upwards until resistance is first felt. If the patient then breathes in and out freely the moving edge of the organ is rarely missed. Percussion is also most helpful; I prefer to use it in the mid-line and of moderate intensity; normally, in these circumstances, the abdomen is resonant to the midriff, for the thin margin of the liver, where it crosses the intercostal angle, fails materially to modify the note, unless the liver edge lies low. Using these methods, early congestion of the liver is generally detectable without difficulty, unless the abdominal wall is unduly thick or tense.

The signs in the veins and in the liver I have emphasized for a chief reason—namely, because they are displayed in early stages of congestion. When the full and classical signs of failure are present, it requires neither close observation nor much discrimination to know it. The diagnosis of early congestion is more difficult, and in the long run it is much more important. It can be accomplished by careful study of the veins and of the liver, and by these means only. Experience teaches that to rely on a single sign is precarious. Compare this sign and that, and confident recognition of the patient's state grows as these signs fall together to form a harmonious picture. Thus, on finding unquestionable evidence of engorged veins in neck, or neck and arms, we look at once at the liver; if we find equally unquestionable evidence that this organ is normal, we know that we are dealing with a local obstruction of the veins. Incidentally, in this connexion observe that veins so obstructed cannot be induced to pulsate. Suppose, however, that in cardiac failure the evidence derived from the veins is indistinct, that there is some doubt whether their pressure exceeds the normal or does not—and this doubt will come to the most or the least experienced observer according to the type of patient under examination—then distinct though slight enlargement of the liver becomes a most important evidence. Generally speaking, enlargement of the liver in its several degrees goes hand-in-hand with engorgement of the veins. In general, the liver does not enlarge before the rise in pressure in the veins can be detected, neither does a distinct venous engorgement manifest itself without the liver edge descending appreciably. There may be cases of difficulty where, owing to fascial obstruction of the upper veins, or enlargement of the liver from causes other than congestion, or failure of the liver to enlarge in congestion owing to cirrhosis, a discord appears. There is also the case in which engorgement of the liver has been present for a very long time; in such, even if the signs of increased pressure in the veins greatly decline, the size of the liver may not decrease much or at least proportionately. But in most instances harmony is found and brings an element of certainty in estimating the degree of failure, and this is so even in regard to early diagnosis. To correlate, and to see accord, in estimating signs is of the utmost consequence, and in this connexion I would emphasize another and most important correlation. *Patients who suffer from general congestion of the venous system are without exception breathless, either at complete rest or upon very slight exertion.* If, therefore, a subject is thought on examination to manifest the early signs of venous stasis, and yet it is clear that breathlessness is not experienced even with quiet or moderate exercise, the opinion first formed must be revised; for it is incorrect. Moreover, there is a perfectly clear relation, constant within narrow limits, between the degree of breathlessness and the pressure in the veins; the relation is so clear that *if it is established that a patient has no congestion of the venous system and is yet breathless in bed, then that breathlessness is not primarily cardiac in origin.* The proper use of this knowledge will save a very large number of serious diagnostic blunders; all that is required is that the point of venous collapse should be proved to occur in any cervical vein at or below the level of the manubrium.

In conclusion, I would repeat that an understanding of cardiac failure of the congestive type is obtainable only by those who truly appreciate the manner in which the symptoms on the one hand and the signs on the other become linked together; the subjective and the objective manifestations are part and parcel of one process, and are dependent on the same fundamental causes, namely, loss of cardiac reserve.

Those who desire efficiently to manage chronic cardiac cases should observe and consider very carefully how little is really gained, and how seldom there is any gain, by repeated auscultation of the heart sounds. Signs so obtained rarely change, they are not signs that indicate improvement or deterioration; but the symptoms and signs upon which emphasis has here been laid do change frequently in one or two directions. They form the chief indications of the course the patient is pursuing and will pursue, for they tell how the blood is circulating in the body generally under various conditions and speak of the capacity of the heart to do work. Those in charge of cardiac patients will do well to acquaint themselves fully with the very definite and sensitive symptoms and the clear signs of early failure here discussed, and to familiarize themselves with the venous manifestations as these occur both in disease and in health.

To understand the phenomena one by one as they are written down and explained is not difficult; to think that such understanding can be brought at once into full play in practical work is to underestimate the situation and to fail in the application; a full grasp and working knowledge can be attained only by diligent observation and thought in which the abnormal is accurately weighed against and considered with the normal.

MYELOMATOSIS, OR BENCE-JONES PROTEINURIA.

BY

A. MACBETH ELLIOT, M.D.

IN November, 1845, Dr. Watson sent a specimen of urine to Bence-Jones, with the question "What is it?" written on a tag of paper. Within a few hours Bence-Jones received a second specimen of urine, this time from Dr. MacIntyre. Both specimens were from the same patient, a man who had been under Watson's care since the previous May. MacIntyre had been called in as consultant.

The man, a well-to-do grocer aged 47, had been ailing for over a year. When first seen by MacIntyre he was thin, emaciated, sallow, pale; his expression was that of suffering, though when not in pain he was cheerful. Pressure along the spine produced little discomfort, but if the pelvis was pressed he complained of severe pain. The arms and legs could be moved freely without any discomfort. Bence-Jones saw the man alive once only, but he received many samples of his urine. The man died on January 2nd, 1846.

In 1847 Bence-Jones read a paper before the Royal Society. After repeated tests and much deep thought, he had arrived at the following conclusions concerning the peculiar deposit in the patient's urine: (1) that the precipitate was an oxide of albumin, and he was satisfied that it was the hydrated deutoxide; (2) that the peculiar characteristic of this hydrated deutoxide was its solubility in boiling water, the precipitate thrown down with nitric acid disappearing on boiling to reappear on cooling. In 1850 MacIntyre published his clinical notes on the case. In the *Dublin Journal* of 1846 Dalrymple had given a full pathological report of the case under the title of "mollities ossium."

I have been unable to trace any further report of a similar nature till the year 1889, when Kahler pointed out the difference between this condition and osteomalacia. Bradshaw, in 1897, described a case, and reported further on it in 1906. Moffat wrote fully on this disease in 1905, and since then there have been various cases reported.

Martin Solon, in his *Traitement d'albuminurie* (Paris, 1838), notes that in one of his cases he came across the peculiar fact that when the patient's urine was treated by nitric acid or heat there was a precipitate which disappeared on boiling; he should therefore be credited with having been the first to draw attention to this peculiar urinary deposit, since apparently it was the same as that found by Watson and MacIntyre.

In October of 1925 a woman was brought up from the country to see me; I was told that it was a case of acute

rheumatoid arthritis of some two years' standing. The following is the history previous to October and subsequently.

The patient was aged 42; both her father and mother were alive and healthy. She had three sisters living, all healthy. She had been married for eighteen years, and had three boys, aged 7, 10, and 15, in perfect health. She had a miscarriage three months after marriage, and another in 1922. As a child she fell and hurt her head, and in 1922 was thrown off her bicycle and injured her knees. She has had no other illness whatever, and was always active in habits. Her periods, which began at 16, were profuse, lasting up to ten days. She was never constipated, and had always been pale.

In 1923, on getting out of bed, her back suddenly "locked," the slightest movement causing agony; she was treated for lumbago for six weeks. As there was no improvement she entered a nursing home, where massage, ionization, radiant heat, and x rays were all tried, with slight benefit for a time. She then returned home, and carried on as well as she could. In 1924 she strained her back when lifting heavy boxes, and the pains became worse.

General Appearance.—Well covered, flabby; intense pallor. While under examination patches of erythema appeared at the root of the neck, spreading up over the left side of the face; also on legs and abdomen. Double dentures. Heart sounds normal, area of dullness increased to right. Blood pressure 160/90. Lungs, a few scattered rales. Liver and spleen not palpable and not enlarged to percussion. No enlarged lymphatic glands found. Abdominal walls flaccid, no glands felt, no tenderness. Knee-jerks slightly increased, especially the left; no tremors, no extensor reflexes; no tenderness of tibiae, and no oedema.

All joint movements were free and painless, and there was no evidence of creaking. She complained of pain in the small of her back, radiating to the left shoulder; during the few previous weeks the pain had shot down both thighs. She never had pain in her arms or head. Turning of the body was obviously painful. She first pushed her body up by fixing her elbows, and turned the body slowly, keeping her spine rigid. The tenth, eleventh, and twelfth dorsal vertebrae seemed fixed. There was no tenderness along the spinal column even after strong pressure; no tenderness along the ribs, but a considerable degree along the iliac crests. There was marked hyperaesthesia to gentle stroking with cotton-wool over the right dorsal and lumbar regions, but not to firm pressure.

On first seeing her, three things struck one: her intense pallor, her fixed expression, and her peculiar gait. With joints fixed she advanced by swinging her body first to the right and then to the left, using the hip-joints alternately as pivots. She asked that she should not be assisted in any way, as she had learned how to move with the least pain and discomfort. There was marked pulsation in the left side of the neck. Her expression was one of constant watchfulness, full of such anxiety as is seen in the early stages of tetanus. Her mind was perfectly clear.

A provisional diagnosis of spondylitis deformans was made, and she was advised to enter a nursing home for further examination.

A specimen of urine showed a faint trace of albumin, not clearing up on the addition of acetic acid; there were no casts, blood, or sugar. A few days later Dr. Herbert Lucey sent me the following report on her blood and urine.

Blood.—Haemoglobin 54 per cent.; red cells, 2,500,000 per c.mm.; colour index, 1.08; white cells, 9,375 per c.mm. Differential count: polymorphonuclears 65 per cent., large mononuclears 2 per cent., lymphocytes 31 per cent., eosinophils 2 per cent. No abnormal red cells seen. Wassermann reaction negative. Tubercle complement fixation test negative. Clotted blood showed hydraemia, marked excess of plasma.

Urine.—Clear; albumin present, estimated at 0.6 per 1,000; no sugar. Centrifuged deposit contained no pus, blood, or casts.

Sir Thomas Horder saw her with me, and suggested that it was a case of Bence-Jones albumosis. Dr. Stanley Melville took x-ray films, and wrote: "I wonder if it may not be a condition of myelomatosis, in which case one ought to find Bence-Jones protein in the urine. The only thing against this is that there are not the multiple fractures that are usually associated."

I still inclined to spondylitis, with considerable endocrine disorganization. During the past few months the patient had noted that she was some two inches shorter in stature.

A further letter from Dr. Stanley Melville put spondylitis out of court. He wrote: "The x-ray picture is unlike one of spondylitis deformans; the latter is in the nature of a sclerosis, whereas the present is an osteoporosis with loss of bone tissue. I am still of opinion that the condition is one of disease of the bone marrow."

It was obvious that no improvement was taking place; the pains became worse, and she was less inclined to try any movement. Further examinations on November 5th resulted as follows.

Blood.—Haemoglobin, 0.45 per cent.; red cells, 2,120,000 per c.mm.; colour index, 1.07; white cells, 6,000. No abnormal red cells were present.

Urine.—Protein: heat shows fair cloud; the proteins present are albumin, globulin, and proteose. Bence-Jones reaction is negative. An occasional hyalo-granular cast in the deposit. Range of function as gauged by urea concentration and specific gravity (Calvert's modification of MacLean's urea concentration test): Maximum concentration of urea 2.4 per cent., minimum 0.7 per cent.; maximum specific gravity 1018, minimum 1006. The maximum concentration is fair and the range of function good. The kidneys are working efficiently, though there may be some kidney damage, as shown by protein present and occasional casts.

Towards the end of the month her condition grew gradually worse. The bowels became irregular, she had a prolonged and very profuse period, and bronchial catarrh supervened.

On December 4th the blood picture was as follows; haemoglobin 34 per cent.; red blood corpuscles 1,670,000 per c.mm.; colour index 1; white blood corpuscles 6,875 per c.mm. Slight irregularity in size of the red cells was noticed.

On December 22nd a blood count showed: haemoglobin 34 per cent.; red cells 1,330,000 per c.mm.; colour index 1.1; white blood corpuscles 10,000 per c.mm. Marked anisocytosis was present.

Examination of the urine on the same day resulted as follows: Total protein greatly increased, including albumin, globulin, and proteose. No evidence of Bence-Jones reaction. Numerous granular casts and leucocytes present.

In January she developed a broncho-pneumonia, which ran for over three weeks, leaving her with a harassing cough, but even this disappeared towards the end of the month. Early in February the kidneys ceased to function, the urine became scanty, and she died.

Many examinations of the urine had been made during the previous months; occasionally there was a Bence-Jones reaction. During her November, December, and January periods she had very severe menorrhagia.

Dr. Lucey's further report on the urine is as follows:

"A coagulum certainly appeared at a low temperature (58° C.), but did not apparently dissolve on further heating. When the urine was diluted twenty times it did not form a ring with strong hydrochloric acid, which Bence-Jones proteose is said to do—a reaction known as Bradshaw's. The following procedure was then carried out: The urine was heated in the water-bath at 58° C. for half an hour, and a dense coagulum ('A') formed at this temperature, and was allowed to settle. The supernatant fluid was then pipetted off and filtered. The clear filtrate was again heated at 72° C. A second dense coagulum ('B') due to albumin appeared. The temperature was raised to boiling point, and this coagulum was removed by filtration. Some of the first coagulum ('A') was then added to the final filtrate and heated. It dissolved, but did not reappear on cooling. You will see that the urine did not give a complete Bence-Jones reaction. I have little doubt, though, that this peculiar proteose was present as the coagulum that appeared at 58° C., and that the tests for it were affected by the salt content and albumin present."

Permission was given to hold a partial necropsy. This was done by Drs. H. J. B. Fry and Herbert Lucey.

Dr. Lucey's Report.

"With the exception of a thin eggshell covering of bone, through which the finger could be easily pushed, the bony structure of the bodies of the lower dorsal and all the lumbar vertebrae was replaced by a soft dark red growth, which reached down to but did not infiltrate the dura mater. The intervertebral discs were intact. The growth also involved both ilia, which were much thinned and very fragile, and secondary deposits were found in the sternum and some of the ribs. No secondary deposits were found in any of the viscera. Microscopical examination of the growth showed that it consisted almost entirely of plasma cells, with practically no stroma. Here and there a larger type of cell, probably the megalokaryocyte, could be seen, but there were no multinucleated giant cells such as are found in a myeloma of a limb bone. The condition was one of myelomatosis. The kidneys showed marked degenerative changes of their tubular epithelium."

Dr. Fry's Report.

"The necropsy showed a marked myelomatosis affecting the sternum, the spinal column, and the pelvis. As far as one could tell the long bones were not affected. The spine from the lower thoracic region to the sacrum showed a sort of fenestrated condition of the bodies of the vertebrae, so extensive was the infiltration. The iliac bones also showed widespread deposits. There was a tiny hypernephroma in the cortex of the left kidney. Apart from wasting, the abdominal viscera were quite healthy, and no growths were present. The lungs and heart were also free from disease. Histologically the growth was a myeloma of the plasma cell type. The hypernephroma of the left kidney was an isolated condition, and not related to the general disease. The Bence-Jones albumosuria which was found by Dr. Lucey was a part of the general myelomatosis."

Here is the case of a woman apparently in perfect health. On rising one morning she is gripped by a sudden intense

pain across the back. Lumbago was the obvious diagnosis; but after six weeks, though easier, the pain was still there, and no line of treatment gave any permanent relief. The weeks became months, and the first year passed into the second. The final months may have been interesting—clinically; they were painful to watch, and emphasized our hopelessness to help. A noteworthy feature was that never once did she realize that she would not recover; she was continually making preparations for going home.

An *x*-ray film taken within four months of the onset gave no evidence of any bone alteration; true, it was not a very good film. There was no fracture of any of her bones; but in this disease the long bones are not usually invaded. She had marked uterine fibroids, which accounted for the severe menorrhagia throughout life. But this cannot be taken as a predisposing cause. What was the cause of the initial lumbar pain? Was it a coincidence—a true attack of lumbago?

In comparing the notes of this case with those taken by MacIntyre in 1845–46 the similarity of the symptoms between the two is very marked. Sex is the chief difference. Myelomatosis is said to occur more frequently in men than in women.

Bence-Jones protein is found in other conditions, but only in a few; its appearance in any urine will naturally call attention to one of them. The fact that it precipitates at between 40° and 58° C., and disappears on boiling, may escape general observation unless a careful watch is kept for it. Many urines with this unusual peculiarity may have been examined and nothing particular noted. The source of this peculiar protein is still a matter of conjecture. Ottenberg, Giesy and Rosenbloom maintain that it is an osseo-albumoid.

THE TUBERCULIN TREATMENT OF ASTHMA.

BY

JAMES MAXWELL, M.D., M.R.C.P.,

ASSISTANT PHYSICIAN, ROYAL CHEST HOSPITAL, LONDON; CHIEF ASSISTANT TO A MEDICAL UNIT, ST. BARTHOLOMEW'S HOSPITAL.

THE multiplicity of methods advocated by various authorities for the treatment of asthma is an eloquent testimony to the complexity of the problem. A method which may give complete success in some cases may be quite valueless in many others not obviously different in any essential particular, and hence it is impossible to write of a "cure" which shall be applicable with certainty even to a majority of sufferers from this complaint.

We are therefore reduced to the employment of many different methods, empirically selected, and of which in most instances the mode of action is imperfectly, if at all, understood. Of these methods, one in particular, the subcutaneous injection of increasing doses of old tuberculin, has been under critical trial in the out-patient department of the Royal Chest Hospital for a period of two years, with results which appear to be worthy of record.

The method was introduced by Professor Storm van Leeuwen as a result of his observation that a considerable number of asthmatic patients were sensitive to tuberculin as shown by the cutaneous test. There was no suggestion that the asthmatic state was the result of sensitization to the protein of the tubercle bacillus, and the beneficial results of tuberculin therapy were ascribed to a non-specific desensitization. In a paper published over a year ago, T. M. Ling[1] reported good results following upon the use of this method in a series of twenty-four children. The initial dose was 0.1 c.cm. of a 1 in 1,000,000 dilution, but the maximum dose was not stated. The results showed two "cures" and fifteen cases improved, and Ling was of opinion that the method was of definite value in the treatment of asthma.

A series of nine cases was also reported by Simpson and Stone[2] a year ago. They found that in four of these cases the patients derived considerable benefit from this method of treatment, and they outlined a simple scheme of dosage. It is noteworthy also that in none of their cases did they obtain a positive skin reaction, a finding which makes the rationale of the treatment a little difficult to understand.

The cases about to be described in the present series presented themselves for treatment at the Royal Chest Hospital during 1928. Thus all have been under observation for more than one year, and several for nearly double this period.

Difficulty was at first experienced in the selection of cases, for it is notorious that some forms of asthma will derive benefit from almost any form of treatment, whereas others appear to need one particular method to bring about a similar result. The obvious explanation of this discrepancy is that many widely different factors can produce asthmatic attacks in a suitably disposed individual, and that not all cases prove responsive to the same exciting stimulus.

In many cases there would appear to be some exciting factor in the home or place of occupation. It is necessary, therefore, in order to gauge the effect of one particular line of treatment, that the patient's routine life should not be disturbed. In other cases a predominant part is played by a septic focus, situated usually in the throat or nasopharynx. It is obviously an elementary principle that such foci should be eradicated in all cases if a permanently successful result is to be obtained, and this procedure was adopted as a routine. Only such cases as did not derive appreciable benefit from this treatment were considered suitable for tuberculin. In addition, routine protein sensitivity tests were performed, with, on the whole, disappointing results; a few positive reactions were obtained, chiefly to the epidermal group, and attempts were made when possible to relieve the condition by avoiding contact with the offending substance, with, as a rule, but scant success. In these cases, also, the failures were passed on and regarded as suitable for tuberculin. No attempt was made at specific desensitization.

The patients were therefore carefully selected, and consisted only of the more severe cases in which routine methods had failed, or were unlikely to afford relief. The total number accepted for tuberculin treatment during the year was thirty-six, and it is the object of this communication to describe the results of treatment in these cases. Of these thirty-six patients, twenty were males and sixteen females; the ages varied from 5 to 49 years, and twenty-one were under 14 years of age when treatment commenced.

A preliminary intradermal test was performed in every instance, after making every effort to exclude the presence of a tuberculous lesion anywhere in the body. The routine test consists in the intradermal injection of 0.1 c.cm. of a 1 in 1,000 dilution of old tuberculin, freshly prepared, in normal saline. The reaction is at its maximum in forty-eight hours, but readings had to be taken on the subsequent out-patient afternoon, so that the interval which actually elapsed in this particular series of cases before the results were read was three days. It was considered that the delay in reading the results made only a negligible difference to the recorded size of the reactions, and they were accordingly noted in the usual manner. The essential feature of a positive intradermal tuberculin test is an area of swelling, erythema being of little significance. The results were as follows:

Negative reactions	24
Positive reactions	8
Strongly positive reactions	4
Total	36

There was a considerable preponderance of negative reactions, a result not in accord with the original observations of van Leeuwen, but nevertheless corresponding closely with the result obtained by me in a separate series of 103 apparently non-tuberculous subjects, of whom 74 were found to yield negative and 29 positive reactions. The objects of this routine preliminary test were, first, to investigate the basis on which the test was originally founded, and, secondly, to furnish an indication as to the appropriate strength of the initial subcutaneous dose. As was to be expected, modifications in technique had to be