells were small blood vessels, with swollen-looking, almost hyaline, walls.[1] Examination of spicules of bone taken from the growth seemed to show that the bone was being absorbed by the tumour formation without undergoing any preliminary process of softening (decalcification), such as is reported to occur in osteomalacia, and in the absorption of the bone trabeculæ in the long bones in some cases of pernicious anæmia.[2]

I have not yet mentioned that behind the right clavicle some enlarged lymphatic glands were found, which the microscope showed to be the site of a growth similar to (but less vascular than) that in the bone marrow. No tumour was discovered in other lymphatic glands, or elsewhere in the body.

Recent re-examination of old sections (stained by the ordinary methods) from the bone marrow growth, and from the affected glands, has confirmed the view and made it practically certain that the growth in the glands is identical with that in the bones. The cells of which the growth consists resemble lymphocytes, except that very many of them have more protoplasm than ordinary small lymphocytes have. The larger cells are rounded, oval, or polyhedral, and the nucleus is often placed eccentrically. Part of the sternum was fortunately preserved in glycerin and formalin in the Museum of the Royal

[1] From recent examinations of portions of the growth from the sternum, I think that some of these supposed vessels are really vesicles remaining from fat-cells.

[2] Cf. "On the Changes of the Bone Marrow in Pernicious Anæmia," by R. Muir, *Journ. Path. and Bacteriol.*, Edin. and London, 1894, vol. ii. p. 363.

College of Surgeons, and this I have lately had an opportunity of examining. Sections of the sternal portion of the growth were stained by Ehrlich's tri-acid stain, and by Mann's eosin-methyl-blue combination. These stains show that hardly any of the cells contain granules. In fact, only one or two coarsely granular eosinophile cells were seen on looking through the sections, and these were probably not tumour cells. The tumour may, therefore, be said to consist of non-granular, lymphocyte-like cells. It must be remembered that in lymphatic leucocythæmia the growths in the various organs may consist largely of cells which, though they are described as lymphocyte-like, have much more protoplasm than have the small lymphocytes of normal blood. Every intermediate form between the cells with much protoplasm, and those with very little, can be found in the growths of lymphatic leucocythæmia, as also in the myelogenic growth from the patient E. P. Moreover, in normal lymphatic glandular tissue many of the cells of the "germinating centres" have more protoplasm than the small lymphocytes further from these centres and in the circulating blood. I feel justified, therefore, in saying that in the case of E. P. the cells of the myelogenic growth were lymphocyte-like, if not actually lymphocytes. Dr. J. M. H. MacLeod has kindly examined the growth after staining specially for plasma cells, and thinks that the cells of which the growth is composed have a greater resemblance to lymphocytes than to the typical plasma cells of the granulomata.[1]

Two types, if not more, of "multiple myeloma" are to be distinguished—(1) a growth, as in the patient J. T., in which the bone marrow only is involved; (2) a growth in which nearly all the cells resemble small or large lymphocytes, and are possibly derived from the non-granular predecessors of the myelocytes.[2] In this second type of "multiple myeloma" lymphatic glands as well as bone marrow may probably be affected. The second type of multiple myeloma would include cases described as myelogenic lymphosarcoma, myelogenic lymphadenoma, and myelogenic pseudoleukæmia (using the German term "leukæmia" in the limited sense of "lymphocythæmia"). Intermediate cases between these two types ("mixed forms") probably also occur.

If the views which I here suggest be correct, it follows that the whole class of leukæmias and pseudoleukæmias (using the German terms for convenience) can be divided into at least the following six types, independently of intermediate forms:—

(*a*) A new growth of lymphocyte-like cells originating in the bone

[1] I may add that in part of the growth in the sternum many of the tumour cells have undergone some kind of degenerative change, owing to which, by Mann's eosin-methyl-blue combination, the nucleus and the rest of the cell are deeply stained by the eosine.

[2] According to A. Pappenheim's views (*Virchow's Archiv*, 1902, Bd. clxix. S. 381) the *large lymphocyte* type of cell, which in the lymphatic "germinating centres" gives rise to the ordinary small lymphocytes of the blood, in the bone marrow gives rise to the myelocytes, and thus indirectly to the polymorphonuclear leucocytes also.

marrow, and not overflowing into the circulating blood. Myelogenic pseudoleukæmia (using leukæmia in the sense of lymphocythæmia), myelogenic lymphosarcoma, lymphadenomatosis of bones, multiple myeloma (myelomatosis) of the lymphatic type.

(*b*) Similar to the preceding, but the lymphocyte-like cells overflow into the blood-stream—myelogenic lymphocythæmia. I do not know of any cases illustrating this type, excepting cases of "acute leukæmia." Those of A. Denning[1] and C. H. Melland,[2] for instance, were examples of acute lymphocythæmia in which, post-mortem, practically no change was discovered in the leucocyte-forming tissues other than the bone marrow.[3]

(*c*) A new growth, formed in large part of lymphocyte-like cells originating in the lymph glands, or spleen, or lymphadenoid tissues generally (the bone marrow may likewise become involved), and not to any great extent overflowing into the circulating blood. Lymphatic, or splenic lymphadenoma, or pseudoleukæmia (using leukæmia in the sense of lymphocythæmia), Hodgkin's disease. In the more chronic and fibrous varieties of this type the microscopic appearances differ, of course, considerably from those in acute cases.

(*d*) Similar to the preceding, the lymphocyte-like cells invading the blood-stream—lymphatic or splenic lymphocythæmia.

(*e*) A new growth originating in the bone marrow from cells derived from the myelocytes, and not invading the circulating blood. Myelogenic pseudoleukæmia (using leukæmia in the sense of myelogenic or spleno-medullary leucocythæmia). To cases of this type and to "mixed cases" partaking of this type the term multiple myeloma (myelomatosis) might, perhaps, be limited.

(*f*) A new growth, differing somewhat from the preceding, and characterised by its myelocyte-like cells overflowing or being drawn out into the circulating blood, and by Bence-Jones albumosuria not occurring as it sometimes does in the last type. Myelogenic or spleno-medullary leukæmia (leucocythæmia).

According to this scheme one must regard the excess of white corpuscles in the blood in all kinds of leukæmia as due to an inroad of tumour cells from a *hyperplasia-like* tumour formation in the leucocyte-producing tissues of the body,[4] all forms of leucocytosis (including lymphocytosis) being merely expressions of some reaction in the tissues in question. A leucocytosis is therefore, strictly speaking, never an early stage of leukæmia (leucocythæmia); yet a true leucocytosis from any cause may perhaps sometimes be followed by true leukæmia, in so far as the reactive growth in the leucocyte-forming tissues (of which reactive growth the leucocytosis is the expression)

[1] *München. med. Wchnschr.*, 1901, Bd. xlviii. S. 140.

[2] *Med. Chron.*, Manchester, 1902, vol. iii. p. 372.

[3] I do not think that cases of *acute* leukæmia should be regarded as altogether different from cases of *chronic* leukæmia, unless the special parasitic theory of the former be confirmed.

[4] Cf. Pappenheim's various writings, *loc. cit.*, etc.

may be supposed to give a start to the kind of tumour-formation (of which the leukæmia is the expression), just as chronic irritation of the skin sometimes acts as the exciting cause of epithelioma.

Remarks on Multiple Myeloma with Bence-Jones Proteid in the Urine.

I shall now consider the present case and similar cases in which multiple myeloma is associated with the presence of Bence-Jones proteid in the urine. Though their microscopic appearances may vary somewhat, the growths in this group of cases are allied to each other by one notable peculiarity—a metabolic one—namely, that they form or cause to be formed in the body a substance which is got rid of by the kidneys as Bence-Jones proteid. Some striking features in the present case deserve special consideration.

Special Features of the Present Case.

The articular disease.—It was the affection of the hands amounting to a "pseudo-paralysis," that obliged the patient to give up work and seek hospital treatment. The history in this respect is important.

He was a stout, middle-aged, sallow-looking man, suffering from tingling sensations in the tips of his fingers (a kind of "acroparæsthesia") and inability to grasp objects. He could not close his hands, and any attempt to bend his fingers caused pain. The backs of the hands had a puffy swollen appearance, especially about the metacarpo-phalangeal joints, and the fingers were tremulous. There was some pigmentation of the skin, and the fleshy portions of the finger-tips were shrivelled. The shoulder-joints were also somewhat affected, and doubtless the wasting noticed in the muscles of the upper extremities could be accounted for by the articular affection. After death, from other causes, marked changes were found in the joints examined, namely, in the hip, shoulder, wrist, and fingers.

There can be no doubt that the patient suffered from a form of rheumatoid or rheumatic[1] arthritis, and that most of the early symptoms which he complained of were due to the arthritic affection, not to the myelomatosis of bones.

Whether or not the tumour formation in the bones had any causal connection with the articular disease must remain doubtful. That joint changes can be induced by the irritation set up by tumour formation in the neighbouring bones is made probable by an observation of Mr. Jonathan Hutchinson.[2] His case was that of a young woman whose thigh was amputated for a tumour of the tibia, and in whose knee-joint changes were discovered such as occur in rheumatoid arthritis.

[1] The evidence of former endocarditis found in the heart suggests that at one time there was acute rheumatism.

[2] *Med. Times and Gaz.*, London, 1881, vol. i. p. 2; quoted in Fagge and Pye-Smith's "Principles and Practice of Medicine," London, 1886, vol. ii. p. 554.

The syphilitic affection.—The gummatous disease of the tongue and rib makes it clear that the patient really had syphilis, although he could not remember having had a secondary eruption. Considering how apt tertiary syphilis is to affect the bones, it is just possible that in this case it may have acted as an exciting cause in regard to the tumour formation (myelomatosis).[1] In a similar way the irritation of the osseous changes in osteitis deformans and chronic osteomalacia[2] may be supposed sometimes to excite the development of primary bone tumours, and chronic malaria seems occasionally to have acted as an exciting cause in the development of leucocythæmia.[3] On the whole, however, it is more probable that in the present case the cachectic condition of the patient led to the outbreak of tertiary syphilis. For, in syphilitic subjects, fevers and other general debilitating conditions, and (locally) traumatisms, favour the onset of gummatous disease.

The duodenal ulceration.—There is no doubt that the severe intestinal hæmorrhage greatly accelerated death in the present case. This may partly account for the fact that in the patient in question the tumour had, at the time of death, caused less destruction of bony tissue than in certain other patients with multiple myeloma; but it must also be noted that the man was strongly built; and the outside of his bones may have been specially resistant. Most patients with multiple myeloma, as I pointed out in 1897,[4] die of pneumonia, but the fatal result of the hæmorrhage in the present case interfered with the ordinary course of events. The duodenal affection is probably to be classed with the duodenal ulcers associated with renal disease.[5] The excretion of an irritant substance by the intestinal mucous membrane possibly accounts not only for duodenal ulceration,

[1] It is worth mentioning that in the case described by Sir H. Weber in 1866 (*Trans. Path. Soc. London*, 1867, vol. xviii. p. 206), which would probably now be regarded as one of multiple myeloma, the patient, a man, æt. 40, had had syphilis fourteen to sixteen years before death, and had amyloid disease of the kidneys and spleen. The sternum, ribs, vertebral column, and cranium were affected by a growth, which Hulke and Cayley, who reported on it, were inclined to regard as sarcomatous. The state of the urine is not alluded to. The alteration in shape of the sternum was so great that it caused pressure on the aorta with physical signs simulating aneurysm.

[2] The occasional occurrence of primary malignant tumours in the bones in cases of osteitis deformans has been recognised since Sir James Paget's original description of the disease in 1876 (*Med. Chir. Trans.*, London, 1877, vol. lx. p. 37). Dr. Wilhelm Schönenberger (*Virchow's Archiv*, Berlin, 1901, Bd. clxv. S. 189) gives the case of a woman, æt. 33, in which the changes of osteomalacia apparently preceded the development of multiple sarcomata (multiple fractures had also occurred). He likewise speaks of solitary or multiple sarcomata often developing in the late stages of "osteomalacia chronica deformans hypertrophica." It may be asked, however, whether these late forms of osteomalacia (showing a kind of hypertrophic reaction with new bone formation) are not identical with osteitis deformans except for their history.

[3] For instance, in the case of leucocythæmia with Ménière's symptoms which I communicated in 1900 (*Med. Chir. Trans.*, London, 1900, vol. lxxxiii. p. 185).

[4] *Trans. Path. Soc. London*, 1897, vol. xlviii., *loc. cit.*

[5] See "On Diseases of the Duodenum," by E. C. Perry and L. E. Shaw, *Guy's Hosp. Rep.*, London, 1893, vol. l. pp. 194–196 and 250–255.

but also for ulcerative colitis when occurring in cases of renal disease.

The Bence-Jones Proteid in the Urine of Multiple Myeloma Cases.

Drs. Hutchison and Macleod, in the report they have kindly furnished, conclude that in the present case the bone marrow was probably the seat of production of the Bence-Jones proteid, and that this proteid is not a non-assimilated digestive proteid, as suggested by Magnus-Levy.[1] As confirming their views, I may mention that in my patient, a great alteration of diet, maintained during two days, had no effect in altering the quantity of proteid excreted in the urine. Moreover, Dr. Bradshaw, in his case, found that meals had little or no influence on the excretion of the proteid in the urine. He found that as much was excreted by night as by day,[2] when the patient was taking meals during the daytime only; and he considered the rate of excretion to be "pretty constant throughout the twenty-four hours."

It seems that when it is free in the blood the Bence-Jones proteid appears in the urine,[3] as hæmoglobin does whenever, owing to various causes, sudden unusual hæmolysis occurs. The fact, therefore, that the quantity excreted in the urine is little influenced by meals and by change of diet speaks strongly against the correctness of Magnus-Levy's views. It is possible that the cells of the new growth in the bone may produce digestive enzymes by the action of which, on the albuminous constituents of the blood serum, the Bence-Jones proteid is steadily and continually manufactured. Then from the circulating blood it would pass through the renal filter with the urine, like hæmoglobin, even in the absence of any kidney disease. As already mentioned, there may be some connection between the excretion of the proteid in the urine and the formation of granules and globules in the cells of the new growth in the present case.

Diagnosis of Multiple Myeloma (Myelomatosis) with and without Bence-Jones Proteid in the Urine.

There is still some uncertainty as to the nature of multiple myeloma (multiples Myelom), a term first employed by J. von Rustizky,[4] who regarded the growth as the result of a simple hyper-

[1] *Loc. cit.*

[2] See the tables at the end of Dr. Bradshaw's first paper (*Med. Chir. Trans.*, London, 1898, vol. lxxxi. pp. 270, 271).

[3] Stokvis found that Bence-Jones proteid, when a not very concentrated solution was injected into the rectum of a dog, was excreted unchanged in the urine. I have to thank Sir Lauder Brunton for directing my attention to these little known experiments made by Stokvis, which were recorded in the "Maandblad der sectie voor Natuurwetenschappen," 1872, No. 6.

[4] "Multiples Myelom," *Deutsche Ztschr. f. Chir.*, Leipzig, 1873, Bd. iii. S. 162.

trophy of bone marrow. As already mentioned, however, the tumours from different cases do not all resemble each other in their histological features, though they possess certain characters in common. The growth is generally so diffuse in its distribution, that it is impossible to determine that any one part represents a primary focus where the neoplasm may be supposed to have commenced. It does not invade other tissues by metastasis through the blood channels as sarcoma does, though in some cases the lymphatic glands have been involved (Case 3 in the Summary at the end).

Owing to the softening and fragility of bones, the pains, and the progressive kyphosis caused by the disease, the diagnosis must, in the first place, be made between this condition and—

(*a*) Osteomalacia. (*b*) Muscular rheumatism, lumbago, sciatica, etc. (*c*) Spondylitis deformans. (*d*) Caries of the spinal column. (*e*) Invasion of the vertebral column and other bones by secondary malignant tumours. Owing to the progressive anæmia and cachexia, one may think of (*f*) pernicious anæmia or other diseases associated with progressive cachexia. Owing to the possibility of confusing Bence-Jones proteid in the urine with albumin, the cases of multiple myeloma in which this body is present in the urine (*i.e.* the cases of "myelopathic albumosuria" of Bradshaw, "Kahler's disease") may at first be mistaken for (*g*) nephritis.

(*a*) *Osteomalacia.*—From the typical osteomalacia of women, multiple myeloma differs in the following respects:—The former attacks women during the child-bearing period of life. It affects, chiefly, the bones of the pelvis and lower extremities. It gives rise to great deformity by bending of the bones, but more rarely to "spontaneous" fractures. Multiple myeloma attacks men as often as women, or more often, and chiefly after middle life. Clinically, it appears to affect the vertebral column, ribs, and sternum specially, though the bones of the extremities have certainly been involved in some cases, as they were in the present case. It is likely to cause fractures of the ribs and deformity by bending of the vertebral column and sternum; in one case (Case No. 20 in the Summary) "spontaneous" fracture of one femur occurred, and in another (Case No. 24 in the Summary) "spontaneous" fractures of both femora are recorded; yet it does not give rise to the characteristic deformities of osteomalacia, resulting from yielding of the pelvis and bending of the bones of the lower extremities. It is possible, however, that there may be true cases of osteomalacia in males and in elderly females, in which the bones of the vertebral column and trunk are specially affected.

(*b*) *Muscular rheumatism, lumbago, sciatica, etc.*—Several cases of multiple myeloma have, at least during some stage of the disease, been arranged under such headings. The occurrence of markedly bilateral thoracic, abdominal, or lumbago-like pains may first direct

attention to the possibility of disease of the spinal column. In my first case of multiple myeloma[1] pain on both sides of the abdomen, together with the presence of an increasing kyphosis, pointed to grave disease of the spinal vertebræ. Sometimes examination of the bones by Röntgen's rays may prove of service (Case No. 13 in the Summary at the end). If grave rheumatoid or rheumatic arthritis is a complication, as in my present case, it obviously is difficult to distinguish pains and paræsthesiæ due to the arthritis from those due to the multiple myeloma.

(*c*) *Spondylitis deformans.*—This affection of the vertebral column may produce a similar kyphosis to that which in several cases has been caused by multiple myeloma. When, however, the kyphosis is due to spondylitis deformans,[2] the spinal rigidity in the cervical region is probably more pronounced than in cases of multiple myeloma, whilst the patient is likely to be less anæmic and cachetic. For comparison with the kyphosis in the present case of multiple myeloma, I would contrast a spondylitis deformans patient under the charge of my colleague Dr. zum Busch, whom I also had formerly seen in the out-patient department (the "spondylose rhizomélique" type of Pierre Marie, at a relatively early stage of the disease). The portrait of Dr. Bradshaw's patient, illustrating his paper before the Medical and Chirurgical Society of London in April 1898,[3] should likewise be consulted for comparison.

(*d*) *Caries of the spinal column.*—The progressive bending of the vertebral column seen in multiple myeloma might be confused with tuberculous caries; that is, with those rare cases occurring in middle or old age, and giving rise to progressive curvature. On the other hand, the curvature due to myeloma is somewhat less likely to be distinctly "angular" than that due to tuberculosis, and in the latter disease the ribs are not likely to be in any way affected simultaneously with the spinal column. The sternum has sometimes become excessively bent in multiple myeloma. The presence of tuberculosis in the lungs might help to clear up the diagnosis.

(*e*) *Invasion of the vertebral column and other bones by secondary malignant tumours.*—Secondary localised malignant tumours may give rise to a progressive curvature of the vertebral column. The vertebral column and ribs may likewise be diffusely infiltrated by

[1] *Trans. Path. Soc. London, loc. cit.*

[2] Cases in which the vertebral column only is affected (von Bechterew's type) may be distinguished from those in which the extremities, especially the hip-joints, are likewise affected (Strümpell's type, Pierre Marie's "spondylose rhizomélique"). Such cases of chronic ossifying arthritis may progress to universal bony ankylosis. (See the Summary of cases by Dr. Joseph Griffiths in the *Journ. Path. and Bacteriol.*, Edin. and London, 1897, vol. iv. p. 284. A number of articles have been written on the subject during recent years in France and Germany.) Of course, when ankylosis of the joints of the extremities has occurred, a case could hardly be mistaken for one of multiple myeloma, but even at the commencement of the disease such a mistake is very unlikely to be made.

[3] *Med. Chir. Trans.*, London, 1898, vol. lxxxi. plate vii.

metastatic carcinoma, but all such metastatic growths are more likely to cause distinct swellings[1] or to give rise to local signs of their presence. Evidence as to a primary malignant growth existing or having been removed from some other part of the body would facilitate the diagnosis, and in localised tumours, as well as in tuberculous caries, help might be obtainable from the Röntgen rays.

(*f*) *Pernicious anæmia, etc.*—Anæmia and progressive wasting and feebleness may be marked features of myelomatosis, at all events in the later stages, when the blood-forming functions of the bone marrow are greatly impaired by the diffuse tumour formation. The pains and other signs of bone disease, such as progressive kyphosis, when these are well marked, will help to distinguish a case of multiple myeloma from pernicious anæmia, and forms of progressive cachexia dependent on visceral cancer, etc.

(*g*) *Nephritis.*—The Bence-Jones proteid, when present in the urine, may be confused with albumin, and the case may be regarded as one of nephritis. This is especially likely to occur if the urine on the first occasion is examined very hurriedly (for example, by heating it without boiling it, or by merely adding picric acid or nitric acid in the cold); and, owing to the copious precipitate of supposed ordinary albumin, it is subsequently examined every day by Esbach's method. This actually occurred in the present case,[2] where the general "puffy" look of the patient seemed to correspond to the finding of albuminuria. Moreover, in this case, as in some others, hyaline casts were found in the urine.[3] Afterwards the testing of the urine by the ordinary methods, instead of by Esbach's solution, led to the detection of the special proteid it contained.

I need not repeat what has already been said in regard to the tests to be employed for distinguishing Bence-Jones proteid in the urine from albumin and from certain albumoses.[4] In the albumosuria occasionally met with in cases of intestinal ulceration and febrile disorders, the quantity of proteid in the urine is generally far less than in Bence-Jones albumosuria. In such a case as that recorded by

[1] In some cases of multiple myeloma, with or without Bence-Jones proteid in the urine, localised tumours connected with the bones could be seen or felt during life (Cases 14, 19, 27, and 33 in the Summary at the end).

[2] The remarkable constancy in the amount, and the large quantity of the proteid in the urine, ought perhaps to have caused some surprise.

[3] The necropsy, it should be remembered, showed the presence of actual interstitial fibrotic changes in the kidneys. In Senator's case (Case No. 7 in the Summary) casts and albumin were present in the urine, and the kidneys were found to be somewhat diseased at the post-mortem examination. In d'Allocco's case (No. 15) there was likewise nephritis; in Ellinger's (No. 9), the urine contained a few hyaline casts; and in Conti's (No. 27), during the last weeks of life, the urine contained albumin and hyaline and granular casts.

[4] I do not think that Dr. L. N. Boston's caustic soda and lead acetate test ("A Rapid Reaction for Bence-Jones Albumose," *Am. Journ. Med. Sc.*, Phila., Oct. 1902, vol. cxxv. p. 568) is likely to be of much service in this connection.

R. Hutchison,[1] where the proteid, though precipitated at as low a temperature as 58° C., was not, even partially, redissolved on heating to the boiling point; the chances of wrongly regarding the precipitate as one of ordinary urinary albumin must be still greater than they were in the present case, where the greater part of the precipitate redissolved on boiling the urine.

I come now to the diagnostic value of finding Bence-Jones proteid in the urine. From a study of cases the following conclusions must be arrived at:—(1) Undoubtedly a considerable number of cases of multiple myeloma have occurred in which the Bence-Jones proteid has not been detected. In some of them the urine may have been examined at a stage of the disease prior to the commencement of the "Bence-Jones albumosuria."[2] In other cases the urine may possibly have been insufficiently examined. Still there remain sufficient cases to enable one to affirm, with almost absolute certainty, that "multiple myeloma" may occur, without giving rise to the presence of Bence-Jones proteid in the urine. It must be remembered, however, that different types of tumour have been included under the heading "multiple myeloma," as mentioned in an earlier part of this paper. (2) Metastatic tumours affecting the skeleton, however extensively the bone marrow be infiltrated, have never yet been known to cause "Bence-Jones albuminosuria." (3) The presence of Bence-Jones proteid in the urine is almost invariably of fatal significance, and it nearly always indicates that the patient is suffering from "multiple myeloma." (4) One or two published cases in which Bence-Jones proteid was present in the urine seem, however, to have been exceptions to this rule, in which they were supposed not to be instances of multiple myeloma. Moreover, the experiments of G. Zuelzer,[3] should they be confirmed, would make the existence of such exceptions more probable. He rendered a dog anæmic by giving it pyrodin by the mouth. On the eighth day from the commencement of the experiment, a substance was detected in the urine giving the typical reactions for Bence-Jones proteid, and no albumin was present. The pure Bence-Jones albumosuria lasted four days, and then albuminuria occurred and the amount of the Bence-Jones proteid diminished. It would be interesting to know what changes occurred in the bone marrow of this animal.

Taking into consideration all the data that I can obtain, it seems

[1] Case No. 30 in the Summary of cases at the end.

[2] In the case of Stokvis and Kühne (Case No. 2 in the Summary) the Bence-Jones proteid is said to have appeared late in the disease, and could not be found three months before the patient's death. Conti says that during the last weeks of life in his case (No. 27 in the Summary) the urine contained albumin but no Bence-Jones proteid.

[3] "Ueber experimentelle Bence-Jones'sche Albumosurie," *Berl. klin. Wchnschr.*, 1900, Bd. xxxvii. No. 40, S. 894. Moreover, Campbell-Horsfall (*Lancet*, London, 1903, vol. i. p. 1166) records a case of temporary Bence-Jones albumosuria in a man, following injury to his leg.

to me quite possible—(1) that Bence-Jones albumosuria is always the result of disease of the bone marrow; (2) that it is due to an abnormal metabolic or degenerative process in the myelocytes or in tumour cells derived from the myelocytes or their predecessors; (3) that the reason it is generally, though not always,[1] associated with myelogenic tumour formation is that the tumour cells derived from bone marrow cells, however much they may morphologically resemble true bone marrow cells, are more prone to abnormality (including unusual degenerative changes) than true myelocytes are; (4) that non-myelogenic tumour cells are not affected in the same way, and therefore metastatic tumours in the bone marrow do not give rise to Bence-Jones albumosuria.

Summary of Literature of Cases.

I now give a summary of publications on cases in which Bence-Jones proteid has been detected in urine,[2] whether the presence of bone disease was verified or not. I include some doubtful cases, in which the reactions of the proteid in the urine were not quite characteristic for Bence-Jones proteid. Amongst doubtful cases are those such as that reported by R. Hutchison (Case No. 30), in which, though a copious precipitate occurs on slightly heating the urine, yet this precipitate is not to any extent dissolved by further heating. In this connection it must be remembered that the experiments of Hammarsten,[3] K. Spiro,[4] Magnus-Levy,[5] and others in regard to various proteids, show, as Hutchison and Macleod pointed out in their report on the present case, that the point of heat coagulation varies with the dilution and composition of the fluid, and the resolution of the coagulum depends likewise, to a great extent, on the composition of the fluid in which it is suspended. Amongst cases which are not included are those of albumosuria (other than "Bence-Jones albumo-

[1] An analogy between Bence-Jones albumosuria and melanuria may be drawn. The presence of melanin and melanogen in the urine is best known in cases of melanotic tumour, but has been noted likewise in wasting diseases. Melanotic tumours, however, are not always associated with the excretion of melanin or melanogen in the urine. Yet, as Dr. A. E. Garrod points out (*St. Barth. Hosp. Rep.*, London, 1903, vol. xxxviii. p. 25), melanuria has been undervalued for diagnostic purposes, because other conditions in which the urine blackens on exposure to air have been confounded with true melanuria.

[2] In preparing the list I am indebted to the summaries given in various previous articles on the subject, particularly to that of Dr. C. E. Simon. I shall not here refer to the cases of "multiple myeloma without albumosuria," several of which are quoted in my paper in the *Trans. Path. Soc. London*, vol. xlviii. On the whole subject of multiple myeloma, the important writings of F. W. Zahn (*Deutsche Ztschr. f. Chir.*, Leipzig, 1885, Bd. xxii. S. 1), Hammer (*Virchow's Archiv*, 1894, Bd. cxxxvii. S. 280), Marckwald (*ibid.*, 1895, Bd. cxli. S. 128), R. Paltauf ("Ergebnisse der allg. Pathologie," edited by Lubarsch and Ostertag, 1896, Bd. i. S. 676), K. Winkler (*Virchow's Archiv*, 1900, Bd. clxi. S. 252), E. Wieland (*ibid.*, 1901, Bd. clxvi. S. 103), and M. Borst ("Die Lehre von den Geschwulsten," 1902, Bd. i. S. 492) may be consulted.

[3] *Arch. f. d. ges. Physiol.*, Bonn, 1878, Bd. xviii. S. 65.

[4] *Ztschr. f. physiol. Chem.*, Strassburg, 1900, Bd. xxx. S. 182.

[5] *Loc. cit.*

suria"), in which no precipitate occurs on merely heating the urine (presumably acid in reaction), but in which the addition of nitric acid to the cold urine gives rise to a precipitate, which dissolves on heating and reappears on cooling.[1]

No. 1.—The case of Watson, Macintyre, and Bence-Jones, of London (H. Bence-Jones, "On a New Substance Occurring in the Urine of a Patient with Mollities Ossium," *Phil. Trans.*, London, 1848, Part 1, p. 55. W. Macintyre, "Case of Mollities and Fragilitas Ossium," *Med.-Chir. Trans.*, London, 1850, vol. xxxiii. p. 211. J. Dalrymple, "On the Microscopical Character of Mollities Ossium," *Dublin Journ. Med. Sc.*, 1846, vol. ii. p. 85).

No. 2.—The case of Doornik, Stokvis, and Kühne (W. Kühne, "Ueber Hemialbumose im Harne," *Ztschr. f. Biol.*, München, 1883, Bd. xix. S. 209).

No. 3.—The case of Kahler and Huppert (O. Kahler, "Zur Symptomatologie des Multiplen Myeloms: Beobachtung von Albumosurie," *Prag. med. Wchnschr.*, 1889, Bd. xiv. S. 33. H. Huppert, "Ein Fall von Albumosurie," *ibid.*, S. 35).

No. 4.—The case of Stokvis, Ribbink, and Zeehuisen (B. I. Stokvis, *Nederl. Tijdschr. v. Geneesk.*, Amsterdam, 1891, vol. ii. p. 36. Zeehuisen, *Nederl. Tijdschr. v. Geneesk.*, Amsterdam, 1893, vol. i. p. 829.[2] See also abstracts, *Jahresb. ü. d. Fortschr. d. Thier.-Chem.*, Wiesbaden, 1891, Bd. xxi. S. 412; 1892, Bd. xxii. S. 525; 1893, Bd. xxiii. S. 577).

No. 5.—The case of Raschkes, "Ein Fall von seniler Osteomalacie mit Albumosurie," *Prag. med. Wchnschr.*, 1894, Bd. xix. No. 51, S. 649.

No. 6.—The case of Professor Stintzing, of Jena (Seegelken, "Ueber Multiples Myelom und Stoffwechsel Untersuchungen bei derselben," *Deutsche Arch. f. klin. Med.*, Leipzig, 1897, Bd. lviii. S. 276. M. Matthes, "Ueber Eiweisskörper im Urine bei Osteomalacie," *Verhandl. d.* 14 *Cong. f. innere Med.*, Wiesbaden, 1896, S. 476. Neumeister, "Lehrbuch d. Physiol. Chemie," 1897, 2te Aufl., S. 804).

No. 7.—Senator's case (H. Rosin, "Ueber einen eigenartigen Eiweisskorper in Harne und seine diagnostische Bedeutung," *Berl. klin. Wchnschr.*, 1897, Bd. xxxv. S. 1044. H. Senator, "Asthenische Lahmung, Albumosurie und Multiple Myelome," *Berl. klin. Wchnschr.*, 1899, Bd. xxxvi. S. 161. The urine has likewise been studied in Sussmann's "Dissertation," Leipzig, 1897).

No. 8.—Bozzolo's case, "Sulla Malattia di Kahler," in the *Transactions of the Eighth Medical Congress*, Naples, October 1897; and *Clin. med. ital.*, Milan, 1898, January, Anno xxxvii. p. 1; referred to also in *Centralbl. f. d. med. Wissensch.*, Berlin, 1898, Bd. xxxvi. S. 572.

[1] A typical example of this is recorded by Hougounenq (*Lyon méd.*, 20th January 1901, tome xcvi. p. 81). See also E. Vidal's case (*Compt. rend. Soc. de biol.*, Paris, October 29, 1898, tome v. Sér. 10, p. 991), in a woman, æt. 24, suffering from tuberculous disease of the right shoulder. Blair's "Case of Albumosuria (*Brit. Med. Journ.*, London, 1901, vol. ii. p. 713) is doubtless of the same kind. He states that the urine "gave no perceptible precipitate on simple heating without acid," but that on adding nitric acid to the cold urine a precipitate occurred which was dissolved on heating and reappeared on cooling. This kind of albumosuria is doubtless much less rare than the "Bence-Jones albumosuria," and is probably sometimes altogether overlooked, owing to the fact that the boiling test for albumin is more often employed than the nitric acid (cold) test. It must be remembered, however, that in true Bence-Jones albumosuria, the urine, if alkaline, should likewise not be expected to give any precipitate on heating until it has been rendered slightly acid. The case described by Grigoriantz (*Ztschr. f. physiol. Chem.*, Strassburg, 1882, Bd. vi. S. 537) was not an example of Bence-Jones albumosuria, as he specially mentions that no precipitate occurred on boiling the urine with or without the addition of acetic acid.

[2] There have been several articles on Bence-Jones albumosuria in Dutch Journals. *Vide* also Case No. 26.

No. 9.—The case of Lichtheim and Ellinger (A. Ellinger, "Das Vorkommen des Bence-Jones'schen Körpers im Harn bei Tumoren des Knochenmarkes und seine diagnostische Bedeutung," *Deutsches Arch. f. klin. Med.*, Leipzig, 1899, Bd. lxii. S. 255).

No. 10.—Bradshaw's case, "A Case of Albumosuria in which the albumose was spontaneously precipitated," *Med.-Chir. Trans.*, London, 1898, vol. lxxxi. p. 259. Bradshaw and Warrington, "The Morbid Anatomy and Pathology of Dr. Bradshaw's Case of Myelopathic Albumosuria," *ibid.*, 1899, vol. lxxxii. p. 251. Bradshaw, *Trans. Path. Soc. London*, 1900, vol. li. p. 140. Bradshaw, "Myelopathic Albumosuria," *Brit. Med. Journ.*, London, 1900, vol. ii. p. 1304. Bradshaw, "Myelopathic Albumosuria," *Lancet*, London, 1902, vol. ii. p. 929.

No. 11.—Case of Naunyn and Magnus-Levy (Naunyn, "Ein Fall von Albumosurie," *Deutsche med. Wchnschr.*, Leipzig, 1898, Jahrg. 24, Vereins-Beilage, S. 217. Magnus-Levy, "Ueber den Bence-Jones'schen Eiweisskorper," *Ztschr. f. physiol. Chem.*, Strassburg, 1900, Bd. xxx. S. 200).

No. 12.—The first case of Dr. Fitz, "The Significance of Albumosuria in Medical Practice," *Am. Journ. Med. Sc.*, Phila., 1898, vol. cxvi. p. 30.

No. 13.—The second case of Dr. Fitz (*loc. cit.*, p. 42. J. H. Wright, "A Case of Multiple Myeloma," *Johns Hopkins Hosp. Rep.*, Baltimore, 1900, vol. ix. p. 359; also *Journ. Boston Soc. Med. Sc.*, 1900, vol. iv. p. 195).

No. 14.—The case of Buchschtab and Schaposchnikow, "Diffuses Myelom der Rumpfknochen mit einer Typischen Albumosurie," abstract in German in *St. Petersb. med. Wchnschr.*, 1899, from *Russ. Arch. patol. klin. méd. bacteriol.*, St. Petersburg, Bd. vii.; also abstract in *Centralbl. f. allg. Path. u. path. Anat.*, Jena, 1899, Bd. x. S. 589.

No. 15.—D'Allocco's case, "Sulla Malattia di Kahler," at the Tenth International Medical Congress, Rome, October, 1899, *Arch. ital. d. med. interna*, 1900, tome iii. fasc. 1 and 2; referred to also by U. Flora in his article, "Sulla Malattia di Kahler," *Riv. crit. di clin. med.*, Florence, 1900, Anno i. Nos. 46 and 47.

No. 16.—The case of Lichtheim and Askanazy (S. Askanazy, "Ueber die Diagnostische Bedeutung der Ausscheidung des Bence-Jones'schen Körpers durch den Harne," *Deutsches Arch. f. klin. Med.*, Leipzig, 1900, Bd. lxviii. S. 34).

No. 17.—Latzko and Sternberg's case (M. Sternberg, "Vegetationsstorungen und Systemerkrankungen der Knochen," Nothnagel's *Spec. Path. u. Therapie*, Wien, 1899, Bd. vii. Heft ii. S. 57).

No. 18.—Barr's case, "Case of Myelopathic Albumosuria," *Liverpool Med.-Chir. Journ.*, March 1901, vol. xxi. p. 23.

No. 19.—The case of a French physician (T. R. Bradshaw, "On the Evolution of Myelopathic Albumosuria," *Brit. Med. Journ.*, London, 1901, vol. ii. p. 75. Obituary notice on Dr. P. F. Colrat, *ibid.*, London, 1901, vol. ii. p. 654).

No. 20.—The case of Iglehart, Hamburger, and Simon (L. P. Hamburger, "Two Examples of Bence-Jones Albumosuria associated with Multiple Myeloma," *Johns Hopkins Hosp. Bull.*, Baltimore, February 1901, vol. xii. p. 38. C. E. Simon, "Observations on the Nature of the Bence-Jones Albumin," *Am. Journ. Med. Sc.*, Phila., June 1902, vol. cxxiii. p. 939).

No. 21.—The case of Osler, Hamburger, and MacCallum (Hamburger, *loc. cit.* W. G. MacCallum, "A Case of Multiple Myeloma," *Journ. Exper. Med.*, Baltimore, 1901, vol. vi. p. 53).

No. 22.—Kalischer's case, "Ein Fall von Ausscheidung des Bence-Jones'schen Eiweisskörper," *Deutsche med. Wchnschr.*, Leipzig, 1901, No. 4, Bd. xxvii. S. 54.

No. 23.—Rostoski's case, "Albumosurie und Peptonurie," at the meeting of the Phys. Med. Ges. zu Würzburg, June 13, 1901, reported in the *Sitzungs-*

Berichte, 1901, Nos. 2 and 3, Ss. 31, 33; abstract in *München. med. Wchnschr.*, July 2, 1901, Bd. xlviii. S. 1115.

No. 24.—The case of Jochmann and Schumm, "Typische Albumosurie bei echter Osteomalacie," *München. med. Wchnschr.*, 1901, Bd. xlviii. S. 1340; and "Zur Kenntniss des Myeloms und der sogenannten Kahler'schen Krankheit," *Ztschr. f. klin. Med.*, Berlin, 1902, Bd. xlvi. S. 445.

No. 25.—Donetti's case, "Sulla Malattia di Kahler," *Riv. crit. di clin. med.*, Florence, 1901, No. 46, Anno ii. p. 789.

No. 26.—The case of Hijmans van den Bergh of Rotterdam (A. Grutterink and C. J. de Graaff, "Ueber die Darstellung einer Krystallinischen Harnalbumose," *Ztschr. f. physiol. Chem.*, Strassburg, 1902, Bd. xxxiv. S. 393. A. A. Hijmans van den Bergh, "Albumosurie," reprint from "Herinnerungs-Bundel Prof. Rosenstein," 1902).

No. 27.—Conti's case, "Albumosuria e Neoplasie Sistematiche delle Ossa," *Clin. med. ital.*, Milan, 1902, Anno xli. pp. 211–247.

No. 28.—The present case.

Uncertain Cases, and Cases in which the Reactions of the Proteid in the Urine were not quite Characteristic.

No. 29.—Dr. Sidney Martin (discussion on Dr. Bradshaw's paper, *Proceedings of the Royal Medical and Chirurgical Society*, 1898, Ser. 3, vol. x. p. 120) referred to the case of a woman under the care of Dr. H. R. Spencer, at University College Hospital, for an ovarian tumour, which was removed. The urine, sometimes milky from precipitation of the proteid, was examined by Dr. Sidney Martin, who states that it contained "the same body or bodies" as those referred to by Dr. Bradshaw in his case. The subsequent history of the case is not given.

No. 30.—Dr. R. Hutchison ("Discussion on the Proteids in Urine," *Trans. Path. Soc. London*, 1900, vol. li. p. 146) referred to a man who died in the London Hospital with multiple tumours of bones (extremities, ribs, and vertebræ). A flocculent precipitate separated out from the urine at 58° C., but did not redissolve on boiling. In this respect, and in its behaviour to nitric acid, the substance present in the urine had not quite the characteristic reactions of Bence-Jones proteid. The case should certainly, however, be mentioned here. Dr. Hutchison informs me that the patient was 38 years old, and died within a week of admission. The upper end of one humerus, preserved in the London Hospital Museum, is much enlarged by a very vascular growth. Sections from one of the growths show it to consist chiefly of rather large, rounded, or polygonal cells, with a good deal of protoplasm around a medium-sized nucleus. The protoplasm of many of the cells, Dr. Hutchison tells me, contained granules, possibly of the same nature as those in the tumour-cells of my case, J. T.

No. 31.—Dr. Lee Dickinson (discussion on the "Proteids in Urine," *Trans. Path. Soc. London*, 1900, vol. li. p. 170) mentioned a case of leucocythæmia in the practice of Mr. Edgecombe Venning, in which Bence-Jones proteid—or, at all events, a proteid coagulating like Bence-Jones proteid at a relatively low temperature—occurred in the urine, and in which no other disease but leucocythæmia could be found.

Additional Cases.[1]

Nos. 32 to 34.—Cases of J. M. Anders and L. N. Boston, of Philadelphia ("Bence-Jones Albumosuria," *Lancet*, London, January 10, 1903, p. 93).

[1] Collected after the preceding list had been drawn up.

No. 35.—J. A. Milroy ("A Contribution to our Knowledge of a Rare Form of Albumose occurring in the Urine," *Journ. Path. and Bacteriol.*, Edin. and London, 1901, vol. vii. p. 95) gives the case of a man, an in-patient at the Manchester Infirmary twice during the year 1898, but whose subsequent history is not known. Dr. Dreschfeld's notes point to there being new growths in the ribs and vertebræ. A hard, painless growth was observed on one of the lower ribs on the right side. Milroy's paper discusses the nature and reactions of the Bence-Jones body in the urine.

No. 36.—Sir Lauder Brunton informs me that Mr. David Young of Rome had a case of Bence-Jones albumosuria in which, on precipitating this proteid in the urine with alcohol, the precipitate seemed to equal the height of one-third of the whole mixture.

No. 37.—A doubtful case was described as an instance of osteomalacia by O. Langendorff and J. Mommsen (*Virchow's Archiv*, 1877, Bd. lxix. S. 452–487). The urine was supposed to contain a small amount of Bence-Jones proteid.

No. 38.—P. Vignard and L. Gallavardin (*Rev. de chir.*, Paris, 1903, tome xxvii. No. 1, p. 91) give the case of a man, æt. 56, who died with multiple myeloma, but whose urine was not specially tested for Bence-Jones proteid.

No. 39.—Dubost (quoted by Vignard and Gallavardin, *loc. cit.*) records the case of a man, æt. 46, said to have albumosuria, who died at Lille, in 1896, with multiple tumours of the ribs, sternum, and vertebræ. His urine was not specially examined for Bence-Jones proteid, but was said to contain 3·5 per mille albumin.

Supposed Cases which have been Incorrectly Included in Summaries of Bence-Jones Albumosuria Cases.

A case described by Byrom Bramwell and Nöel Paton ("On a Crystalline Globulin Occurring in Human Urine," *Rep. Lab. Roy. Coll. Phys.*, Edinburgh, 1892, vol. iv. p. 47) was at one time regarded by Huppert ("Ueber einen Fall von Albumosurie," Hoppe-Seyler's *Ztschr. f. physiol. Chem.*, Strassburg, 1897, Bd. xxiii. S. 500) as an instance. But after himself examining the proteid from the urine in question, he altered his mind ("Ueber den Nöel-Paton's chen Eiweisskorper," *Centralbl. f. d. med. Wissensch.*, Berlin, July 9, 1898, p. 481), and regarded the substance as a globulin. The case is remarkable for the spontaneous precipitation of the proteid in crystalline form on allowing the urine to stand for a longer or shorter period, sometimes a day or two, sometimes weeks or months.

Simon (*Am. Journ. Med. Sc.*, Phila., 1902, vol. cxxiii. p. 954) wrongly cites a case reported by Karl Ewald ("Ein Chirurgisch Interessanter Fall von Myelom," *Wien. klin. Wchnschr.*, 1897, Bd. x. S. 169). The patient was a man, æt. 62. The diagnosis of myeloma was made during life, owing to the examination of part of a growth removed from the right clavicle in April 1894. Death occurred in May of the same year. No necropsy is recorded, and no mention is made of Bence-Jones proteid in the urine. The case, therefore, cannot be accepted as an example of multiple myeloma with Bence-Jones albumosuria, although Jochmann and Schumm (*Ztschr. f. klin. med.*, Berlin, 1902, Bd. xlvi. S. 467), as well as Simon, have referred to it as such.

A supposed case of Dr. Vladimir de Holstein (*Semaine méd.*, Paris, 1898, tome xviii. p. 206, and 1899, p. 83) is likewise referred to by Simon (*loc. cit.*, p. 955), who states that the diagnosis of "multiple myelomatosis" was made during life, owing to the state of the urine, and that the diagnosis was confirmed by a subsequent necropsy. However, on looking up Simon's references, I found a notice of Bradshaw's case, and a short résumé of the subject by Dr. V. de Holstein, but no new case.

In their review of the subject, Dr. Anders and Dr. Boston[1] speak of

[1] *Loc. cit.*

symptoms having been present in a certain percentage of the cases, but it is not clear which these authors have admitted as genuine cases of Bence-Jones albumosuria. They allude to thirty cases which they have collected from the literature, but amongst them they seem to have included several in which there is no evidence that any albumosuria was present. The case of Professor von Jaksch, to which they refer, was shown at the Society of German Physicians, in Prague, on December 2, 1892. The patient was a woman with typical symptoms of Graves' disease, and with a swelling of the lower extremities which von Jaksch thought might be of myxœdematous nature; but no albumosuria was reported.[1] They quote K. Ewald's case of myeloma already alluded to. They have apparently likewise included H. F. Vickery's case[2] of "pseudoleukæmia" in a patient, æt. 19, whose urine contained the "slightest possible trace of albumin," but nothing of the nature of the Bence-Jones body. Nor was any kind of albumosuria reported in either of the patients of J. H. Musser,[3] to whom they refer as having published a case.

In conclusion, I must express my thanks to those who have so kindly helped me in this account, only a small part of which I can fairly call my own. Besides Dr. R. Hutchison and Dr. J. J. R. Macleod, I have already mentioned a number of those to whom I am indebted for assistance: Professor R. Muir, of Glasgow, for his report on the tumour tissue and for other information; Dr. J. M. H. MacLeod and Dr. Gustav Mann, in regard to the examination of some of the tumour cells; Dr. F. E. Batten, for examination of the nervous tissues; and Dr. J. H. Drysdale, for examination of the blood. Mr. S. G. Shattock has helped me very much in the pathological examination of the skeleton and viscera, and Dr. A. E. Garrod in the examination of the urine. I must likewise thank Dr. Dengler, the house physician during the time that the patient was in the hospital, for the trouble he has taken in connection with the case; and my colleague, Dr. J. P. zum Busch, for kindly allowing me to use the photograph of the spinal arthropathy patient for comparison. To Dr. T. R. Bradshaw, of Liverpool, I am indebted for more than his published works on the subject; he took the trouble to come to the German Hospital specially to examine the patient, and owing to his previous experience, he was able to give valuable confirmation to the diagnosis. Through his kindness, moreover, I had previously become acquainted with some of the reactions of the Bence-Jones proteid in urine, for owing to some correspondence in regard to my previous case of multiple myeloma, he sent me a bottle of characteristic urine from the patient he then had under observation (June, 1898, Case No. 10 in the Summary).

[1] See report of the case in *Prag. med. Wchnschr.*, 1892, Bd. xvii. p. 602.

[2] "Pseudoleukæmia with Chronic Relapsing Fever," *Internat. Clinics*, Ser. 12, 1902, vol. ii. p. 89.

[3] "Note on the Fever of Hodgkin's Disease," *Am. Med.*, Phila., January 4, 1903, vol. v. p. 13. In this paper Musser describes two cases, one of which he regards as an example of Hodgkin's disease with tuberculosis, the other as "so-called Hodgkin's disease, in which the clinical course was that of tuberculosis," and in which tubercle bacilli were present in the sputum. In neither of these cases was any albumosuria recorded.