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**THE
NEUROLOGICAL ASPECTS
OF
MULTIPLE MYELOMATOSIS.**

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INTRODUCTION

It has recently become apparent that multiple myelomatosis is more common than has been hitherto considered. Thus, in 1941 only forty-two deaths from this disease were recorded in England and Wales, whereas in 1951 the figure had increased sevenfold to three hundred and four (Registrar General, 1953). The literature concerning myelomatosis also reflects this change, for in the period from 1850 to 1928 Geschickter and Copeland (1928) found case reports of four hundred and twenty-five patients, but Aegerter and Robbins (1947), when discussing the changing concepts of myelomatosis almost twenty years later, say that the total is now more than a thousand. The increasing incidence is further illustrated, and perhaps more vividly, by the findings of Rosenthal and Vogel (1938) at the Mount Sinai Hospital of New York City. From 1916 to 1935 only three cases were diagnosed, but in a period of two and one-half years (1935-1938) the diagnosis was made on thirteen occasions.

This apparently increased frequency is due not to any change in the disease itself but rather to three extraneous factors. Firstly, there has been great improvement in diagnostic procedures and secondly, more adequate knowledge of the varied clinical appearances is now available. The



third factor concerns the average age of the population, for as this becomes greater more persons enter the age group (the fifties, sixties and seventies) where myelomatosis is most often encountered. (Adams, Alling and Lawrence, 1949).

One of the commonest events in the course of this disease is involvement of the nervous system, for Geschickter and Copeland (1928) in their classical study found that 40 per cent of four hundred and twenty-five patients had been so afflicted. The corresponding figure given by Batts (1939) was 35 per cent, by Fowler and Gordon (1950) 38 per cent and by Snapper, Turner and Moscovitz (1953) 40 per cent. Although it is realised that authors have occasionally varied in their conception of neurological features, these high figures are not altogether unexpected when one considers that the bony structures surrounding the central nervous system, and the bones that lie in close relationship to roots and peripheral nerves, are very frequently attacked in this disease. The occurrence of nervous system complications may of course be even greater than a survey of the literature suggests, for as Sparling, Adams and Parker (1947) have pointed out, the neurological features may have been overlooked or the patient too ill for a detailed examination of the nervous system.

The neurological aspects of multiple myelomatosis would therefore appear to be an important part of the

overall clinical picture, and it is surprising that no comprehensive study of them is available. Several authors have however dealt with a proportion of the problem (Pines and Piragowa, 1928; Denker and Brock, 1934; Davison and Balser, 1937; Scheinker, 1938; Peyrache, 1939; Sloan, Keeton and Limarzi, 1946; Sparling et al., 1947; Khondkarian, 1951). Further, the literature contains several inaccuracies and certain unjustifiable statements, such as that of Snapper (1949, p.235), who says, "no convulsive seizures have been observed, and the optic discs never show evidence of increased intracranial pressure". He was no doubt referring to the report of Sloan et al. (1946), who were dealing with a very small number of cases, but unfortunately this information has reached authoritative textbooks (Fairbanks, 1951).

The object of this Thesis is, therefore, to present a study of the nervous system involvement in multiple myelomatosis, aided by the presentation of twenty-six illustrative cases.

METHOD OF STUDY

Several attempts have been made to classify the neurological complications of myelomatosis. Verebely (1906) suggested the grouping used by Sternberg (1899) when dealing with multiple bone tumours:-

1. Cranial nerve palsies, often transient.
2. Paraplegia dolorosa (Charcot).
3. Various neuralgias.
4. Absence or weakness of reflexes.
5. Pains of various character.

Although this certainly accounts for many of the cases, it is not nearly adequate. Sparling et al. (1947), when considering the effects of lymphomatous diseases upon the nervous system, pointed out four outstanding clinical syndromes and it was thought that they could also be used for multiple myeloma:-

1. Spinal cord compression.
2. Cranial nerve palsies and involvement of the cerebral cortex.
3. Meningeal invasion.
4. Primary cerebral lymphomas.

This, however, is not by any means satisfactory as far as myelomatosis is concerned, for the last two events do not occur in this disease.

Other authors have put forward similar schemes (e.g. Khondkarian, 1951) but one that includes all the possible neurological aspects has not been perfected. The simplest method seems to be the orderly consideration of each anatomical portion of the nervous system, and after an introduction dealing with relevant and recent aspects of the primary disease, this plan will be carried out.

First the brain will be considered, and included here are the cranial nerves and orbit. It is convenient to deal with the latter in relation to the brain because of its close contiguity rather than in the next section which has to do with ophthalmological manifestations. These must be mentioned because they are closely related to the neurological aspects. Involvement of the spinal cord, the cauda equina, other spinal roots and finally the peripheral nerves follow in sequence. Each section is dealt with in a similar manner in that the literature is first reviewed and illustrative cases are given (collected for ease of reference in Appendix I). Next, pathology is discussed and clinical features, treatment and prognosis receive consideration.

These portions deal principally with the direct pressure effects of myeloma tissue upon the nervous system, but in addition there are others which are not dependent upon local compressing lesions. Thus the influence of

"toxins" and primary amyloidosis must be considered, and also various vascular changes. These states are best dealt with separately, and finally alterations in the cerebrospinal fluid (C.S.F.) are grouped together under one heading. Conclusions derived from this study and a summary of the findings conclude the work.

The world's literature on multiple myeloma has been surveyed, as far as possible, and great care has been taken to accept only true examples of the disease. This has, of necessity, been difficult when dealing with cases reported before the clinical and pathological picture of the disease was fully recognised. Only histologically verified cases have been accepted and usually the authority of other authors upon the problem has been sought. If any doubt existed concerning an individual case, it has been rigorously excluded from consideration. As in other subjects, the development of our ideas relating to myelomatosis has at times been retarded by the inaccurate reporting and uncritical acceptance of clinical and pathological data.

MULTIPLE MYELOMATOSIS

It is intended first to review briefly the main features of this disease, so that its effect upon the nervous system can be more readily appreciated.

HISTORY.

The neurological aspects of this mysterious yet fascinating disease figure in its history and a short account of it will be given.

It is of interest to note that multiple myelomatosis has been traced back to the ninth and thirteenth centuries A.D. in pre-Columbian America, by Ritchie and Warren (1932) and Williams, Ritchie and Titterton (1941), respectively. These authors described skeletal lesions which they believed were compatible with multiple myeloma rather than other diseases. Courville (1945, fig.174, p.364) presents what was also probably a case of myelomatosis in an Incan and reproduces a photograph of the skull. The case described and beautifully illustrated by Cruveilhier (1835-42) in 1838 is possibly another example. The cranium was involved in each of these cases but no clinical details are, of course, available except those given by the last-mentioned author, and neurological features are not included. Indefinite as they are, these cases all antedate that reported by Dalrymple

(1846), Bence Jones^{*} (1848) and Macintyre (1850), which is justifiably accepted as the first authentic example of myelomatosis. Rustizky (1873) suggested the name "multiple myeloma" and Kahler (1889) correlated the clinical features with the urinary findings. Both these authors reported cases that had much of neurological interest and which will be mentioned later. Similarly Bozzolo (1898), whose name is sometimes applied to the disease by the Italians, described a patient with spinal cord compression. Meanwhile, the celebrated neuropathologist Ramon y Cajal (1890) had described the plasma cell and Wright (1900) was thus able to link the clinical, pathological and biochemical features into one distinct disease entity, multiple myelomatosis.

PATHOLOGY.

Fortunately, recent advances have simplified our conceptions of the pathological, as well as the clinical aspects of this disease. They will be considered briefly, for they help us to understand more clearly the various forms of nervous system involvement.

^{*} The incorrect form "Bence-Jones" is almost universal; see Hodgkinson, R.G. and Hodgkinson, R. (1952) Henry Bence Jones (1814-1873), in Med. ill. 6:134-138, (March).

It is the consensus of modern opinion that multiple myelomatosis is a neoplastic process arising in many foci in the red bone marrow and that it is a disease of the blood-forming organs rather than a neoplasm of bone itself. The characteristic lesions - plasma cell myelomas - are powerfully osteolytic and occur in flat and long bones, including the skull and vertebrae which are very common sites. Extra-osseous involvement also occurs and, as Hayes, Bennett and Heck (1952) in their review of the subject point out, almost any tissue may be affected; nervous elements, however, are without exception exempt.

The plasma cell is invariably the constituent cell of the myeloma, and thus the names employed for the tumour are "plasma cell myeloma", "plasmacytoma" and "plasmocytoma". Until recently it was thought that other types of bone marrow cells might take part in the creation of these tumours, and in the literature one finds a confusion of terms, depending upon the parent cell suspected. However, by the use of routine bone marrow biopsy Bayrd and Heck (1947) with eighty-three cases and Snapper (1949, p.244) with eighty found only plasma-cell-containing myelomas.

The plasma cell of the myeloma may occasionally be confused with that produced by chronic inflammation, which may be gathered together in granulomatous masses. This is particularly germane to our considerations because the latter occur in the orbit, upper air passages and petrous

bones, and may cause confusion in diagnosis. Clinical and histological differentiation, although of great importance, is however not usually difficult.

CLINICAL FEATURES.

We are now aware that, clinically, myelomatosis is a disease of many guises. The classical and better-known variety with bone pains and fractures, anaemia, loss of weight and Bence Jones proteinuria (Kahler, 1889) is, of course, the commonest and the patient usually survives about two years. At one extreme of the clinical syndrome, however, is a rapidly fatal "plasma cell leukemia" and at the other the "solitary" myeloma. This latter is of particular importance to us, for it figures largely in our dealings with the neurological disturbances of the disease.

The "solitary" lesion may be of bone (Christopherson and Miller, 1950) or extra-osseous tissue (Hellwig, 1943). It is generally conceded that a single myeloma is but a premonitory manifestation of the generalised disease, although several years may separate the two. Thus, if the necessary criteria are observed the term "solitary" could never be employed. These criteria demand that all possible investigations should be carried out to exclude multiple myelomatosis (see below), that the patient must be observed over a long period and that a microscopic examination of the entire skeleton should be made at autopsy. If these had been

fulfilled, many so-called "solitary" cases appearing in the literature would have been rejected. Thus Bayrd and Heck (1947) at the Mayo Clinic, since employing bone marrow biopsy in all cases, have not discovered a true "solitary" myeloma. It is important to note, however, that Christopherson and Miller (1950) have produced strong evidence to suggest that a true single plasma cell myeloma, distinct from myelomatosis, does in fact exist. They cite cases where a single myeloma had been removed and the patient had survived many years with no evidence of myelomatosis.

Special investigations in cases of multiple myeloma reveal a widespread pathological process. X-rays of bones demonstrate osteolytic lesions; there is anaemia and a high erythrocyte sedimentation rate (E.S.R.); the serum proteins are increased in amount with a striking elevation of the globulin fraction; the urine often contains Bence Jones protein and a bone marrow biopsy shows an abnormally high content of plasma cells. All of these findings may be present in a case or perhaps only one or two. Even if only one is found a "solitary" lesion ceases to be single. In certain cases only one lesion may be producing symptoms, and yet when these investigations are carried out the patient is found to be suffering from a widespread disease. An excellent example of this is Case One of the present series, for until additional tests were

carried out the myeloma of the skull base could have been considered to be "solitary".

TREATMENT.

Unfortunately, the treatment of myelomatosis is very unsatisfactory and a cure is not possible. Medical measures, which include urethane, stilbamidine and other histiotoxic drugs, can only be expected to produce symptomatic relief. Urethane, if tolerated by the patient, appears to be the drug of choice at the moment (Harrington and Maloney, 1950; Luttgens and Bayrd, 1951). Radioactive isotopes and A.C.T.H. have been used recently but their results have not been encouraging. Radiation therapy has been employed with some relief of local symptoms, especially pain, and in some instances the results have been strikingly good. The course of the disease, however, is probably uninfluenced by it. Surgery, excluding that at times necessary for biopsy and excluding the cases with spinal compression, is rarely indicated and would only be considered in cases where the lesion was apparently solitary and readily accessible, or the progress of the generalised disease was very slow.

PROGNOSIS.

The patient with the usual type of the disease survives about two years, on an average, but occasionally

cases with generalised lesions may have a much slower course (e.g. Case One). Those that begin with "solitary" myelomas usually pursue a slower course and Gootnick (1945), describing patients with the osseous type of "solitary" lesion, gives an average survival of seven years. The extra-osseous tumours may likewise exist for many years before other features of the disease supervene and prove fatal; the longest survival, quoted by Jaeger (1942) - 25 years - is quite unique and perhaps strengthens the argument of Christopherson and Miller (1950) already mentioned, concerning a genuine solitary myeloma. In the vast majority of cases death is due to generalisation of the disease.

TERMINOLOGY.

There is considerable confusion in the literature of this subject due to the varying terminology employed. It is thus impossible to accept some of the early cases on the merit of their nomenclature alone and, conversely, all the cases described as "myelomas" cannot be accepted as such. Only those cases in which histological examination has revealed findings in keeping with the present-day concepts of the disease have been included in this study.

Throughout this thesis, the term "myeloma" will be applied to the plasma cell myeloma that is a manifestation of the disease, multiple myelomatosis. As the plasma cell is invariably the constituent element, the term "plasma

cell myeloma", "plasmocytoma", "plasmacytoma", "plasmo-sarcoma" and "plasmoma" are redundant and ambiguity could be avoided if they were used only when dealing with the plasma cell granuloma. Similarly the terms erythroblastoma, myelocytoma etc. are no longer valid. In this work the term "plasmacytoma" is reserved for the non-myelomatous tumour produced by chronic inflammation. The expression "solitary myeloma" is used with caution, for there are few, if any, cases in which it can be accurately employed.

INVOLVEMENT OF THE BRAIN.

CRANIAL NERVES, DURA MATER AND ORBIT.

Of all the bones attacked by myelomatosis, the skull is one of the commonest, for it is involved in over 70 per cent of cases (Batts, 1939; Bayrd and Heck, 1947). Yet despite the frequency of skull myelomas, encroachment upon intracranial structures, with the production of symptoms and signs, is quite rare. The incidence of such events is, however, difficult to determine because authors have rarely given separate figures for the various parts of the nervous system. That they are uncommon is evident from the fact that in Bayrd and Heck's (1947) series of eighty-three cases of multiple myelomatosis none had direct brain involvement. An impression of their rarity in neurological practice may be gained from Cushing (1932)* who found that among two thousand intracranial tumours there were four cranial myelomas. Courville (1945, p.362)*, reporting on thirty thousand autopsies (representing one million general hospital admissions), had thirty-six tumours of the skull and six of them proved to be myelomas. These figures,

* The term "myeloma" used by these authors is taken to imply the lesion characteristic of multiple myelomatosis, although one cannot be quite certain of this because of the considerable confusion in terminology that has existed in the past. The term "myeloma" is still used by some when referring to a primary neoplasm of bone.

however, include material examined before a clear conception of myelomatosis had been established, and an unduly low incidence is to be expected. In common with all the statistics concerning this disease, re-evaluation in the light of our present knowledge of its clinical and pathological aspects will be necessary in the future. Despite the many advances in the technical aspects of medicine, there will always be a need for clinico-pathological correlation as rare diseases are recognised more commonly.

CLASSIFICATION OF CASES.

The cases to be considered here are those in which myelomas of the cranial bones extend into the cranial or orbital cavities and also those in which the lesion grows from intracranial or intraorbital structures other than from bone. Because of the close relationship that the orbit bears to the cranial cavity, its involvement will be dealt with here rather than with the other ophthalmological features.

It is possible to classify these various cases clinically, and three groups are readily formed.

Group I. Syndromes of cranial nerve palsies.

One or more myelomas in the base of the skull can produce single or multiple cranial nerve palsies.

Group II. Intracranial tumour syndromes.

The clinical picture is like that of a brain tumour,

and cases can be further subdivided into those in which a cranial myeloma extends intracranially and those where the lesion originates primarily from intracranial structures. Thus there may or may not be involvement of the skull bones.

Group III. Intra-orbital tumour syndromes.

The orbit may be invaded and the clinical picture of an orbital space-occupying lesion produced.

GROUP I. SYNDROMES OF CRANIAL NERVE PALSIES.

The base of the skull as well as the vault may be the site of single or multiple myelomas and the structures most commonly involved thereby are the cranial nerves.

INCIDENCE.

Some idea of the rarity of this type of case can be gained from the fact that among the four hundred and twenty-five cases collected by Geschickter and Copeland (1928) cranial nerve palsies were reported in only nine of them. Their infrequency is further suggested by Epstein and Davidoff (1951) who, when dealing with fifty examples of skull base destruction, as well as making extensive use of the literature, do not mention the myeloma. It could be objected, however, that these authors were dealing with selected surgical material and might therefore be unlikely to see cases of myelomatosis.

That they occur somewhat more commonly however is shown by Snapper and his co-workers (1953, p.34) when

dealing with a series of ninety-seven cases of multiple myeloma. Of these, three had cranial nerve palsies, the incidence thus being about 4 per cent.

It is possible that there are several typical examples of this condition adequately described in the literature but placed under an incorrect diagnosis. Thus Seeligmann (1896) collected several basal neoplasms and there seems little doubt that one or two of them ("round cell sarcoma", "malignant tumour", etc.) may have been plasma cell myelomas.

LITERATURE.

In the literature there are at least thirty-five cases with single or multiple cranial nerve palsies produced by a myeloma of the skull base. Only twenty-four, however, are described in adequate detail including histological verification, and these are collected together in Table I.

Before dealing with this selected group, it will be necessary to mention the eleven cases that have been excluded and four others that in the past have been considered acceptable but which for various reasons cannot be included. This syndrome has not been described in detail before, and no collective survey with critical appraisal of the available cases is to be found.

Firstly, the four dubious and rejected cases (Senator, 1899; Canestro, 1927; Neumann, 1929; Bruch, 1934) will be

TABLE I. GROUP I: 25 CASES WITH CRANIAL NERVE PALSIES PRODUCED BY MYELOMAS OF THE SKULL BASE.

CASE NO.	AUTHOR AND DATE	SEX	AGE	INITIAL FEATURES OF ILLNESS	DURATION OF CRANIAL NERVE PALSIES	TOTAL DURATION OF ILLNESS	CRANIAL NERVES INVOLVED	PRINCIPAL LESION OF SKULL BASE	MULTIPLE OR SINGLE	OUT-COME
1	Stokvis (Kühne, 1883)	M	40	Loss of weight and back pain	1 week	9 months	5, 7	Basal myeloma? (Kahler, 1889)	M	Death (no P.M.)
2	Hammer (1894)	M	47	Joint and back pain	6 months	13 months	6	Middle fossa	M	Death
3	Ritter (1921)	M	57	Pain in limbs Back pain	2 years 9 months +	2 years 10 months +	6	?	M	?
4	Pallestrini (1927)	M	45	Mass in nasal cavity	?	?	2, 5	?	?	Death (no P.M.)
5	Riser & Sorel (1929)	M	61	Headache and facial palsy next day	13 months	13 months	4, 5, 6, 7, 8, 9, 10, 11, 12	Sella) (X-ray Clivus) ray)	M	Death
6	Sabrazès et al. (1931)	M	71	Rheumatic pain and fractures	5 months	8½ years	6, 7, 8	Petrous bone	M	Death (no P.M.)
7	M.G.H. Case Record no. 20031, (1934)	M	39	Trigeminal palsy	14 months	14 + months	3, 4, 5, 6, 7, 8 (R) 6 (L)	Sphenoid bone Petrous bones	M	Death
8	Pollock (1934) Case 2	M	39	Facial palsy	14 months	14 months	7 +	Sphenoid bone Cavernous sinus	M	Death
9	Cappell & Mathers (1935)	F	57	Facial palsy	4 years	4 years	6, 7, 8, 9, 10, 11	Sphenoid bone Petrous bone	?	Death
10	Fowler (1938)	M	61	Loss of weight	?	About 8 months	8	Petrous bone	M	Death
11	Langdon (1939)	F	41	Headache	14 months	16 months	1, 6 (R) 1, 2, 3, 4,	Sella (X-ray)	M	Death
12	Christophe & Divry (1940) Case 1	F	56	Headache	9 weeks	3-4 months	1, 2, 3, 4, 5, 6	Sphenoid bone and orbital fissure	M	Death
13	Christophe & Divry (1940) Case 2	F	42	Amenorrhea Polydipsia	3 years +	9 years	1, 2 (R) 1, 2 (L)	Sphenoid bone Petrous apice	?S	Death

TABLE I cont.

CASE NO.	AUTHOR AND DATE	SEX	AGE	INITIAL FEATURES OF ILLNESS	DURATION OF CRANIAL NERVE PALSIES	TOTAL DURATION OF ILLNESS	CRANIAL NERVES INVOLVED	PRINCIPAL LESION OF SKULL BASE	MULTIPLE OR SINGLE	OUT-COME
14	Godtfredsen (1944)	M	52	Nasal	? 4 months	8 months	6	?	?S	Death from intercurrent disease
15	Gros (1945)	F	67	Deafness	4 years	4 years	5, 6, 8	Petrous apex	?S	Alive
16	Figi, Broders & Havens (1945) Case 6	F	47	Nasal obstruction and deafness	2½ years	2½ years	2, 8	Sella	?S	Alive
17	Welsh (1947) p. 1052	-	-	Sudden blindness	?	?	1, 2, 8	Sella Petrous apices (X-ray)	?	?
18	Sparling et al. (1947) Case 20	M	70	Headache	6 months	11 months	5, 6, 7, 8, 9, 10, 11, 12	Sella Petrous bones	?S	Death
19	Sparling et al. (1947) Case 21	M	66	Weakness and weight loss	?	1 year 11 months	6 (R) 2 (L)	Sphenoid bone	M	Death
20	Smith & Gault (1948) Case 65	M	56	Headache	?	6 months	2, 6	Sella Middle fossa	M	Death
21	Calvet et al. (1950)	M	16	Apathy and fatigue	4 months	6 months	3, 4, 5, 6, 7, 8, 9, 10, 11, 12	?	?S	Death (no P.M.)
22	Lane (1950)	F	46	Pain in left knee	1 month	14 months	10, 12	?	M	Death (no P.M.)
23	Cagnoli & García Novales (1950) Case 3	M	42	Pathological fracture right ulnar	3 months	7 years	3	Sella (X-ray)	M	Alive
24	Delmas-Marsalet et al. (1951)	M	64	Diplopia	1½ years	1½ years	3 (R) 3, 4, 5 (L)	Sella Left petrous apex	M	?
25	Case One	F	61	Diplopia	6 years	6 years	2, 5, 6, 8 (R) 8 (L)	Sella Petrous apices	M	Alive

considered. Considerable discussion has been aroused by the case reported by Senator (1899) and also by Rosin (1897) and Süssmann (1897). Although there were palsies of the last three cranial nerves, Oppenheim could find no lesion of the brain stem to account for them. The author termed them "myasthenic" paralyses and suggested that they were due to anaemia and toxins but, as Antoni (1936) points out, the cranial nerve foramina at the base of the skull were not described. Owing to the dispute concerning this case it has been excluded from this section but will be discussed later (p. 201). Another case to be rejected is that of Canestro (1927), for there is no autopsy report and the disease was not fully verified. The patient had deafness but it is impossible to say whether this was due to nerve involvement or myelomatous infiltration of the petrous temporal bone, or perhaps both as in Fowler's (1938) patient (Case 10 in Table I). (A similar problem is presented by the patients of Kahler (1889), Anders and Boston (1903, Case 1) and Denker and Brock (1934, Case 1) in which deafness or tinnitus occurred.) Neumann (1929) described a case that is suspect and Bruch (1934) reported a very similar one. They both had bilateral temporal bone-destroying tumours and it is possible that the latter at least was an example of eosinophilic granuloma of bone, for it is alike in many respects to Dill's (1948) case where this pathological process was verified.

Undoubted cases of myelomatosis with cranial nerve palsies that have been inadequately described will be dealt with next. Venturi (1901) reported the case of a patient with blindness and a left abducens nerve palsy. The condition of the retina was described by the author as that of "? nevrite retrobulbare", but repeatedly in the literature this case is referred to as an example of central retinal artery thrombosis (see p. 79). As the autopsy report is incomplete and neither cranial nerves nor orbit are described, the case will not be considered further. Owing to multiple cranial nerve palsies Heilmann^{*} considered that his patient was harbouring a pontine tumour, and was thus very like Pollock's (1934) second patient (Case 8 in Table I). At autopsy, a myeloma of the skull base was discovered but a detailed description of the case is not given. Similarly, the case of Meyerding (1925, Case 3) with diplopia and skull myelomas lacks sufficient information. It is likely that this patient had an ocular nerve palsy as occurred, for example, in Hellner's (1938, p.129) case, where a partial third nerve palsy was produced by a sphenoid bone myeloma. Both Wright (1900) and Bloodgood (1906) also reported cases of multiple myeloma with diplopia, but in the former it may have been due to neurosyphilis. They are both excluded. In the eighth patient of Coley (1931) a vocal cord paralysis without a local lesion was discovered, but as no further mention is made of it the case cannot be entertained here.

^{*}(1928)

In their recent review, Snapper et al. (1953) mention a patient with an isolated sixth nerve palsy as well as another with a complete ophthalmoplegia, the result of myelomatous invasion of the sphenoid bone. Their third case had paralyses of nerves seven to twelve on one side, again caused by a large destructive basal myeloma. None of these, however, is described in detail. Likewise, Epstein and Davidoff (1953) figure a typical case but do not supply adequate data. Wright's (1953) case belongs to this group but has been excluded from Table I because of inadequate clinical information and appraisal of the case; there was severe bilateral deafness (cf. Case One) but the presence of cranial nerve palsies was denied.

Finally, mention should be made of five patients in which the divisions of the fifth cranial nerve were affected extracranially. The authors of these cases are Lecène (1919), Pallestrini (1927), Greenfield (1948) and James and Turner (1952): the second case of Anders and Boston (1903) probably had a supra-orbital nerve lesion, although a post mortem was not carried out.

Thus, in a survey of the literature, twenty-four adequately described and histologically verified cases of multiple myeloma with cranial nerve palsies have been discovered, and to these another is added to make a total of twenty-five. (Case One, Appendix I.)

CASE ONE: Female, 61. Four years of diplopia, right visual impairment and bilateral deafness. One year of

nasal obstruction and tingling right face. Involvement of right 2nd, 5th, 6th and 8th cranial nerves and left 8th. Nasopharyngeal mass shown by biopsy to be a plasma cell myeloma. Extensive destruction of skull base with evidence elsewhere of multiple myeloma. Treatment with deep X-rays and urethane, with considerable improvement. Survival 6 years after first symptom.

PATHOLOGY.

It is necessary first of all to consider the relationship of these cases to the disease entity multiple myelomatosis. Then the lesions of the skull base and their origins will be discussed and the actual dysfunction of the cranial nerve considered.

Of the twenty-five cases of myeloma of the skull base with cranial nerve palsies (Table I), fifteen had unequivocal evidence of the generalised disease at some stage. The remainder were either presented as examples of the "solitary" type of myeloma or the information is insufficient to assess them. In the case of the former (Cases 13, 14, 15, 16 and 21 in Table I) however, it is not possible to be certain that they were single because all the necessary criteria had not been satisfied in any of them. It is obviously pointless to discuss this subject further, for in retrospect an accurate evaluation of the individual cases is not possible. Case One is a good example of a patient with symptoms referable only to a single lesion. Without further investigations the basal myeloma could have been considered to be solitary, but adequate investigations revealed the true position and that it was but a part of a widespread disease process.

The lesions of the skull base.

The vault of the skull is a well-recognised and common site for plasma cell myelomas but the base can also be affected. Unfortunately, our knowledge of the latter is limited because the skull base is less commonly X-rayed and is rarely described in autopsy reports. In addition to the twenty-five cases contained in Table I, there are others in the literature where basal myelomas were discovered, but either they were small and therefore silent clinically or the clinical information in the case reports is entirely lacking or inadequate. They are of value to consider now in dealing with the pathology of the myeloma of the skull base, and they are presented in Table II.

In the vault the myelomas may be large and single (Courville, 1948) or small and multiple, but occasionally a combination of these two varieties is brought about. The same events occur in the base. Thus an example of a large, solitary basal myeloma has been seen in Case One and also in that of Cappell and Mathers (1935). The diffuse involvement is represented by Case Three (Appendix I). In the latter there were innumerable lesions of the base (Fig.9) but they were all smaller than 1.0 cm. in diameter and had produced no clinical features. The case presented by Aronsohn (1931) is of this type too, and the lesions were clearly visible after maceration of the skull. Donhauser and de Rouville (1941) also describe diffuse basal involvement in their first case, although clinically this process was silent.

TABLE II. 18 CASES WITH MYELOMAS OF SKULL BASE. SILENT, OR
CLINICAL DATA INADEQUATE

AUTHOR AND DATE	SEX	AGE	LOCATION OF MYELOMA	REMARKS
Winkler (1900)	M	47	Petrous apices, Right orbital roof.	Right pupil constricted (Also ependymoma of 4th ventricle)
Hoffmann (1904)	M	68	Middle fossa, right, extending to orbit. Temporal muscle and sinuses.	C.N.S. not described.
Gluziński & Reichenstein (1906)	M	47	Greater wing of sphenoid.	*
Warstat (1913)	F	48	Petrous temporal bones	Symptomless
Morax (1919)	M	42	Anterior fossa. Lesser wing of sphenoid. Near internal auditory meatus.	Also orbital tumour (see Group III) Other lesions small
Masson & Wolf (1920)	M	62	Middle fossa	*
Weinberg & Schwartz (1920) Case 2	M	60	Clivus	*
Wallgren (1920) Case 8	M	58	Basilar part of occipital bone	A small lesion
Schmidtman (1921)	M	64	Sphenoid	*
Oppikofer (1926) Case 2	M	54	Clivus. Dorsum sellae, sphenoidal sinus and extending to nasopharynx	Had headaches and nasopharyngeal tumour but cranial nerves said to be normal
Kleine (1928)	M	53	Petrous temporal bones.	*
Pines & Pirogova (1928) Case 1	F	42	Petrous bone	C.N.S. normal
Hallermann (1929) Case 3	M	63	Sphenoid	*
Pinsy & Riach (1931) Case 1	F	53	Near sella and extending to foramen magnum, orbital and nasal fossae and upper part of hard palate	*
Case 2	F	54	Infiltration of base of sella	*
Grögler (1932) Case 2	M	45	Lesser wing of sphenoid and extending into middle fossa	*
Donhauser & de Rouville (1944) Case 3	F	62	Floor of sella and left middle fossa	Symptomless
Toušek & Vortel (1947)	F	65	Sphenoid bone, mainly dorsum sellae.	*

* Inadequate clinical data.

Unless the myelomas occur in close proximity to the basal foramina, cranial nerve complications would not be expected to occur.

One of the more detailed accounts of the large single myeloma is given by Wright (1953) and the lesion must have been very similar to that in Case One. The tumour was soft and fleshy with haemorrhagic areas and cystic spaces. It lay extradurally and was eroding all of the body of the sphenoid, including the pituitary fossa (the pituitary itself was, however, intact), as well as the wings and the petrous temporal bones (presumably the apices). Posteriorly, it extended to the foramen magnum. It is of interest to note that despite the destruction in and about the pituitary fossa, features of hypopituitarism are rarely, if ever, produced. Epstein and Davidoff (1951) have also noted this with other invasive tumours in the same region. If its connections with the hypothalamus are undisturbed and its blood supply intact, the gland will presumably continue to function normally despite adjacent bony changes.

Location of the basal myeloma.

As far as the location of the myelomas is concerned, there is a grouping in the middle fossa and in and around the sella turcica. Inspection of Tables I and II reveals that the sphenoid and petrous temporal bones are the most frequently involved and figure 1 gives a diagrammatic representation of the distribution of basal myelomas.

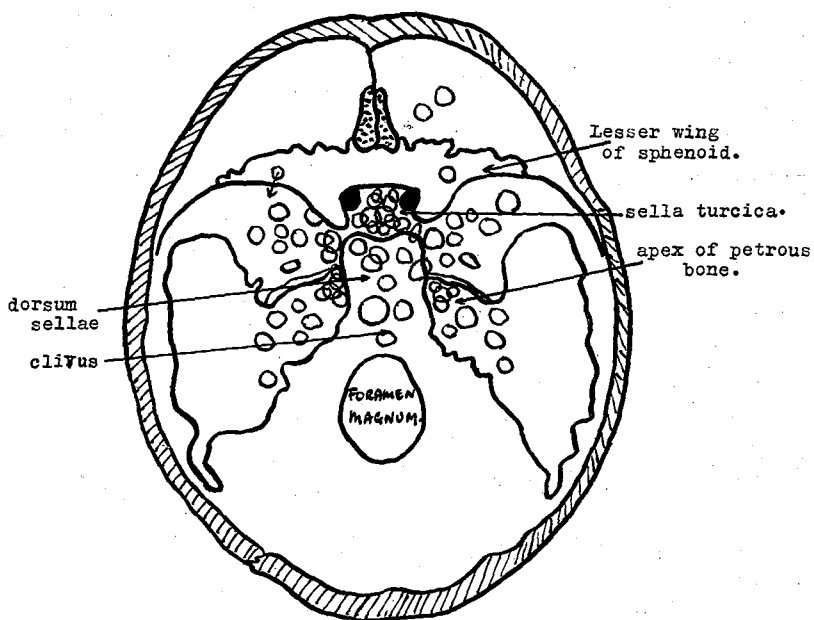


FIG. 1 Diagram of the base of the skull seen from above. Circles represent the myelomas found in the cases belonging to Table I and II. Size and location are depicted diagrammatically.

There are altogether forty-three cases in Tables I and II and to these can be added the case of Hellner (1938, p.129), that of Wright (1953) and the second case of Snapper et al. (1953, p.34), for although the exact location of these myelomas is known other details are deficient and they are included in neither Table I nor II. Thus, of forty-six cases it is found that the sphenoid bone was involved on thirty-one occasions (67 per cent) and the petrous portion of the temporal bone on fifteen (32 per cent). It is to be noted that these figures give only an approximate indication of the commonest sites, for authors have probably only noted the most prominent lesions. Any part of the sphenoid or petrous bones may be affected but the most vulnerable parts are the body of the former and the apex of the latter. It is interesting to note in passing that the myeloma, the reticulum-cell sarcoma and the lymphosarcoma all have a special affinity for these bones. The reason for this predilection is quite unknown.

A large tumour may involve several regions eventually and it is difficult or impossible to say which bone was involved initially. The myeloma in Case One, for example, was eroding much of the sphenoid bone and both petrous apices, and it would be impossible to suggest the site of the original focus. Other basal sites are the clivus (other than the part formed by the sphenoid bone), the orbital roof and other parts of the cranial fossae.

Origin of the basal myeloma.

In individual cases, it is usually difficult to determine the tissue from which the myeloma has initially arisen, but study of the whole group reveals the commonest source. The tissues that may be responsible are the bones of the skull base, the dura mater covering them or the mucosa of paranasal sinuses or nasopharynx.

That the bones alone may be the site of myelomas has been shown by Case Three and Aronsohn's (1931) macerated specimen. Fowler (1938), after sectioning the petrous bones of his patient, had no doubt that the myeloma had originated in bone marrow, and Weinberg and Schwarz (1920), Riser and Sorel (1929), Piney and Riach (1931) and Wright (1953) were equally certain.

As myelomas of the dura mater over the convexity occur, and will be dealt with later, a similar lesion at the base of the skull might be expected, but the only author to suggest this possibility is Rustizky (1873). Other authors make no reference to it, but it cannot be excluded entirely and may on rare occasions be the tissue of origin, although no definite proof has been found.

The next structure to be considered is the mucosa of the paranasal air sinuses, especially that of the sphenoid sinus. Plasma cell myelomas can grow from the mucous membrane of the upper respiratory pathways (Hellwig, 1943), and as the sphenoid bone, especially its central portion contain-

ing the sinus, is frequently the site of myelomatous involvement, it is reasonable to suppose that the neoplasm may occasionally originate from the mucosa rather than the surrounding bone. Similarly, it could be postulated that the frequency of myelomas in the petrous bone is due to the fact that they can grow from the mucous membranes contained within this bone. Although Fowler (1938) excluded this with confidence, Cappell and Mathers (1935) felt that they could not ignore entirely the mucous membrane lining the middle ear.

Finally, another tissue that may possibly be incriminated is the mucosa of the nasopharynx. Stout and Kenney (1949) made a careful selection of plasma cell myelomas of the upper air passages and found that of twenty in the nasopharynx only one, the case of Figi, Broders and Haven (1945, case 6), had bony destruction. The latter authors were certain, however, that the tumour had originated from the bone or sphenoidal sinus and involved the nasopharynx secondarily. Occasionally in the cases of Group I (e.g. Case One) a nasopharyngeal mass was present, but Oppikofer (1926) and Cappell and Mathers (1935) as well as Figi et al. (1945, Case 6) considered that this was an extension of a myeloma of the skull base, the course of events being comparable with those in the first case of Piney and Riach (1931) where extension was into the nasal and orbital cavities rather than the nasopharynx. Wright (1953) points out that the

lack of mucosal ulceration in his and other cases would indicate that the tumour is not derived primarily from the mucous membrane. Thus, it can be concluded that nasopharyngeal involvement is the result of an encroaching myeloma of the skull base and a lesion of the mucosa in this region never invades the skull.

By reviewing the whole group it is possible to state that in the vast majority of cases of myelomas occurring in the region of the skull base, the original focus is in the bone marrow, and other structures are affected secondarily. Although no direct evidence is available, a myeloma of dura mater or mucosa of sinuses or middle ear with subsequent bony involvement may at times occur.

The cranial nerve lesion.

The cranial nerves are found in most of the regions that have been mentioned, and damage to them therefore readily occurs.

For example, the trigeminal nerve in the case M.G.H. Case Record No.20031 (1934) was completely destroyed and structures in and near the jugular foramen in the case of Cappell and Mathers (1935) were involved by a widely destructive myeloma. Occasionally the nerves in the cavernous sinus are involved when a myeloma invades this area. Invasion of the nerves such as occurs with other forms of malignant lymphadenomas (Sparling et al., 1947) and with metastatic carcinoma (Jentzer, 1930) has not been described

in these cases. The abducens nerve in case 21 of Sparling et al. (1947) was surrounded but not invaded by plasma cells, and this was apparently sufficient to jeopardise its function. There is no evidence in the literature that a process akin to carcinomatosis of the leptomeninges (Jacobs and Richland, 1951) with the production of multiple cranial nerve palsies takes place in myelomatosis.

In all of the cases, except those of Pollock (1934, case 2) and M.G.H. Case Record No.20031 (1934), the dura mater overlying the tumours, although frequently distorted, was never penetrated and the inner surface of the membrane was always healthy. Cranial nerve involvement therefore is almost invariably extradural. The only way in which basal structures of the brain, other than cranial nerves, are involved by a myeloma is by distortion and never by direct destruction. Langdon (1939) attempted to attribute the cranial nerve palsies in his patient to toxic influences, but there was ample evidence of local myelomas and his hypothesis is untenable. This subject will be dealt with in more detail later (p. 199).

CLINICAL FEATURES.

There are twenty-five proven cases of myeloma of the skull with cranial nerve palsies that are reported in enough detail to make intimate consideration possible (Table I).

Age and Sex.

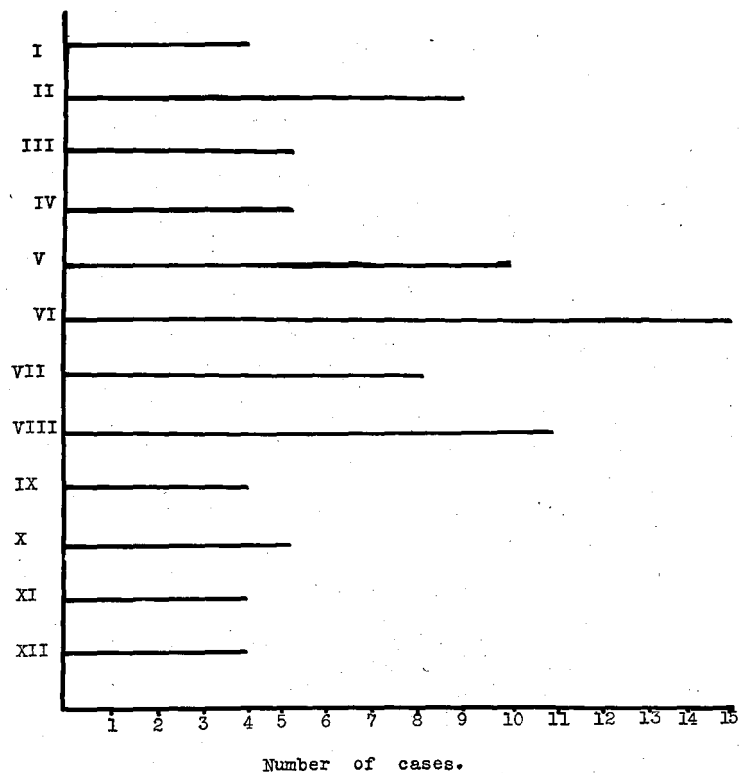
These were comparable with the findings of Geschickter and Copeland (1928) and others who have studied large series of cases of multiple myeloma. The age of the patient at the onset of the illness could be estimated in twenty-two cases and the range was thirty-three to sixty-nine years, with an average of fifty-one. (The sixteen-year-old patient of Calvet, Claux, Gayral, Rascol and Cadenat (1950) has been excluded because of the unusual age of onset of the disease.) There were twice as many males as females.

Initial features of the disease.

The first manifestation of the disease was due to the cranial lesion in fourteen of the twenty-five cases. Thus five began with headache, three with ocular symptoms (diplopia or visual impairment), two with deafness, two with a facial nerve palsy and one with trigeminal nerve palsy. Finally, the second case of Christophe and Divry (1940) presented with amenorrhoea and polydipsia, which was thought to be due to hypothalamic or pituitary involvement. In the remaining eleven cases the neurological features developed during the course of the generalised disease.

Cranial nerves affected.

Table III indicates the number of times that each individual nerve was involved by a myeloma of the base. The sixth nerve was the most frequently affected (fifteen



Cranial Nerves.	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
Number of patients with palsies.	4	9	5	5	10	15	8	11	4	5	4	4

TABLE III Frequency of Cranial Nerve Palsies in 25 reported cases of basal myeloma.

times among twenty-five cases), and when it is realised that most of the lesions are either located somewhere along its course or are able to distort it, this high incidence is to be expected. On two occasions there was paralysis of both abducens nerves (M.G.H. Case Record No.20031, 1934: Langdon, 1939). In three cases (Hammer, 1894: Ritter, 1921: Godtfredsen, 1944, Case 18, Table 30) the sixth nerve alone was involved; similarly in Case Two and the first case of Snapper et al. (1953, p.34), which are not included among the twenty-five cases owing to the lack of pathological details.

The eighth cranial nerve was the next most commonly incriminated, but the aural features may in some cases have been due to direct invasion of the petrous bone rather than to a lesion of the nerve itself. For this reason, the case of Canestro (1927) was excluded and the case of Figi et al. (1945, case 6) is perhaps suspect. In Case One both structures were involved, for there was a mixture of nerve and middle ear deafness on each side and on the right the caloric responses were absent. Likewise, nerve deafness was present in the patient of Fowler (1948), but there was also diffuse invasion of the petrous bones. Case One is the only example of bilateral eighth nerve affection.

The fifth nerve was the third most frequently involved and in the M.G.H. Case Record No.20031 (1934) it was entirely destroyed, whereas in Case One the trigeminal features were

only subjective. Four cases with extracranial involvement of branches of this nerve (Lecène, 1919, ophthalmic division; Pallestrini, 1927, ophthalmic and maxillary; Greenfield, 1948, maxillary; James and Turner, 1952, mandibular) have been mentioned already. The remainder of the cranial nerves were affected in the following order of frequency:- 2, 7, 4, 3, 10, 1, 9, 11 and 12. The patient of Delmas-Marsalet, Pauly, Leger, Pouyanne and Leman (1951) eventually had bilateral third nerve palsies and this is the only such instance. The cases of Calvet et al. (1950), Riser and Sorel (1929), Sparling et al. (1947, case 20) and Cappell and Mathers (1935) presented syndromes of the third to twelfth, fourth to twelfth, fifth to twelfth and sixth to eleventh cranial nerve palsies respectively. The third case mentioned by Snapper et al (1953, p.34) had a combination of seven to twelve cranial nerve palsies caused by a large basal myeloma; it has not been included in Table I because of a paucity of clinical data, nor has their second case with ophthalmoplegia on one side. In the third case there was a unique feature, for the tumour presented within the external auditory meatus and a biopsy could be made of it.

In five cases, only one cranial nerve was involved (Hammer, 1894, sixth; Ritter, 1921, sixth; Fowler, 1938, eighth; Godtfredsen, 1944, Case 18, Table 30, sixth; Cagnoli and García Novales, 1950, Case 3, third). Case

Two with an isolated sixth and the patient said by Laesecke (1928) to have only a fourth nerve palsy can be mentioned here, although they do not belong to the present group because of deficient details. The remaining twenty cases had multiple palsies ranging from two to nine nerves affected.

INVESTIGATIONS.

Cerebrospinal fluid.

This will be dealt with in greater detail later (p.223), but suffice it to say that changes are rare and no constant abnormality occurred in these cases.

X-rays of the skull.

Occasionally X-rays revealed osteolytic lesions of the calvarium as well as the base. The basal myelomas could be huge and widely destructive (Fig.4) or small and diffuse (Fig.9).

Urinalysis.

In only seven cases was Bence Jones proteinuria looked for, and in only three was it found.

Bone marrow biopsy.

This was carried out on four occasions (M.G.H. Case Record No.20031, 1934: Fowler, 1938: Case One: Case Two) but it was only of definite diagnostic aid in the first.

DIFFERENTIAL DIAGNOSIS.

All lesions that destroy the skull base and produce

cranial nerve palsies must be considered, and the most important in the age group in which multiple myeloma occurs is the nasopharyngeal carcinoma. In the absence of evidence of myelomatosis differentiation may be impossible without biopsy. The mixture of nerve and conduction deafness is apparently characteristic of the basal myeloma as well as the nasopharyngeal carcinoma, for they interfere with the middle ear or Eustachian tube as well as with the nerve. A chordoma may produce a similar clinical picture, and other intra-sellar or para-sellar lesions that must be considered are metastatic neoplasm, sarcoma of the sphenoid (the sarcoma, like the myeloma, has a special affinity for the sphenoid bone) and extra-sellar extension of a chromophobe adenoma (Epstein and Davidoff, 1951). Confusion with an eosinophilic granuloma of bone is possible, for a case with cranial nerve palsies has been described (Osborne, Freis and Levin, 1944) and a generalised form occurs (Green and Farber, 1942 and ^{Kaplan,} Grumbach, Tetu and Lau, 1952). Their differentiation is important for the granuloma responds much better than the myeloma to radiation therapy and the prognosis is quite different. Chronic inflammation may promote the formation of plasma cell masses particularly in the conjunctiva, the upper air passages and the temporal bone; Eagleton (1936) has described the latter involvement as "plasmocytic mastoiditis", which begins with suppuration of low virulence in the petrous apex and fills the mastoid

process with plasmacytes. In Gros' (1945) case, this was suspected but cultures were sterile and there was a definite morphological difference between the plasmacytes present and typical plasma cells. Differentiation from the plasma cell myeloma is therefore not difficult, and this also applies to the plasmacytic granulomas. The myeloma in the third case of Snapper et al. (1953, p.34) was found to be extending into the external auditory meatus, and this feature taken together with the cranial nerve palsies and bone erosion would make differentiation from a glomus jugulare tumour (Henson, Crawford and Cavanagh, 1953) impossible on clinical grounds alone.

The diagnosis of a myeloma of the base of the skull producing cranial nerve palsies rests finally on biopsy examination and the search for other evidence of myelomatous disease.

TREATMENT.

This, unfortunately, is a gloomy aspect of the subject. As mentioned already, there is no specific cure for myelomatosis and the measures employed in the treatment of the cases of basal myelomas are as limited and ineffectual as when used in the treatment of other forms of the disease.

Only fourteen of the twenty-five cases were treated. The effects of medical therapy could not be evaluated and operation when attempted resulted in five deaths among eight

patients. One gains the impression that those given irradiation made better progress, but the follow-up has not been adequate nor the number of cases large enough. In addition, the cases benefited most were of the slowly progressive type, so the response to therapy must be evaluated with caution (cf. Case One).

One would suggest, therefore, that operation (other than a biopsy procedure) should be avoided and that the patient will benefit most from deep X-ray therapy. (Case One was given a total dose of 4,900r. directed to the base of the skull), combined with a course of urethane, if tolerated.

PROGNOSIS.

The average length of the whole disease was about two years, and this corresponds with the survival figures usually quoted for myelomatosis of any type. The range was from six months to nine years; the latter case (Christophe and Divry, 1940, case 2), however, died soon after operation. In twenty cases it was possible to determine the duration of the cranial nerve palsies, and this varied from one week (Stokvis, 1883: this case was also described by Kühne, 1883, Ribbink, 1892 and Zeehuysen, 1893) to six years (Case One). The period from the onset of the palsies to death could be calculated in thirteen cases but three of these died post-operatively (Christophe and Divry, 1940, cases 1

and 2: Sparling et al., 1947, case 20). The true natural history of the cranial nerve palsies could thus be observed in only ten cases and the average duration was one year. Three patients are known to have been alive when their cases were reported, having survived six years (Case One), four years (Gros, 1945) and two years, eight months (Figi et al., 1945, case 6). In only three cases was there any evidence of improvement in the palsies, unaided by therapy, and in each of them (Hammer, 1894: Sparling et al., 1947, case 21: Case Two) a sixth nerve palsy either disappeared or regressed.

The cases with multiple spread, on the whole, ran a shorter course than those with a so-called "solitary" myeloma, but exceptions can be found readily. Case One is still alive after six years, despite the presence of widespread lesions. The cases with apparent solitary lesions, on the other hand, usually had a longer survival (Christophe and Divry, 1940, case 2: Godtfredsen, 1944, case 18, Table 30: Gros, 1945: Figi et al., 1945, case 6) but that of Sparling et al. (1947, case 20) lived only eleven months. Excluding those patients that died after operation, and perhaps those with bulbar palsies, death was due to the generalised disease and not to brain involvement.

GROUP II. CASES SIMULATING BRAIN TUMOURS.

A plasma cell myeloma growing from the skull vault or dura mater of the convexity may extend intracranially to produce the clinical picture of a space-occupying lesion. On the other hand, a myeloma may originate from intracranial structure and produce the same end result (here cases belonging to Group I are excluded). These cases constitute Group II and are necessarily divided into two further groups depending upon the site of origin of the tumour. If it is from the calvarium or underlying dura a bony lesion will be present, whereas it will be absent from the purely intracranial lesions. Thus the sub-grouping is into:-

- A. Cases with myeloma of the skull or convexity dura.
- B. Cases without myeloma of skull or dura.

A. CASES WITH MYELOMA OF THE SKULL VAULT OR CONVEXITY DURA MATER.

Although the vault of the skull is a very common site of myelomas, they rarely produce symptoms and signs.

LITERATURE.

As with the other groups of cases of myelomatosis, it has been necessary to examine each example in the literature with care. Cases that have been accepted by some

authors have been rejected on insufficient evidence, and if any doubt arose the case has been excluded. Those described prior to 1900, and therefore before the recognition of the true histological appearances, are in many instances suspect, for confusion with various bone sarcomas frequently occurred.

Firstly, Guibert and Ratié's (1929) case was probably a myeloblastic sarcoma and the tumour's extension into the brain tissue differentiates it from the myeloma. The diagnosis in the first case of Kudrowetsky (1892) was "sarcoma (myeloma)", although it was presented as an example of myelomatosis with cerebral involvement. The "solitary" skull myeloma of Schwartz (1945) was a giant-cell bone tumour, as was the neoplasm described by Beneke and Stieda (1930) and often accepted as a myeloma.

On the other hand, there is a group of cases where the authors thought that they were dealing with primary bone neoplasms but in all probability they were plasma cell myelomas (Arnold, 1873, Case 2; Delfino, 1905; Herscher and Thevenard, 1924; Baldenweck and Perrot, 1933). In any case, because of the doubt they will not be considered further.

These cases have been detailed because they have in the past been readily included under the title of myeloma. Thus a distorted and inaccurate conception of the neurological aspects of myelomatosis is at times to be found in the

literature.

PATHOLOGY.

Involvement of the skull varies considerably from case to case. First of all, the lesion may be large and single, and such cases have been described by Mathias (1935), Peyton (cited by Cutler, Bushke and Cantril, 1936), Tilden (1941), Esposito (1943), Koufman (1945), Nida (1947) and Ward and Hendrick (1950) (Table IV). On the other hand, the calvarium may be diffusely involved so that no part of it escapes, and this is illustrated by the unique case of Meyer and Cajori (1924), where no part of the skull escaped. Finally, a combination of these two varieties is possible and one or more large tumours are accompanied by smaller satellite ones. There are no particular sites of election.

As they grow, they eventually destroy the whole thickness of the bone so that on X-ray a sharp-edged osteolytic area is seen. They press upon the dura mater and may become loosely adherent to it, but only very rarely do they penetrate this membrane, as was also seen when dealing with the basal myelomas. Even if they penetrate the dural barrier invasion of cerebral substance never occurs. Their intracranial extension varies in degree and the resulting cerebral compression determines the clinical features produced. Likewise, their growth outwards beneath the scalp is variable and a huge tumour may result (cf. Case

Four). They are usually highly vascular, as was verified in Case Four and the case of Ward and Hendrick (1950) by the large blood vessel channels seen on X-ray and the findings at operation. Occasionally a bruit can be heard over the tumour, as for example in Case Seven.

The cranial myeloma is usually a part of the generalised disease, myelomatosis, and as none of the so-called "solitary" lesions has been adequately investigated they cannot be thought of as being truly single. The conception of a true solitary lesion of Christopherson and Miller (1950) must, however, be remembered and cannot be entirely rejected.

Myelomas of the dura mater will be discussed later (p. 58), but suffice it to say that on rare occasions the tumour may grow from the calvarial dura. Their appearances are exactly the same as their osseous counterparts and even erosion of the overlying skull occurs, so that clinically differentiation is impossible and even at autopsy it may be difficult.

CLINICAL FEATURES.

The clinical manifestations that are produced by myelomas of the calvarium and its underlying dura mater can now be considered. They are determined by the site and the degree of invasion of the cranial cavity. The external size of the myeloma is not necessarily a guide to

the latter, for in most of the cases of large "solitary" myelomas (Table III) mentioned above and reviewed by Courville (1948) the authors do not mention any neurological complications. The dural myeloma produces the same clinical features as the bony tumour and differentiation clinically is not possible, nor is it necessary.

Before dealing with the results of focal brain lesions one general symptom must be alluded to. Boston (1903) believed that headache was to be found in 70 per cent of patients with myelomatosis, but this is much too high a figure. If headache is taken to include all types of head pain, deep or superficial, it is remarkable how frequently involvement of the skull is symptomless and, quite unlike the bony lesions elsewhere in the body that are characterised by severe pain. Some patients have discovered large myelomatous lesions of the skull quite by accident.

Except in a few rare instances (Case Four), other evidence of myelomatosis is usually present in these cases and the classical picture of the disease eventually results.

It is convenient to discuss the neurological complications under the following headings:-

- 1). Increased intracranial pressure.
- 2). Focal neurological features.
- 3). Epileptic manifestations.
- 4). Diabetes insipidus.

5). Mental changes.

1). Increased intracranial pressure.

Myelomatous invasion of the cranial cavity may be sufficient to produce a rise in the intracranial tension. Meyer (1913) mentions a case with numerous calvarial myelomas, complicated by features of increased intracranial pressure and internal hydrocephalus. The second patient of Meyerding (1925) with multiple skull lesions, one of which was large, had intracranial hypertension, as did the first case of Kalischer (1928) where there was a left parietal skull tumour compressing the underlying cerebral hemisphere. A similar lesion producing death from cerebral compression was found in the patient of Wilson and Milkman (1932); the myeloma was fronto-temporal in location and was growing from the dura mater. There was clinical evidence of high intracranial tension in the patient of Balan and Ballif (1932), confirmed by cerebrospinal fluid (C.S.F.) examination; at autopsy there were several cranial myelomas that were pressing upon the brain beneath. A similar case was that of Denker and Brock (1934, Case 1) where there was diffuse skull involvement and increased intracranial pressure, verified by lumbar puncture; an autopsy was not carried out. The clinical picture in the patient of Krainin, D'Angio and Smelin (1949) closely paralleled that

of an intracranial tumour, with blurring of the discs bilaterally. The patient described by Baumann and Bras (1947) was somewhat similar but information is scanty. Finally there is the patient of James and Turner (1952) with a large occipital myeloma, terminal papilloedema and other features of intracranial hypertension.

These eight cases (excluding that of Baumann and Bras, 1947) all had multiple lesions of the skull or dura, but in five at least (Meyerding, 1925: Kalischer, 1928: Wilson and Milkman, 1932: Balan and Ballif (1932) and James and Turner, 1952) one or more of the myelomas were larger than their fellows and compressed the underlying brain. In the other two (Meyer, 1913: Denker and Brock, 1934, Case 1) information was scanty but the skull was said to be diffusely involved, and the mechanism of cerebral compression in these cases therefore is not obvious. The myeloma in one case (Wilson and Milkman, 1932) had arisen from the outer surface of the dura, but this did not alter the clinical picture. The dura was intact in all of them and no direct invasion of the brain occurred.

Eskelund and Noring (1953) have described an interesting case where death was due either to raised intracranial tension or brain stem haemorrhages. This case will be

discussed later when the vascular aspects of myelomatosis and the nervous system are under consideration. The case will be described in more detail then.

The cases in Group I may also be mentioned at this juncture because occasionally signs of increased pressure existed in addition to cranial nerve palsies; Pollock's (1934, Case 2) patient was thought to have a brain stem neoplasm but a basal myeloma was the causative agent.

Thus encroachment upon the cranial cavity may result in a picture of raised intracranial pressure, but in all the literature only eight definite examples are to be found.

2). Focal features.

If a myeloma extends intracranially it will eventually press upon the brain and, depending upon the site, will on occasions produce focal features.

Thus in the patient of Kalischer (1928, Case 1) there was a contralateral facial weakness (as well as focal fits) and motor and sensory disturbances appeared in the opposite limbs of the patient reported by Villata (1928). The presenting feature in Balan and Ballif's (1932) patient was a hemiplegia due to a convexity myeloma in the fronto-parietal region and, as there was also increased intracranial pressure, the picture of a cerebral tumour was closely simulated. In M.G.H. Case Record No.20031 (1934) there was a basal

myeloma as well as others elsewhere in the skull. The unilateral hyper-reflexia may thus have been caused by a convexity lesion. The hemiplegia in the patient of Christophe and Divry (1940, Case 2) was thought, however, to be caused by the basal tumour. The only example of hemianopia was reported by James and Turner (1952). Terminally there was, among others, a left calvarial myeloma in Case Six which had produced a right hemiplegia, and Snapper et al. (1953, p.34) mention a case with a similar deficit.

Khondkharian (1951) has recently suggested a cerebral syndrome (hemiplegic type) when dealing with the neurological aspects of myelomatosis. His second patient began her illness with a hemiplegia, and he postulates that this could have been produced by plasma cells in the subarachnoid space as well as vascular changes; there was, however, no autopsy.

Thus, all varieties of focal features may be produced by compressing cranial myelomas, but they are very rare when the total incidence of skull lesions is considered. Case Four belongs to this group.

CASE FOUR. Male, 53. Lump on left side of head for 4 years gradually increasing in size. Weak left arm and leg, headaches and giddiness for 2 months. Left-sided cranial tumour 17 x 17 x 8 cms. with minimal left hemiparesis. Partial removal of myeloma and treatment with radiation. Tests for multiple myeloma not done. Death after fits, aphasia and paralyses had appeared. Six years survival. No autopsy.

3). Epileptic manifestations.

Epileptic attacks have been described in a small number of cases of multiple myeloma, and they are no doubt due to direct irritation of the cerebral cortex by the compressing tumour. Owing to a paucity of pathological information it is not possible to say whether in the seven cases that showed this phenomenon the myeloma had transgressed the dura mater. It is possible it had not, because extradural pressure from any source may itself induce fits.

Massive frontal lobe compression was responsible for the epileptic seizures in Dick's (1904) patient and that of Kalischer (1928, Case 1) had raised intracranial pressure as well as localised twitching of the right lower facial muscles due to a compressing left parietal myeloma. The patient reported by Ellermann and Schröder (1933) had skull myelomas and experienced "attacks" as a presenting feature of his illness. These were described as atypical epileptiform seizures, and although an autopsy was not included in the report Levison (1933) was in favour of direct brain involvement by the cranial myelomas, as was the case also in the patient of Denker and Brock (1934, Case 1) with recurrent convulsions. Pollock's (1934, Case 2) patient suffered "attacks of unconsciousness" but the author does not elaborate upon this statement and the information concerning the patients of Christophe and Divry (1940, Case 2) with epi-

leptiform attacks and that of Snapper et al. (1953, p.34) with "repeated convulsive seizures" is likewise scant.

Kahler (1889) mentions disorders of consciousness and hallucinations in his patient but they were almost certainly related to the considerable degree of anaemia present. Similarly, the "twitching movements" in Case 11 of Davison and Balser (1937) were due probably to terminal uraemia rather than cerebral compression as the authors suggest. And finally, the convulsions which were a prominent feature in the case of Rundles and Reeves (1950, Case 12) were probably independent of the myelomatosis.

Features of cortical irritation are remarkable for their rarity, for Snapper et al. (1953, p.34) describe only one patient with fits out of a series of ninety-seven. No electro-encephalographic studies have been carried out.

4). Diabetes insipidus.

This condition was a distinctive feature of six cases and it is convenient to deal with it here.

Meyer (1913) thought that it was due to dilatation of the third and fourth ventricles in his patient with myelomatosis, and Denker and Brock (1934, Case 1) suspected a lesion of the floor of the third ventricle or the pituitary, as did Bach and Middleton (1931), although their case was not histologically verified. The presenting symptoms

of the second patient of Christophe and Divry (1940) were polyuria and amenorrhoea, and at operation a tumour in the region of the optic chiasm was discovered. Aronsohn (1931), on the other hand, incriminated small myelomatous deposits in the floor of the pituitary fossa which had encroached upon the posterior lobe of the pituitary. There were, however, no microscopical changes in the pituitary, although the central connections of the neurohypophysis are not described. Even if there had been changes in the pituitary gland itself, this would not necessarily have accounted for the diabetes insipidus, for the patients of Coste, Delbarre, Tissier and Sors (1948) with myelomatous infiltration of the posterior pituitary lobe, and Piney and Riach (1931, Case 1) where the neurohypophysis and the infundibulum were invaded, displayed no polydipsia or polyuria. In addition, in Case 2 of Collier, Reich and King (1951) there was sellar enlargement and posterior clinoid erosion but no features of diabetes insipidus.

It is suggested that another example of this complication is the patient of Iglehart cited by Hamburger (1901) because "since the past summer, she had drunk more water than usual and voided a larger quantity of urine". However, in the first case of Anders and Boston (1903), often quoted as an example of diabetes insipidus occurring with myelomatosis, the polyuria was probably due to chronic nephritis

and this might also have explained the terminal polyuria in Cosins' (1935) patient, as well as in that of Conti (1911). Babonneix, Lhermitte and De Martel (1935) described a puzzling case, but despite their title it is doubtful if this was an example of myelomatosis.

It is of importance to note that in none of these cases already mentioned was renal function investigated nor treatment of the diabetes attempted. It is therefore impossible to exclude the rare "water-losing nephritis" which produces a picture clinically indistinguishable from that of diabetes insipidus, and which has been observed in a case of multiple myeloma (Roussak, 1953).

The lesion responsible for diabetes insipidus is either in the supra-optic nuclei of the hypothalamus, the posterior pituitary lobe, or the pathways connecting them. In the Hand-Schuller-Christian disease, and in sarcoidosis, these structures are involved by tumours or actual infiltration but as the invasion of brain tissue does not occur in myelomatosis, local distortion is likely to be the aetiological factor. Although no direct proof of this is available, in at least three of the cases cited (Aronsohn, 1931: Bach and Middleton, 1931: Christophe and Divry, 1940, Case 2) there were myelomatous lesions in the sellar region of the skull base. Invasion of the posterior pituitary lobe did not produce the syndrome in two cases,

and in French's (1947) case, where there was a hypothalamic myeloma (Group IIB), it did not occur.

The only investigation of the hypothalamic region in myelomatosis was carried out by Smereker (1951) who demonstrated changes correlated to alterations in protein metabolism. Diabetes insipidus is not mentioned. This interesting complication of myelomatosis deserves further study.

5). Mental changes.

As a terminal event, mental changes such as confusion, disorientation and drowsiness are not uncommon and are probably related to the toxic and anaemic state of the patient at this stage of the disease.

There are few cases of specific mental disorder in the literature, unless one accepts the fifth case of Davison and Balser (1937). This patient had a paranoid psychosis which the authors related to the very extensive involvement of the skull and dura and the resultant ischaemic cell changes in the cerebral cortex due to pressure. It seems more likely, however, that the psychosis was either coincidental as in the cases of Wallgren (1920, Case 6), Branham and Lewis (1921), Beck (1942) and Armstrong, Faulds and Stewart (1946), where the mental derangement was present before the onset of the disease or was related to the

anaemia present. Among the ninety-seven cases of multiple myeloma reported by Snapper et al. (1953, p.34-35) psychoses not associated with terminal states were seen in eleven. Two were paranoid reactions and the rest resembled toxic psychoses. The brain was examined pathologically in seven of the eleven cases and was found to be normal in all of them.

It is likely that the factors involved in the production of abnormal mental states are "toxic" influences and anaemia, as well as terminal phenomena, produced when these combine with uraemia and factors at present unknown. The brain lesion is perhaps a biochemical one, thus explaining the inability of our present day methods to detect it.

DIFFERENTIAL DIAGNOSIS.

The diagnosis in this group of patients is not usually difficult, for other features of multiple myeloma are frequently present. If they are not looked for adequately, however, and the skull tumour is single, the diagnosis may not be so easy.

Metastatic deposits of the osteolytic variety are particularly likely to cause confusion, for they are common in the age group containing myeloma. In addition, they are usually multiple, and on rare occasions there is Bence Jones proteinuria (Pines and Pirogova, 1928: Bayrd and Heck, 1947, Table I). In particular, Geschickter and Copeland

(1928) emphasise that the age of onset in myelomatosis coincides exactly with that of metastatic skeletal tumours. The margins of the individual cranial defects as seen by X-ray, however, are less sharp than those of a myeloma. Although intracranial extension of secondary cranial deposits is slight and the dura usually intact, intracerebral metastases may also occur so that the similarity could be even closer.

The clinical and X-ray changes produced by a meningioma may at times simulate those of a "solitary" myeloma of the skull, for although hyperostosis is usual destruction may result infrequently. Thus Cushing and Eisenhardt (1938) admit that they once mistook a "myelocytic myeloma" for a meningioma, and the provisional diagnosis in the case of Wilson and Millman (1932) was "endotheliomata of skull and dura". Christophe and Divry (1940) considered that their first case had a sphenoidal wing meningioma. Armstrong et al. (1946), and Ward and Hendrick (1950) made similar mistakes and in Case Four meningioma was one of the suggested diagnoses.

Although very uncommon nowadays, gummas of the skull have been confused with myelomas as, for example, the case of Fessler and Pohl (1929). The eosinophilic granuloma has only recently been fully recognised, and in the vault as well as the base a single lesion may closely resemble the

bony destruction of a myeloma. In the first described case (Finzi, 1929) the tumour was in the frontal bone and was actually termed a "mieloma". Sarcoma of the skull has caused much confusion in the literature because of histological as well as clinical likenesses to myeloma. Cases illustrating this have been dealt with earlier in this section.

Concerning the individual neurological manifestations present in the cases of Group IIA, the important differentiation of diabetes insipidus from "water-losing nephritis" has already been spoken of and the occurrence of pathological long bone fractures simulating a hemiplegia (Case 21 of Sparling et al. 1947) should be noted in passing.

In the presence of the many diagnostic pitfalls, the only reliable method of differentiation is either by biopsy of the skull tumour or, if myelomatosis is sufficiently suspect, by subjecting the patient to the various investigations aimed at revealing other evidence of the disease.

TREATMENT.

As with the other types of myeloma, treatment has been by drugs, surgery or radiotherapy. The only drugs that have been of any value are stilbamidine and urethane, but the former was of no use in the patient of James and Turner (1952). The more accessible situation of convexity

myelomas makes them more suitable for operation, but even so, complete removal is rarely indicated or achieved.

Only two patients (Villata, 1928 and Case Two) with significant intracranial extension have been treated actively, but six cases of "solitary" myeloma without this complication have received surgical or radiation therapy. Although this latter group is not our immediate concern, consideration of the therapeutic results (Table IV) shows what may be expected with the large skull myelomas. In three patients (Cases 1, 3 and 5 in Table IV) only operation was employed and one (Case 1) died of a recurrence; the other two had been followed for only short periods. Two cases (Cases 4 and 6) had radiation therapy alone and the result in one (Case 6) was excellent, whereas in the other, generalisation of the disease followed rapidly. Both surgery and irradiation were used in three cases (Cases 2, 7 and 8) and in one (Case 2) the disease process was perhaps retarded, but in the other two survivals of four years have been reported.

Thus from a small and inadequate series, the treatment of choice would seem to be radiation therapy, with surgical excision employed in selected cases; for example, when a more rapid method is required for reducing raised intracranial pressure. The ultimate fate of the patient is determined by the behaviour of the disease as a whole. In those cases, however, where progression appears to be

TABLE IV

The results of treatment in cases of single cranial myelomas:
the first two had neurological features and the remainder did not.

CASE NO.	AUTHOR	OPERATION	RADIATION	RESULTS
1	Vallata (1928)	+	-	Recurrence and death
2	Case Two	+	+	Death 2 yr. 10 mth. after operation.
3	Mathias (1935)	+	-	Symptom free 8 mth. later.
4	Peyton (Cutler et al, 1936)	-	+	Tumour disappeared but generalization occurred 1 mth. later with death 11 mth. later.
5	Tilden (1941)	+	-	Alive when case reported.
6	Esposito (1943)	-	+	Tumour disappeared.
7	Kaufman (1945)	+	+	Well 4 yr. later.
8	Nida (1947)	+	+	Satisfactory result.
9	Ward & Hendrick (1950)	+	+	No recurrence and in good health 4 yr. later.

slow and the cranial lesion is the only active evidence of the disease, therapy should be considered.

B. CASES WITHOUT MYELOMA OF THE SKULL.

As well as the extension of a skull lesion into the cranial cavity, a myeloma may on very rare occasions grow from intracranial structures and so produce the clinical picture of a non-specific space-occupying brain lesion. Bone changes will therefore be absent. This is the rarest form of myeloma affecting the brain, for in the literature only one example can be found.

French (1947) described the case of a forty-two-year-old female who one year before admission to hospital had suffered headache, confusion, somnolence and loss of memory, but had made a complete recovery. Eight months later, however, these symptoms returned, together with irregular menstruation. On examination she was disorientated, had bilateral papilloedema and an equivocal left plantar response. Skull X-ray and electroencephalogram were normal, but ventriculography showed a tumour in the region of the third ventricle. At autopsy, a "plasmacytoma" (plasma cell myeloma) was found to be occupying all of the hypothalamus and seemed to be arising from intracranial tissues, although the base of the skull and the dura mater were not described. All other organs and tissues were normal. As the diagnosis

was made at autopsy a search for other evidence of myeloma had not been made and this tumour cannot therefore be accepted as a true solitary myeloma. Its tissue of origin is unknown although the author considered it to be of "extra-medullary" source. Case Five shows some similarities.

CASE FIVE. Female, 58. 2 years of intermittent occipital headache worse for 3 months and with vomiting, drowsiness and periodic breathing. Signs of increased intracranial pressure and minimal left arm weakness and hypertonia. B.P. 190/110 and heart enlarged. Ventriculogram and operation revealed an extracerebral plasma cell myeloma of the dura of the tentorium cerebelli. Death. Autopsy. No other evidence of myeloma.

Case Five and the case of French (1947) are the only ones belonging to this group. They both presented clinically as an intracranial space-taking lesion and no evidence of multiple myeloma was obtained from the investigations carried out. The skull bones were not involved. In Case Five the tissue of origin was the basal dura mater, but in French's (1947) case it was unknown.

Diagnosis in these cases cannot be made until the tumour is studied microscopically. Other features of myelomatosis would however suggest the pathological diagnosis.

Treatment is that of an intracranial neoplasm, unless generalisation of the disease contraindicates this. Complete removal is desirable, for as the tumour is not invasive a complete "local" cure would be expected with surgery and would be made more certain with radiation therapy.

MYELOMA OF THE DURA MATER

In view of the fact that the myeloma in Case Five originated from the dura mater, it is necessary to describe the various ways in which the cranial portion of this membrane may be involved by myelomatous changes.

Armstrong et al. (1946), presenting two cases with dural myelomas, claimed that apart from a similar case published by Carlisle (1938) this type of myeloma had not appeared before in the literature. That it seems to be very rare, is apparent from the report of Hayes, Bennett and Heck (1952) who surveyed one hundred and eighty-two extra-osseous myelomas. Almost every tissue and organ was included, but the dura mater was not mentioned. However, during a survey of the literature several references to it have been found. As with other nervous system changes, this rarity is only an apparent one.

A myeloma of the skull vault, although usually separate from the underlying dura, is occasionally loosely adherent to it. However, actual involvement of the dura can occur in two ways:-

- (a). Discrete myeloma of the dura mater.
- (b). Diffuse myelomatous infiltration of the dura mater.

(a). Discrete myeloma of the dura mater.

The cases of Armstrong et al. (1946) and Carlisle (1938) illustrate well this type of dural involvement, for myelomas of varying sizes were arising from the external layer of the convexity dura mater, and eroding the skull. Like dural metastases from malignant neoplasms, they invariably grow from the outer layer, and the inner layer of the dura is normal so that the only brain lesion is that from local compression.

Several authors describe myelomas of the convexity dura mater, although it is sometimes difficult to determine from the reports whether the myeloma was arising from the membrane or originating from the bone and adherent to it. Rustizky (1873), Hammer (1894) and Hoffmann(1904) mention them. Morax (1919) found myelomas spread out over the dura mater which was nevertheless normal and intact. Myelomatous nodules growing from the dura were described by Pentman (1925), and in the cases of Saupault, Gutmann and Bertrand (1929) and Wilson and Millman (1932) dural myelomas caused perforation of the skull in each. As with bone myelomas, if they penetrate the dura invasion of brain tissue does not take place. Myelomas of the basal portion of the dura have been considered already (p.26), but no adequate evidence is available to suggest that the dura covering the basal bones ever gives rise to them. In this region they originate,

probably exclusively, from bone. The dura mater of the tentorium cerebelli must also be included here, but Case Five seems to be the only proven plasma cell myeloma of it. In the latter case, the largest lesion caused considerable brain compression. In the cases of Villata (1928) and Kalischer (1928, Case 1) the myelomas were attached to the dura and produced focal neurological abnormalities. It is not, however, possible to say whether the lesions arose primarily from bone or dura mater, and this difficulty also occurs with the case of Pincy and Riach (1931, Case 1), whereas in Cosin's (1935) case they occurred together.

The myeloma of the convexity dura does not produce any distinctive clinical features of its own. If large enough, it compresses the brain, like its osseous counterpart. Clinical manifestations may have been present in more of these cases but limited observations and records prevent adequate evaluation.

(b). Diffuse myelomatous infiltration of the dura mater.

As well as discrete myelomas of the cranial dura mater, diffuse infiltration of this membrane occurs, as has been described in the spinal dura (Davison and Baker, 1937, Case 1). It does not often appear in autopsy reports but it is probably more common than would be considered. Histological examination of the meninges has rarely been carried out in

cases of myelomatosis.

Warstat (1913) describes this as well as Piney and Riach (1937, Case 2), and Batts (1939) speaks of "infiltration of the meninges" in one case and "infiltration of the dura (from the calvarium)" in another. Similarly, the cerebral dura was the site of many myelomatous nodules, some of microscopic size, in the fifth case of Davison and Balser (1937), and in Case 19 of Sparling et al. (1947) plasma cells had invaded it diffusely. The former author presents this process in a photomicrograph (Fig.7).

Clinically, there are no distinctive features of these dural changes and the picture seen with carcinomatosis or sarcomatosis of this structure (Russell and Cairns, 1934) never occurs. However, Davison and Balser (1937, Case 5) claimed that the extensive involvement of the skull and dura mater had resulted in cortical ischaemia and thus psychotic changes, but doubts have already been cast upon these deductions.

Invasion of the meninges as in carcinomatosis (Jacobs and Richland, 1951) likewise is never found with myeloma, but the case reported by Laurentius (1938) is germane to the present discussion. In a child with skull myelomas, there was meningeal irritation and a cerebrospinal fluid pleocytosis which the author thought could be explained by myelomatous involvement of the meninges, but had no autopsy veri-

fication.

This case will be referred to again when the C.S.F. changes are under discussion. It can, however, be said that the author's evidence is very slender and not at all convincing. If it were an established happening in this disease, there would surely be more evidence of it, and there is not. Further, it has been noted how immune the nervous system remains from the advances of myelomatosis, and the almost invariable absence of cells in the C.S.F. lends additional support to this. It would thus appear that clinical evidence of dural invasion is not found and progression of the disease beyond the dural barrier does not occur. A striking demonstration of how the dura may arrest the progress of myeloma cells is shown by Fig.48.

It can thus be appreciated how the behaviour of myelomatosis of the dura mater differs markedly from sarcomatosis and carcinomatosis (Russell and Cairns, 1934) and from leukaemic infiltration (Schwab and Weiss, 1935) of the same membrane.

GROUP III. INTRA-ORBITAL TUMOUR SYNDROMES.

The orbit may be invaded by a plasma cell myeloma and on rare occasions this may be the initial feature of multiple myelomatosis. Only verified cases have been admitted to this group, and that of Walsh (1947, p.1115) has been excluded because the author could not be certain whether the tumour in his patient was a "pseudo-tumour" or not. Other doubtful examples will be noted when dealing with diagnosis.

INCIDENCE.

The exact incidence of myeloma of the orbit is difficult to discover, for those dealing with orbital tumours are unlikely to see all cases of myelomatosis with this complication. Authors who have reviewed multiple myeloma do not mention it, and it is possible that in the past the myeloma has not been differentiated from kindred neoplasms. Thus, Birch-Hirschfeld (1930) in an exhaustive treatise on orbital tumours does not mention it directly but includes an occasional case with other types of tumours. A measure of its rarity, however, can be obtained from the fact that Forrest (1949), reviewing two hundred and twenty-two intra-orbital tumours, found only one "plasmacytoma" (myeloma),

and that there were two myelomas in a series of six hundred and seventy-six tumours described by Offret (1951). Pfeiffer (1941) had only one example among two hundred cases of exophthalmos. The absence of myelomas is specifically noted by Godtfredsen (1947) when dealing with seventy-eight cases of orbital tumour, representing ten thousand admissions to an ophthalmological clinic in fifteen years.

CLASSIFICATION.

Cases of myelomatosis with orbital involvement fall into two groups:-

- A. Primary myeloma of the orbit. The patient presents with ocular features, suggestive of an orbital tumour.
- B. Secondary myeloma of the orbit. The patient has a para-orbital myeloma and eventually develops symptoms and signs of an orbital tumour due to orbital invasion.

Some of the cases in the literature, however, cannot be so grouped because of a paucity of information concerning them (Grosz, 1927: Verhoeff, 1939: Batts, 1939: Pfeiffer, 1941: Godtfredsen, 1944, Table XXX, Case 18: Forrest, 1949: Bichel, 1950, Case 6: Campbell, 1951: Madonick and Solomon, 1953, Case 5). It is possible, of course, that they were

not all true plasma cell myelomas, as is almost certainly the case with the children described by Berkheiser (1924) and Gilmore (1925); they had exophthalmos but may well have been suffering from Hand-Schuller-Christian disease. The case of Elizalde cited by Scheinker (1938) and others could not be traced. Scheinker's (1951) statement that the first case of myeloma had orbital involvement and was described by Burns (1824) is not correct; the case in question is the first example of chloroma.

A. PRIMARY MYELOMA OF THE ORBIT.

The literature includes at least thirteen cases of orbital myeloma where the information given is sufficient to place them definitely in this group (Table V). All of them are verified and each had other evidence of myelomatosis. Case Six (Appendix I) may be added to make a total of fourteen.

CASE SIX. Male, 67. One year of diplopia, 2 months of left ptosis and proptosis. Left supraciliary mass and X-rays showed osteolytic lesions in this and other regions. Partial removal of left orbito-frontal tumour (verified as myeloma) and radiation therapy given, but generalisation and local recurrence took place. Death. Total survival $3\frac{1}{2}$ years. No autopsy.

PATHOLOGY.

The myeloma in these cases apparently grows from the orbital contents or walls, but at a late stage of its development it is usually impossible to identify the structure

TABLE V. PRIMARY ORBITAL MYELOMAS

AUTHOR	SEX	AGE	INITIAL FEATURES	EYE AFFECTED	DURATION		TREATMENT	OUTCOME
					OCULAR FEATURES ALONE	TOTAL		
Quackenboss & Verhoeff (1906)	M	58	Diplopia. Proptosis	Left	4 mths	8 mths	Operation	Death (no p.m.)
Mieremet (1915)	F	57	Proptosis	Right	c. 5 mths	12 mths	Sodium cacodylate Salvarsan	Death (no p.m.)
Morax (1919)	M	42	Proptosis	Right	8 mths	c. 8 mths	Operation	Death (no p.m.)
Branham & Lewis (1921)	M	63	Pain; tumour of leg	Right	Not known	3 mths	None	Death (p.m.)
Greenough et al. (1921) Case 52	M	43	Proptosis	Left	c. 1 yr.	-	Irradiation	Alive (4½ yrs. follow-up)
Holm (L. orbit) (1932)	F	73	Tumour below eye	Left	14 mths	2 yrs	Operation. Irradiation	Death (p.m.)
Grickshank (1937)	M	30	Pain and proptosis	Left	13 mths	19 mths	Operation. Radium	Death (no p.m.)
Flynn & Sailer (1944)	M	68	Proptosis, ptosis, visual loss	Right	5 mths	7 mths	None	Death (p.m.)
Olaisse et al. (1949) Case 8	M	31	"Ocular disorders" Orbital mass	Left	9 mths +	-	Diethylstilboestrol	Alive (9 mths follow-up)
Gereb & Könyves-Kolonics, (1950) Case 2	F	56	Lumbago, general malaise, inflammation of eye	Left	-	Not known	None	Unknown
McEvoy (1950)	F	80	Orbital mass	Right	3 mths	-	Operation. Irradiation	Alive (no follow-up)
Driessens et al. (1951)	F	45	Proptosis	Left	1 mth	Few mths	Stilbamidine	Death (no p.m.)
Offret (1951)	F	57	Proptosis. Headaches	Right	6 mths	-	Operation. Irradiation	Alive (2½ yrs follow-up)
Case Six	M	67	Diplopia	Left	2 yrs	3½ yrs	Operation. Irradiation	Death (no p.m.)

from which it arose. Morax (1926) thought that this was invariably the roof of the orbit, but Flynn and Sailer (1941) noted that in their case the tumour was limited to the contents of the orbit and that its confines were intact. In addition, no X-ray evidence of bony erosion could be found in the cases of Claisse, Bonduelle and Lavergne (1949, Case 8), McEvoy (1950) and Offret (1951). The primary myeloma may thus be a product of the orbital contents and therefore of extra-osseous origin; unfortunately there seems to be no information concerning the actual tissue that is initially responsible. Frequently the tumour eventually destroys the surrounding bone (Mieremet, 1915; Morax, 1910 and 1919; Holm, 1932: Case Six), and it may extend through the roof and compress the under surface of the frontal lobe of the brain as in the cases of Morax (1919), Branham and Lewis (1921), Holm (1932) and Case Six.

CLINICAL FEATURES.

In all but one of the fourteen cases, symptoms referable to the eyes were either the earliest, or amongst the earliest, manifestations of the disease. The commonest complaint was that of progressive protrusion of an eye, the globe being displaced in any direction. Whereas malignant orbital neoplasms usually present with ocular immobility, proptosis is much commoner as an initial symptom in these

cases of plasma cell myeloma. Occasionally the tumour can be palpated within the orbit and is of a firm consistency but never tender. Reduction of the eye is rarely possible and marked pulsation does not occur, although a minor degree was present in the cases of Rustizky (1873), Quackenboss and Verhoeff (1906), Ribbert (1904) and Lecène*. The next most common feature is impairment of vision which varies from total blindness to only slight involvement; the mechanism of its production has not been investigated. Diplopia due to restricted ocular movements is less frequent and papilloedema and pupillary changes have been only rarely mentioned. Unfortunately clinical details in several reports are scanty; no accounts of visual fields nor detailed fundus examinations are available. Unlike other malignant orbital neoplasms, and myelomas elsewhere, pain is rarely experienced.

It is important to note that in twelve cases these clinical features were the initial manifestations of multiple myelomatosis, being present alone for several months (one to twenty-four, average eight). When other evidence of myeloma appeared, the process usually proceeded to the rapidly fatal termination that is to be expected in this disease. The shortest duration was three months (Branham and Lewis, 1921) and the longest four and a half years (Greenough, Simmons and Harmer, 1921, Case 52). The latter case is an example of one of the variants of myelomatosis where the course of

*(1919)

the disease is slower than in the classical type. If this case be excluded, the average survival of the patients with primary orbital myelomas (eight cases) was fifteen months. Four were still alive when reported, the longest follow-up being that of Greenough et al. (1921).

DIAGNOSIS.

A myeloma of the orbit must be considered whenever an orbital tumour with bony destruction occurs. Evidence of the disease elsewhere will help in the diagnosis but the overall picture may be closely simulated by a metastasising neoplasm, for the orbit is a favourite site for a secondary deposit.

It is important to be aware of the non-myelomatous, granuloma-like plasma cell masses ("plasmacytomas") that grow in the orbit and may on occasions be confused with true myelomas. Their homologues in the nasopharynx and temporal bone have already been discussed when dealing with the cases of Group I. They grow from the conjunctiva, cornea, lids and lacrimal gland or sac and are in no way related to multiple myeloma. Their differentiation from myelomas is therefore of considerable importance, for it affects both prognosis and therapy. Certain cases of orbital plasma cell tumours found in the literature have been rejected as examples of myelomas because of their doubtful origins.

Despite the opinions of the authors, the cases of Parker (1937) and Francois, Kluyskens and Rabaey (1949) have been excluded. There is some evidence that the orbital mass in each case was a true myeloma and not a granuloma such as Przybylska (1924) described, but neither report includes information concerning full investigations, progress or autopsy.

A further lesion that may have several features in common with the orbital myeloma is the eosinophilic granuloma. It has led to some confusion as is evidenced by the case report of Krümmel (1950), and its localisation within the orbit has been described by Beller and Kornblueth (1951) and Babel (1950. As in the previous groups, however, differentiation should not be difficult.

TREATMENT.

Of the nine patients with primary orbital myelomata (Table V) that are known to have died, two had no treatment, two had medical therapy with no effect upon the course of the disease, and five were operated upon but only partial removal of the tumours was possible and recurrence followed in each instance despite the addition of radiation therapy in three. The surviving patients were given irradiation, either alone or supplemented with surgery. The best form of therapy, however, is probably a judicious combination of

the three modes. Only partial surgical removal of an orbital myeloma would in most cases be possible, but this would be followed by deep X-ray irradiation and a course of urethane. Active treatment of the orbital lesion would be resorted to only if it alone was producing symptoms or the disease was only slowly progressive and the patient's general condition and expectation of life warranted it.

B. SECONDARY MYELOMA OF THE ORBIT.

In these cases the primary focus is in the para-orbital structures - cranial bones, paranasal air sinuses, nose or nasopharynx - and the orbit is encroached upon secondarily. Again, if the case is seen at a late stage it may be impossible to say which structure was affected first, but the initial features of the illness are usually suggestive. Myelomas of tissues adjacent to the orbit will be dealt with in turn. (Table VI).

CRANIAL BONES.

The bones of the cranium are said to be involved in over 70 per cent of cases of myelomatosis (Bayrd and Heck, 1947) and it is therefore not surprising that occasionally a myeloma is found to extend into the orbit. Lesions in the temporal region, which entered the orbit to produce ocular symptoms and signs, have been described by Rustizky

TABLE VI. SECONDARY ORBITAL MYELOMA

AUTHOR SKULL BONE	SEX	AGE	INITIAL CRANIAL FEATURES	OTHER EVIDENCE OF MYELOMA	TOTAL DURATION	TREATMENT	OUT- COME
Rustizky (1873)	M	47	Swelling of tem- poral region	Yes	8 months	None	Death (p.m.)
Ribbert (1904)	M	42	-	Yes	-	-	Death (p.m.)
Locène (1919)	F	55	Swelling left fore- head	Yes	10 months	None	Death (p.m.)
de Harven et al (1927)	F	66	Swelling left tem- poral region	Yes	10 months	None	Death
Lapointe (1929)	M	51	Swelling right frontal region	Yes	-	Irradiation	Unknown
Ibáñez Puiguari et al. (1930)	F	42	Frontal tumour	Yes	5 months+	None	Death
Cseréb & Könyves- Kolonic (1950)	F	63	Pain, ptosis right eye with diplopia	Yes	? 6 months	Irradiation	Alive
Ferrand (1951)	M	38	Swelling in tem- poral region	Yes	2½ yr.	Enuclea- tion DXR	Death
Pages et al. (1952)	M	40	Fronto-temporal tumour & proptosis (L)	Yes	?	Orbitotomy DXR	?
Case Seven	F	60	Headaches and left frontal swelling	Yes	c.5 months	Operation	Death (p.m.)
<u>MUCOSA</u> Hajek (1926)	M	53	Nasal	-	-	Operation	Death (no p.m.)
Pallestrini (1927)	M	45	Mass in R. nasal cavity	Yes	11 months	Operation (biopsy only)	Death (no p.m.)
Holm (1932) (R. orbit)	F	73	Epistaxis and frontal swelling	Yes	-	Irradiation	Death (p.m.)
Saarni (1933)	M	39	Nasal obstruction	Yes	3½ yr.	Operation Irradiation	Death (p.m.)
Tokumitsu & Takigawa (1936) Case 2	M	21	Nasal obstruction and proptosis	Yes	1½ yr.	None	Death
Greenfield (1948)	M	20	Nasal obstruction and cheek swelling	Yes	7 yr. +	DXR	Alive
Fuerste & Zuckerman (1950)	M	56	Nasal obstruction and cheek swelling	Yes	9 months	None	Death (p.m.)

(1873), Ribbert (1904), de Harvon, Murdoch and Cahen (1927), Ferrand (1951) and Pages, Betoulières and Cazaban (1952). Similarly, frontal bone myelomas invading the orbit occurred in the cases of Lecène (1919), Dick (1904), Lapointe (1929), Ibañez Puiggari, Balado and Gaviña Alvarado (1930) and Geréb and Könyves-Kolonics (1950, Case 1); and probably those of Duc (1937) and Krainin, D'Angio and Smelin (1949) also had orbital extensions. In Case Six the events were reversed and the frontal bone was invaded after the orbit. The end result, however, is the same and the only method of differentiating the two groups is by the clinical information. Case Seven illustrates this type of orbital involvement.

CASE SEVEN. Female, 60. 9 months of headache following left frontal injury. 3 or 4 months of left frontal tumour with left ptosis and proptosis. Biopsy revealed a plasma cell myeloma. Bence Jones proteinuria. Partial removal with development of coma and right hemiplegia, not influenced by further decompression. Death. Total survival about 9 months. Autopsy. Myeloma involved sinuses and orbital roof.

All these cases had evidence of myelomatosis elsewhere and the frontal or temporal tumour was usually noticed before the orbit was invaded. The ocular features produced thereby were similar to those already considered in the preceding group. The outcome was much the same as in any other case of multiple myeloma, death being invariably due to generalisation of the disease, which, in fact, was fre-

quently already present when the cranial tumour appeared. Treatment seemed to have little or no effect upon these patients, the methods used being the same as in the previous group.

Myelomas of the bone of the skull base extending forward into the orbit and behaving like space-occupying lesions have been described by Rustizky (1873), Hoffmann (1904), Heilmann (1928), Seemann (1930), Pincoy and Riach (1931, Case 1), and Christophe and Divry (1940, Case 1). The clinical picture is usually complex because cranial nerves and structures other than the orbit are involved, but in at least one of them (Seemann, 1930) the initial diagnosis was that of malignant orbital tumour.

MUCOUS MEMBRANE.

One of the commonest extra-osseous sites for myelomas is the mucous membrane of the upper respiratory pathways (Hellwig, 1943), although here as with the ocular structures there has been considerable confusion caused by authors failing to differentiate between plasma cell myelomata and plasma cell granulomas (plasmacytomas). Ringertz (1938) surveyed three hundred and ninety-one neoplasms arising from nasal, paranasal and pharyngeal regions, and found eleven plasma cell tumours, although it is possible that some of them were not myelomatous. Nevertheless, although

distortion from a distance was common, none is recorded as having invaded the orbit. The patient reported by Hajek (1926) had a myeloma of the frontal and ethmoid sinus, and this had also occurred in the right orbit of a patient reported by Holm (1932). Fuerste and Zuckerman (1950) described a case with a myeloma of the antrum which grew to an enormous size with orbital invasion and hideous facial disfiguration. The myeloma grew from nasal or sinus cavities in the cases of Pallestrini (1927), Saarni (1933), Chase (1948) and Tokumitsu and Takigawa (1936, Case 2); in the last, there was bilateral orbital involvement, a feature which was present also in the patients of Holm (1932) and Dick (1904). A case described by Greenfield (1948) is interesting, for a naso-pharyngeal myeloma is said to have extended to the orbit, but as no radiological or pathological proof is presented, it is possible that there was more than one myeloma present.

The first indications of cranial involvement in these cases were symptoms referable to the nose, and nasal obstruction predominated; it was thus possible to detect the site of origin of the myeloma. As with the cranial bone myelomas, the ocular features developed later but were in no way distinctive except that as with any other tumour originating from the nose or sinus, the globe was displaced forwards and laterally. The local spread of myelomatous

tissue was usually extensive but, apart from the case of Pallestrini (1927) where meningitis was the terminal event, death was due to the generalised disease as much as to the cranial myeloma. As in the other cases of orbital myeloma treatment is not very helpful, especially as the lesions are often deep as well as invasive. The measures described already are adopted.

OPHTHALMOLOGICAL MANIFESTATIONS

It is impossible to deal with the neurological aspects of myelomatosis without considering also the ophthalmological manifestations, for the two are intimately associated. They have not previously been described in detail by ophthalmologist or by physician and they will be gathered together here, although some of them have been discussed already in the foregoing sections. Others that have not been mentioned will be included. They can be conveniently grouped under the following headings:-

- A. Vascular changes in the retina.
- B. Myeloma of the inner eye.
- C. Papilloedema.
- D. Ocular muscle nerve palsies.
- E. Orbital myelomas.
- F. Involvement of the optic pathways.

A. VASCULAR CHANGES IN THE RETINA.

As will be seen later in this work (p. 210), a haemorrhagic tendency may occur in multiple myeloma and the manifestations may be widespread. Of these, the retinal changes are to be considered. Accounts of these are very

sparse in the literature, but this is no accurate measure of their occurrence. Being variable in severity and at times symptomless, their incidence is directly dependent upon the frequency with which ophthalmoscopy is carried out in patients suffering from this disease. It can, however, be stated that changes severe enough to produce marked visual impairment are very rare.

The various vascular complications that do occur are:-

- 1). Thrombosis of the central retinal vein.
- 2). Retinal haemorrhages.
- 3). Thrombosis of the central retinal artery.

These will be considered in turn.

1). Thrombosis of the central retinal vein.

In the patient described by Wintrobe and Buell (1933),- bilateral thrombosis of the central retinal veins occurred and the typical appearances of extreme venous dilatation and extensive haemorrhages were seen. The retinal arteries were thought to be smaller than normal but they were patent. In addition, there was evidence of haemorrhagic disturbances elsewhere, for there had been epistaxis and bruises and petechiae were discovered in the skin. Foreman and Mettler (1947) discuss a very similar case but the fundal appear-

ances were less marked. This ocular complication is fully reported by Walsh (1947, Case 359, pp.1052-1054), who gives an account of a patient with bilateral retinal haemorrhages and partial retinal vein thrombosis in the left eye; the retinae were of a pale yellow colour.

Haemorrhagic glaucoma is a not uncommon complication of retinal vein obstruction, due probably to the excessive transudation of protein-rich fluid derived from venous stagnation, and Jochmann and Schumm (1901) found this condition in their patient.

Foord (1935) showed that by pressure on the eyeball he could slow the retinal circulation in his first patient with myelomatosis; arterial flow could be stopped and venous stasis thus produced. As the latter was occurring, the column of venous blood would break up to give what has of late been termed "cattle-trucking". This is presumably a prodromal stage of the complete vessel occlusion.

2). Retinal haemorrhages.

As in leukaemia, where they occur in about 30 per cent of cases (Schwab and Weiss, 1935), retinal haemorrhages are occasionally found in cases of myelomatosis. Snapper et al. (1953, p.19) found them in eight patients (9 per cent). They may be punctate as in the patients of Foreman and Mettler (1947), Ellinger (1899) and Schindler (1943), but

flame-shaped haemorrhages have been seen by Ellinger (1899), Rosenthal and Vogel, (1936, case 7), Foreman and Mettler (1947) and Loge and Rundles (1949, case 3).

The punctate haemorrhages usually cover the whole retina but they sometimes crowd around the disc, as do the larger variety (see, for example, Loge and Rundles, 1949, case 3). The reverse was the case in the patient described by Bonnet (1947) for the haemorrhages were larger and more numerous at the periphery of the retina and the maculae were also involved. His description is the best in the literature, and he was probably dealing with a case of plasma cell leukaemia. The constricted arteries, the dilated tortuous veins and the pale, oedematous retina suggest that some degree of venous obstruction was also present. It is interesting to note in this case that the two eyes were not strictly comparable in appearance, for the left was the more severely affected. This occurrence in a generalised disease suggests that intra-ocular tensions are involved - as presumably also occurs with some cases of unequal degrees of papilloedema. Bonnet (1947) compares the fundal picture in his patient with that produced by malnutrition, and he points out the very unusual distribution of the haemorrhages; in fact, he states that he has not seen it before. His coloured plates of the fundi (Bonnet, 1947, Planche XIV, fig. 3 and 4) are the only ones of their

kind in the literature.

Cosin (1935) is the only author to describe subhyaloid haemorrhages in myelomatosis. They occurred bilaterally and interfered with vision considerably at first but improvement occurred as they were absorbed.

On rare occasions the retinal haemorrhages may be associated with accompanying hypertension rather than the myelomatosis primarily, and this was so in the patient of Bing (1936, Case 2) in which the retinal lesions had produced blindness. The hypertension and a myelomatous renal lesion preceded the other features of myelomatosis. Boston (1903) describes "a diffuse retinitis" with "sclerosis of blood vessels" in his patient, which was probably of the same aetiology.

3). Thrombosis of the central retinal artery.

As far as can be discovered, this condition does not occur in myelomatosis. Venturi (1901) recorded a patient with unilateral blindness and the fundus was described as revealing "? novrite retrobulbare". This case has been cited on many occasions as an example of central retinal artery thrombosis but perusal of the original report does not suggest this diagnosis. The patient died but the orbits and the eyes were not examined. Although there was evidence of thrombosis elsewhere, for the intracranial

sinuses were also affected, the ocular lesion in this case was probably due to the local pressure of a myeloma.

PATHOLOGY.

The aetiology of these retinal vascular events will be considered when the problem of vascular syndromes associated with myelomatosis is tackled.

The various features outlined are degrees of this same process, venous obstruction. Thus, it may range from "cattle-trucking" to complete central retinal vein occlusion. The retinal haemorrhages are merely a reflection of the venous engorgement consequent upon obstruction.

Unilateral retinal haemorrhages may be the product of venous stasis due to local pressure, as for example in cases of orbital myeloma (Lapointe, 1929), but this type is not to be included with the present group because of the different aetiology.

No histological examination of these changes has been made but the appearances will, presumably, be identical with those produced by other causative agents.

In all of the cases cited, the diagnosis of myelomatosis was above suspicion and there was usually evidence of the disease elsewhere than in the retina. In addition, certain abnormalities related to the haemorrhagic tendency were shared by them all.

CLINICAL FEATURES.

If the haemorrhages are few and punctate, there will be no symptoms and they will be discovered incidentally on ophthalmoscopy. If the macula is involved, however, the patient will note decreased vision which may lead eventually to blindness. The eyes are never equally affected.

There is no information available to assess the prognosis. However, in most of these cases the disease was at an advanced stage and its progression resulted in an early exodus. The blood abnormalities had produced changes elsewhere that contributed to the patient's death.

No treatment has been attempted nor is it possible when the disease is advancing uncontrollably. A vasodilator such as "priscol", which is known to affect retinal vessels favourably (Cholst, Schilback, Handelsman and Levitt, 1952), might however be employed to diminish retinal ischaemia.

B. MYELOMA OF THE INNER EYE.

This form of myeloma is exceptionally rare and, in fact, only one example has been discovered. This was reported by Stock (1918) and concerned the pathological examination of a blind and painful eye that had been enucleated. The tumour lay in the vitreous and was thought to have originated from the choroid. The accompanying photomicrograph seems to confirm its histological nature.

Unfortunately, however, the patient and his subsequent fate are not described and thus one cannot be absolutely certain that he had myelomatosis.

C. PAPILLOEDEMA

This finding has already been noted, for cases of myelomatosis with intracranial encroachment on rare occasions manifest features of raised intracranial pressure (Group II). Thus in ten cases (Meyer, 1913: Meyerding, 1925: Kalischer, 1928: Wilson and Milkman, 1932: Balan and Ballif, 1932: Denker and Brock, 1934: Krainin et al., 1949: French, 1947: James and Turner, 1952: Case Five) papilloedema of varying degree was present as well as other features of intracranial hypertension.

They all had myelomas of the skull vault or the convexity dura mater except the two cases where the lesion grew from intracranial structures (French, 1947: Case Five). Here there were no clinical means of differentiation from other forms of intracranial space-consuming masses until a biopsy examination had been made.

Unilateral papilloedema has been found with orbital myelomas and, like the accompanying retinal haemorrhages, is a manifestation of venous engorgement due to local pressure. It was seen in the patients of Lapointe (1929) and Christophe and Divry (1940, Case 1). Other evidence of

an intra-orbital space-occupying lesion was also present.

D. OCULAR MUSCLE NERVE PALSIES.

When the base of the skull is invaded by a plasma cell myeloma the commonest sequel is the paralysis of an ocular motor nerve.

These lesions have been dealt with already (Brain, Cranial Nerves and Dura Mater, Group I, pp.17-37) and most of the cases to be considered are found in Table I. Cases 1, 2, 5, 6, 7, 9, 11, 12, 14, 15, 18, 19, 20, 21, 23, 24 and 25 had involvement of one or more ocular nerves, but to these can be added cases that could not be included on account of limited data. They may be discussed here and are Case Two, the cases of Venturi (1901), Laesecke (1928), Hellner (1938) and the first two cases mentioned by Snapper et al. (1953, p.34). However, the patients described by Wright (1900), Bloodgood (1906) and Meyerding (1925) had diplopia or strabismus, but as no further details are given they cannot be considered further. Moreover, in Wright's (1900) patient the added effect of tabes dorsalis cannot be conclusively excluded. Pollock's (1934) second patient had a brain stem type of clinical picture and, as is also probably so in Heilmann's (1928) patient, ocular muscle nerve palsies were undoubtedly present, although the authors do not give full case reports.

Some indication of the relative frequency of these nerve palsies has already been given in Table III but the twenty-three cases reviewed above appear in Table VII. It can be seen that the sixth cranial nerve is the most frequently involved and, as revealed by Table III, it is the commonest of all the cranial nerves to be affected by myelomatosis. On one occasion (Langdon, 1939) both sixth nerves were palsied. The fourth nerve was weak in five cases but it only appeared once as a lone finding (Laesecke, 1928), for other eye muscles were usually also affected. Only one example of bilateral third nerve palsy (Delmas-Marsalet, et al., 1951) is on record. In six cases the ocular nerve palsy occurred alone, but in all the others a varying number of cranial nerve palsies accompanied it. Four patients (Table I, Cases 7, 12 and 21: Snapper et al., p.34, second case) were found to have a complete ophthalmoplegia on one side.

The mechanism of the production of these nerve lesions has been discussed already. A basal myeloma compressing the cranial nerve is the essential finding, but it is to be remembered that such a myeloma may involve the orbit directly and produce muscle dysfunction without any actual neural interference. An abducens palsy attributable to increased intracranial pressure, and thus acting as a false-localising sign, has to be considered but has not been reported.

Treatment may dispel the ocular nerve palsy, as in

TABLE VII

The frequency of ocular nerve palsies among 23 cases.

(Including one example each of bilateral third and sixth nerve palsies).

CRANIAL NERVE	3	4	6
NUMBER OF TIMES EACH NERVE PALSY OCCURRED	8	7	20

Case One, showing that at times the process is a reversible one. The effect of therapy, however, must be evaluated with caution because of the spontaneous improvement in the abducens nerve weakness that was a feature in the cases reported by Hammer (1894) and Sparling et al. (1947, Case 21) and was also observed in Case Two. This finding perhaps suggests that the process incurring the nerve palsy is an intermittent one and that the blood supply to the nerve may be subjected to variable degrees of pressure. There was no evidence that the palsy was a false-localising sign.

E. MYELOMAS OF THE ORBIT.

A full description of this ophthalmological manifestation is to be found in the section on Brain, Cranial Nerves and Dura Mater, Group III (pp.63-74). It need only be indicated that two clinical forms exist:-

- 1). Primary myeloma of the orbit, where the patient presents with the features of an orbital neoplasm and the tumour is found to have arisen from the walls or contents of the orbit.
- 2). Secondary myeloma of the orbit, where the patient first notes a para-orbital mass due to a bone or mucosal lesion which later invades the orbit to produce the features of an orbital neoplasm.

It does not seem to be generally recognised that this form of myeloma may be the first sign of multiple myelomatosis. The differentiation of the true myelomatous tumour from the plasma cell granuloma occurring in this region is again emphasised.

F. INVOLVEMENT OF THE OPTIC PATHWAYS.

It is necessary to consider here patients who complained of diminished visual acuity which was not due to any of the conditions already detailed. This was usually on one side only and due to a lesion compressing the optic nerve or, less commonly, the chiasm.

Thus, in Table I there are eight such cases (Case numbers 4, 11, 12, 16, 17, 18, 20 and 25). In three of these (11, 12 and 17) there was complete unilateral blindness, due apparently to pressure on the optic nerve. The development of this state is depicted by Langdon (1939), although his conclusions concerning toxic rather than pressure effects arising from the basal myeloma have already been rejected. His patient first had a central scotoma detectable only with colours, and as the scotoma grew larger vision decreased and pallor of the optic disc increased. The term "retrobulbar neuritis" was used in this case as in that of Venturi (1901) where unilateral blindness occurred, but in each it is certain that the ocular changes were due

to local pressure by a myeloma. Venturi's (1901) case had to be excluded from Table I because of a paucity of information concerning it. In the patient of Christophe and Divry (1940, Case 1) the blindness seemed to be due to gross papilloedema and retinal haemorrhages which, as in Lapointe's (1929) patient, were in turn produced by local pressure of a more acute nature with venous obstruction. As some degree of orbital invasion had taken place, this case should perhaps be included with the cases of orbital myeloma.

The remaining five cases from Table I had varying degrees of visual impairment, and all except Case One had evidence of what was probably optic nerve involvement. In Case One the chiasm and perhaps the optic nerves too were being compressed. In Case 6 of Figi et al. (1945) no details are available, and apart from a contracted temporal field in one eye the patient of Smith and Gault (1948, Case 65) is not described further. Full ophthalmological investigations were, however, carried out in Case One and the results of optic nerve and chiasmal pressure are evident. Vision in the right eye in particular was decreased (finger counting only), the disc was pale and the visual fields (Fig.3) showed evidence of considerable encroachment upon the optic pathways. The most likely aetiological agent in these cases is also local pressure, although Sparling et al. (1947, Case 21) could find no lesion in the optic nerve or

retina to account for the unilateral amaurosis in their patient.

The optic pathways more central than the chiasm were affected in only one case. This was the patient of James and Turner (1952) with a large occipital skull myeloma and a homonymous hemianopia resulting from cerebral compression.

In those cases in which the disease is not advanced, some attempt to save the patient's vision should be made. Surgical decompression of the optic nerve may be necessary as in the case of orbital myelomas and especially if the visual impairment is acute in onset. Otherwise radiation therapy should be used and, as seen in Case One (cf. Fig.3 and Fig.8), a gratifying degree of recovery of vision may be effected.

INVOLVEMENT OF THE SPINAL CORD AND CAUDA EQUINA

Like the skull, the spinal column is frequently attacked in multiple myelomatosis and Batts (1939) found X-ray evidence of it in 70 per cent of his cases. Compared with the skull, however, involvement of the underlying nervous tissue, in this instance the spinal cord and its prolongation the cauda equina, is more common. Pressure upon these structures is thus a not infrequent event. It is, in fact, the commonest neurological complication of this disease if root pain is excluded. Adams et al. (1949) corroborate this impression and an extensive survey of the literature makes it a certainty. Whereas cerebral complications are rare, spinal compression is relatively common. Further, it has been suggested that conditions occur in which spinal cord lesions are produced by changes other than compression.

Spinal cord and cauda equina complications of myelomatosis must, therefore, be dealt with under two headings:-

- A. Cases with extramedullary compression of the spinal cord or cauda equina.
- B. Cases with intramedullary lesions not due to compression.

A. COMPRESSION OF SPINAL CORD OR CAUDA EQUINA.

The clinical picture in these cases is that of spinal cord or cauda equina compression, although the pathological process responsible may vary. Before dealing with these different lesions the literature and the incidence of the aspect of myelomatosis will be dealt with. In these considerations, the term spinal cord refers not only to the actual cord but also to its prolongation within the spinal canal, the cauda equina.

LITERATURE.

In a review of the available literature, one hundred and seventy-seven cases of multiple myelomatosis with compression of the spinal cord or cauda equina were found.

Only adequately verified examples were accepted and it is necessary at the onset to mention seven cases that have been excluded from our considerations. Because of the uncertainty as to the histology, the third case of Arnold (1873) cannot be definitely admitted as a case of myelomatosis, despite the weight of evidence in its favour. That of Bertoye (1904), although almost certainly a true case, was not examined histologically. The case of Kudrewetsky (1892) is often quoted as an example of this complication but it cannot with certainty be accepted.

Howard and Crile (1905, Case 22) described their case as an endothelioma although it had several features of myeloma. There is doubt concerning Case C of Hopkins and Savory (1911) but as the patient was under the care of Dr. James Taylor at the National Hospital, Queen Square, it was hoped that these difficulties would be resolved by consulting the old records. Unfortunately, however, the case notes could not be found. The case report of "de Elizalde and Lambdias, 1913" cited by Geschickter and Copeland (1928) could not be traced, but in any event there was some dispute as to the diagnosis and Wallgren (1920) has rejected it. None of the numerous references given by Schoinker (1951, p.252) could be traced, either by the author's name or by the date cited. Finally, Charlone's (1933) case is suspect on histological grounds.

The case reported by Toušek and Vortel (1947) requires special mention. It concerns a patient with myelomatosis who suffered the sudden onset of a cervical cord compression syndrome. At autopsy there was an epidural haematoma sufficient to compress the cord. Although the authors do not acknowledge the fact, however, the C.4 myeloma, also present, had probably contributed to the spinal compression and the haemorrhage may have been produced by its collapse, as was seen to a lesser degree in the patient of Beck (1942). A thrombocytopaenia was also present and this may have encouraged more extensive bleeding. In any event, this

problem is to be dealt with later when haemorrhagic complications are described (p. 215).

The one hundred and seventy-seven cases have been grouped according to the information that the authors have made available and lists are to be found in Appendix II:-

- A. Cases with adequate clinical and pathological data: 141 cases. These form the main source of data for the ensuing discussion.
- B. Cases deficient in either clinical or pathological details: 24 cases. Some information however is of use.
- C. Cases that are only mentioned and are therefore lacking in both clinical and pathological information: 12 cases.

To this collection are added seventeen cases (Appendix I, cases Eight to Twenty-four) to make a total of one hundred and ninety-four. Their salient features are to be found in Table VIII, from which Case Twenty-four has been excluded because of insufficient pathological data.

In addition, there are eleven further cases either missed during the survey of the literature or published too recently to be incorporated into all the aspects of

TABLE VIII. 16 CASES OF SPINAL MYELOMA WITH CORD COMPRESSION

No.	SEX	AGE	MYELOMA		MULTIPLE OR SINGLE *	PRESENTING SYMPTOM	OUTCOME **	TOTAL SURVIVAL
			SITE	PART OF BONE				
8	M	37	T4	Body	M	Weak legs	A	3 1/2 years +
9	M	37	T4	Body	? M	Back pain	D	6 months
10	M	67	T8	Body	M	Back pain	D	5 1/2 months
11	M	40	C7	Laminae	?	Neck pain	A	12 months +
12	M	54	T2	Bone normal	M	Back and foot pain	D	7 months
13	M	49	L3	Body	? M	Buttock pain	A	2 1/2 years +
14	M	30	T8	Laminae ?	M	Back pain	A	2 1/2 years +
15	F	53	T5	Body	M	Shoulder pain	A	2 1/2 years +
16	F	61	T4	Body	S	Back pain	A	2 1/6 years +
17	F	62	T2 to T4	Bone normal	S	Shoulder pain	A	13 years +
18	M	32	T8	Pedicles	?	Weak legs	A	5 years +
19	F	53	T11	?	M	Weak and numb legs	D	2 years
20	F	48	T2 to T9	?	? S	Back pain	D	3 1/2 months
21	M	57	L1	Body	M	Back pain	A	4 years +
22	F	66	T8	Body	M	Back pain	D	5 1/2 months
23	M	50	L3	Body	M	Back pain	D	8 years

* M = Multiple. S = Single.

** A = Alive. D = Dead.

KC. 1
 H.H. 2
 J.D. 3
 R.S. 4
 L.S. 5
 K.H. 6
 L.A. 7
 S. 8
 K.S.T. 9
 B. 10
 N.W. 11
 G.S. 12
 E.B. 13
 S. 14
 F.H. 15
 J.S. 16
 17
 18
 19
 20

this review. They are detailed at the end of Appendix II. In particular, the contribution of Svien, Price and Bayrd (1953) from the Mayo Clinic is to be noted. Their conclusions correspond closely to those which had already been derived from the present work.

The total number of cases of multiple myelomatosis with spinal compression is therefore two hundred and five.

INCIDENCE.

Few authors presenting large series of cases of multiple myeloma have dwelt in detail on the neurological aspects. Only a few have dealt with the various forms and given an impression of the frequency of each. Unlike other portions of the nervous system, information concerning spinal cord involvement is more plentiful, although not altogether adequate.

It is highly likely that evidence of cord compression is commoner than reported for terminally patients with myelomatosis are bed-ridden and suffer from generalised weakness and malaise, so that minor degrees of muscle weakness or sensory impairment in the legs may be overlooked and sphincter disturbances might not be considered unusual in these desperately ill individuals. Furthermore, they may be too ill and in too much pain to be subjected to frequent neurological examination. Illustrations of this

include the case of Permin (1907, Case 3) where definite cauda equina compression was found at autopsy, but the author denied that clinical features were present during life, despite the occurrence of sciatic pain and absent knee reflexes. In Glynn's (1914) second patient the paraplegia was masked by overwhelming weakness of the disease, and a similar state of affairs possibly occurred in the first case of Dalgaard and Dalgaard (1952), where cauda equina compression found at autopsy had probably occurred terminally but its clinical manifestations had not been observed.

1). Incidence of spinal compression in myelomatosis.

First of all, to deal with the frequency with which cord compression complicates myelomatosis. On surveying the literature, it readily becomes apparent that there is considerable disparity between the figures quoted by various authors. Thus a range of 45 to 5 per cent is found. The former (Kirschbaum, 1947) is much too high and is probably not altogether reliable; this also applies to Coley's (1930) figure of 40 per cent. The 5 per cent, however, is given by Magnus-Levy (1932) when dealing with three hundred and seventy-five cases, and by Sarasin (1950). The 7 per cent of Snapper et al. (1953, p.32), together with the 8 per cent of Rundles and Reeves (1950), suggest that the lower is the more accurate figure. Other authors have estimated a

higher incidence but usually, although not invariably, they have been dealing with smaller collections of cases: Fowler and Gordon (1950), 11.5 per cent of fifty-two cases: Limarzi (1951), 13 per cent of seventy-five cases: Batts (1939), 18 per cent of forty cases: Evans and Johnston (1949), 20 per cent of twenty cases. Unfortunately Geschickter and Copeland (1928), who when surveying four hundred and twenty-five cases were in the best position to give a true incidence, do not subdivide the various complications of multiple myeloma. Bayrd and Hock (1947) similarly group cord compression with root pain, but even so their figure (14 per cent) seems low.

Summarising this divergence of opinion, it seems that about 6 per cent of patients with myelomatosis have sufficient compression of the spinal cord to produce significant paraplegia - that is, enough to make the physician consider surgical intervention, a point emphasised by Rundle and Reeves (1950). These conclusions are adequately substantiated by the recent findings of Svien et al. (1953) who, when surveying a series of five hundred and twenty-four patients, stated that 6 per cent were paraplegic when examined. The actual incidence of spinal cord compression, however, is probably higher and in the order of 20 per cent.

These figures tend to be borne out by a survey of a

small series (twenty cases) of myelomatosis occurring in a general hospital (Hammersmith Hospital). Four had clinical evidence of spinal cord involvement (25 per cent) although only one (5 per cent) had enough to warrant exploration. Thus, if cases are carefully examined a higher proportion of them will be found to have features of cord compression.

2). Incidence of myelomas among vertebral tumours.

From the point of view of spinal column tumours, Schlesinger (1898, cited by Frazier, 1918, Table XX, p.554) reported six myelomas among one hundred and seven cases (5.6 per cent), but any statistics arrived at during the last century must be suspected because the disease was very rarely recognised at that time. However, we have probably not established the true incidence even to-day, for as Mazet (1951) and Young and Funk (1953) have recently shown, vertebral involvement in malignant lymphoma, myeloid leukaemia, secondary carcinoma and myelomatosis occurs more commonly than is usually considered. Full post mortem studies, including microscopic examination of the vertebral bones, will reveal their greater frequency.

3). Incidence of myelomas among spinal tumours.

Considering now all types of spinal neoplasm that produce cord compression, several authors have recorded

their experiences. Thus Elsberg (1941, p.428), whose authority on this subject is everywhere recognised, had seen five myelomas producing rapidly progressive spinal compression. These occurred in his series of two hundred and seventy-five cases of spinal tumour, eighty-one of which were extradural neoplasms. The myeloma, therefore, represented 6 per cent of extradural tumours and Grosz (1925) gave an equivalent figure of 4.8 per cent. Browder and de Veer (1939) reported a similar figure (6.0 per cent), but it should be noted that they were dealing only with malignant epidural tumours and the true occurrence of myelomas cannot be detected. Further, they had only sixteen cases. It is interesting, nevertheless, to note from those authors that the proportion of myeloma to metastatic carcinoma is 1 to 4. Shenkin, Horn and Grant (1945) found that of fifty-four lesions in the epidural space producing cord compression, seven (13 per cent) were myelomas. Only twenty of the total number, however, were neoplasms and thus the true incidence is 35 per cent, which is at considerable variance with the statistics of Elsberg (1941, p.428). It is difficult to account for this disparity, but some of the difference may be explained by the varying sources of the patients. Elsberg (1941, p.428) was working in the Neurological Institute of New York, where he saw carefully selected cases. It is unlikely that patients with general-

ised myelomatosis as well as cord compression would be referred to him, whereas Shenkin and his colleagues were working in a neurosurgical department attached to a large general hospital and would have more experience of them. .

4). Incidence of myeloma as a cause of paraplegia.

Finally, what is the incidence of myelomatous cord compression among all cases of paraplegia of any aetiology? Stratemeyer (1950) supplied some of this information from the autopsy records of the Philadelphia General Hospital. He found that among one hundred and twenty-one examples of paraplegia, in 40 per cent the clinical picture had been produced by epidural metastatic tumours and 5 per cent were cases of multiple myeloma. However, it is not possible to deduce the frequency of the latter among all paraplegics, because only the patients that died were considered.

A few general statements concerning the incidence of spinal cord compression in myelomatosis will summarise the above information. Six per cent of patients have evidence of severe cord involvement but probably in 20 per cent the cord is encroached upon. Myelomas represent a high proportion of malignant epidural neoplasms, possibly about one quarter. These statistics, however, are derived partially from authors who have been dealing with the disease before

the days of bone marrow biopsy and other diagnostic advances. The figures are therefore all likely to be distorted and the accurate incidence will only be detected when all cases of myelomatosis can be diagnosed. This ideal state is gradually being realised.

PATHOLOGY.

It is necessary at the outset to mention seven cases where, despite clear clinical evidence of spinal compression, none was found at autopsy, according to the authors. Wright (1900) reported such a case, which was further complicated by the disturbing evidence of neurosyphilis. Devic and Beriel (1906) described a similar case and Scott, Stanton and Oliver (1933), despite finding extensive vertebral lesions, thought that there was no spinal cord compression. Likewise Schuppli (1939) and Brass (1948) could find no pathological evidence to support the existence of cord compression despite the adequate clinical picture of a focal cord lesion. It is suggested that these incongruous findings are based upon defects of observation, and this was almost certainly so in the case of Stumm (1912) and Donhauser and de Rouville (1941, Case 3). In the latter, the cord was removed by the anterior approach and features of cord compression may have been overlooked. It seems preferable to adopt this explanation of otherwise unaccountable findings and not to hazard

any further conclusions. Schuppli (1939), as will be noted later (p.205), attempted to explain the lack of clinico-pathological correlation by advancing the theory of "toxins". These cases will not be further considered from the pathological aspects.

The Mechanism of Spinal Compression.

There are at least two possible ways whereby compression of the spinal cord or the cauda equina may be brought about, and in each of them myelomatous tissue is found within the epidural space, pressing upon nervous structures. The clinical picture is thus not necessarily dissimilar and the grouping is on a purely pathological basis.

1. Extension of the myeloma from the affected vertebra into the spinal canal.
This may be supplemented by subsequent collapse of the vertebral body.
2. Growth of a myeloma within the epidural space and not associated with adjacent bony disease.

1. Vertebral Myeloma extending into the
Spinal Canal.

This is by far the most common event for, in the literature, it occurred in all but a few of the one hundred and twenty-eight cases where information was adequate. Of the sixteen cases in Appendix I (Cases Eight to Twenty-four) and Table VIII, twelve fit into this group.

In cases of spinal myeloma more than one vertebra may be attacked, and evidence of this may be obtained by radiological, operative and pathological observations. About 60 per cent of the cases reviewed here had single vertebral tumours but it is highly unlikely that this figure is an accurate one. The spine was rarely investigated in full detail and, as noted earlier, a much higher incidence of vertebral involvement in malignant disease is to be expected from more careful study (Mazet, 1951: Young and Frank, 1953). In the rest of the cases more than one vertebra had been attacked, and occasionally it was difficult to find out from the report which lesion was causing the spinal compression.

The various factors involved in producing the picture of spinal compression will now be dealt with in turn.



(a). Site of the vertebral myeloma.

The localisation of the tumours producing spinal compression will be discussed first.

In one hundred and eighty-six cases it was possible to detect the portion of the spinal column that was involved, and this is indicated in Table IX. In one hundred and fifty-seven cases, however, the actual level of the lesion could be determined and their distribution is indicated in graphic form in Figure 2. As several contiguous vertebrae were affected in some cases, it has been necessary to include more than one in some instances, but an attempt has been made to depict only the myelomas that were responsible for the neurological complications.

It is obvious that there is a much higher incidence of compressing myelomas in the thoracic part of the spine than elsewhere. From the total figures in Table IX it might be suggested that this was on account of the larger number of component parts of this portion of the vertebral column. Figure 2, however, shows that there is a greater absolute preponderance of lesions in the thoracic vertebrae. Further, it can be readily seen that T.4, T.5 and T.6 are the most frequently involved and the highest incidence is in the middle five vertebrae, with more at the lower than upper end of this part of the spine. In all, the lower nine bones can be said to be maximally affected and of these

TABLE IX. LOCATION IN THE SPINE OF MYELOMAS
PRODUCING CORD COMPRESSION IN 186 CASES.

CERVICAL SPINE	33	
THORACIC SPINE	127	
LUMBAR SPINE	26	
	186	CASES

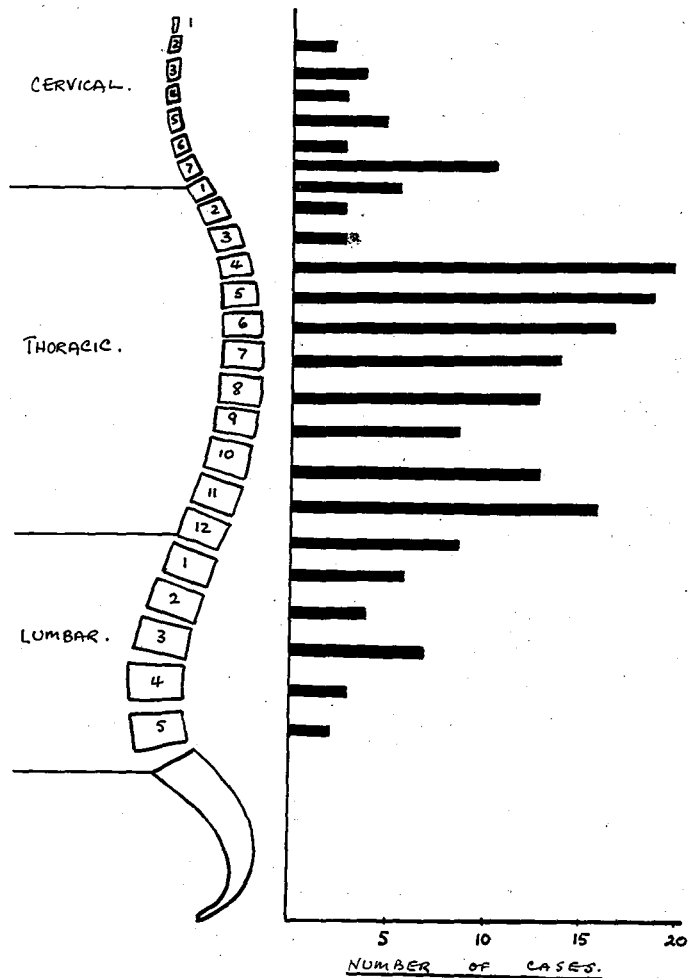


FIG.2. The Location of Myelomas producing Spinal Compression in 157 cases.

T.4, 5 and 6 bear the brunt of the disease, for altogether fifty (about one-third) of the spinal myelomas occurred in them. It is of note that towards the upper and lower portions of the column myelomas became more and more rare, so that its extremities were uncommon sites for these lesions.

These findings partially endorse the statements of Geschickter and Copeland (1928) who incriminated the lower thoracic spine; they also mention the lumbar region but this can be seen to be a less common site. However, Lichtenstein and Jaffe (1947), speaking of vertebral myelomas with and without cord compression, but principally the latter, gave the following order of frequency:- lumbar, thoracic and cervical. The non-compressing lesions are presumably commoner in the lumbar region, a fact borne out by the frequency of low back pain. The location of spinal myelomas is also dealt with by Sproul (1941) when summarising current knowledge. She says that they are commonest in the lower dorsal spine, so that the above findings are again in agreement.

Why this part of the spine should be so frequently the site of myelomas that compress the cord, is unknown. It is of interest to observe (Figure 2) the sudden change in incidence between the first three thoracic vertebrae and the fourth. The degree of movement is not a factor,

because the cervical region is a relatively rare site and T.3 and T.4 are both equally immobile. The varying blood supply to the vertebral bodies may be a factor, but no data on this subject correlated with pathological changes in the vertebrae can be discovered. In fact, the whole subject of the location of spinal tumours is uninvestigated, but it seems to be a useful subject of research. A study of other types of vertebral tumours does not help. Frazier (1918, Table XXI, p.557), when dealing with a series of forty-five primary bony neoplasms of all types, found that half were in the thoracic spine. It can be assumed that this is merely due to the greater number of bones in this part.

(b). Location of the myeloma within the vertebra.

Information derived from both pathological and radiological studies, as well as the operative findings, can be used in dealing with this problem.

Any part of the vertebra may be attacked by a myeloma but lesions of the body are of greatest frequency. This is accounted for by the larger volume of bone available and also by the fact that the disease restricted to this location often produces dramatic clinical, radiological and pathological events and they are thus noticed and described more frequently.

However, other parts of the vertebra are not free

from attack and the laminae and spinous processes have not infrequently been shown to be harbouring myelomatous tissue. Frazier (1918, p.553) notes that about one-third of vertebral neoplasms grow from the arches or other processes. In Bell's (1933) case, the tumour seemed to be arising from these structures and extending into the vertebral canal. Similarly, X-rays showed laminal invasion in the M.G.H. Case Record No.26072 (1940) although the bodies were normal. Kamman (1941) and Snyder and Wilholm (1948) reported cases where the laminae were affected and the third case of Christopherson and Miller (1950) was the same. Case Eleven is a further example and the destruction visible on X-ray was confirmed at operation. The presence of tumour in this portion of the vertebra, however, had on occasions not been detected radiologically and was only discovered by the surgeon when removing the laminae on his way into the spinal canal. The fallacies of bone X-rays in myelomatosis will be examined later when dealing with radiological aspects (p. 140). In some cases the laminal neoplasm was an extension from elsewhere in the vertebra (Case Thirteen), but occasionally the myeloma producing cord compression arose from the bony lesion (Bell, 1933: Case Eleven) and the rest of the vertebra was free from invasion. Sometimes, the only evidence of bony involvement was to be found by inspection of the pedicles when the spine was X-rayed.

(Pines and Pirogowa, 1928, Case 1: M.G.H. Case Record No.24192, 1938: Ectors, 1943: Shenkin et al., 1945, Case 10 and 11: Snapper et al, 1953, p.33). In Case Eighteen, erosion of only one pedicle was found by X-ray (Figure 42) but at operation the body was seen to be included in the myelomatous invasion.

On three occasions it was seen that a myeloma of the posterior part of a rib had eventually involved the adjacent vertebra with spread to the neighbouring bones, and finally had reached the spinal canal to compress the structures contained therein. (Thomas, 1901: Wells, 1921: Ford, 1952, Case Path.12819u-8625).

(c). Osteoporosis of the vertebra.

Occasionally, instead of the more usual focal invasion of the bone, a diffuse process is present and X-rays either reveal normal bones or a picture of generalised osteoporosis which may be severe in degree. Even at autopsy it may be difficult to detect these myelomatous changes macroscopically, and Lichtenstein and Jaffe (1947, Fig. 3B) illustrate such a case. Microscopical study, however, readily indicates the diagnosis, for the bone shows substantial replacement by tumour tissue.

Turner (1921) found considerable rarefaction of the vertebral column in his patient and the appearances probably

approximated to Stumm's (1912) description - "like rotten, worm-eaten wood". In addition, however, there was a readily detectable tumour in one of the vertebral bodies. The French identify the osteoporotic type of multiple myeloma with the names of Weissenbach and Lièvre (1938), and Gilbert-Dreyfus, Mamou and Attal (1947) have reported such a case. The osteomalacic bony changes were widespread and there was spinal cord compression, which the authors were content to attribute to the vertebral osteoporosis. Some collapse of vertebral bodies, however, is necessary to explain the features of cord compression and would readily result from the demineralisation of the bone. In Case Twenty-Four there was a similar state of affairs; the osteoporosis had been so severe that X-rays of the bones were almost impossible on account of their translucency. Of the vertebrae that could be seen, however, several were distorted and the few neurological signs found in this patient were no doubt due to their encroachment upon the spinal cord. Unfortunately, as in the preceding case an autopsy study was not carried out.

(d). Invasion of vertebral and paravertebral structures.

The body of a vertebra may be entirely replaced by tumour, and Wright (1937) describes the appearance at operation of a pulsating mass of tissue that had taken the place

of the bony structure. The tumour tissue can readily extend posteriorly from the body and, having broken through the posterior longitudinal ligament, it reaches the spinal canal. Here it can grow within the epidural space and the results of this extension are twofold.

(1) It soon encircles the dural tube and compresses the cord or roots within. Thus a frequent operative finding is a collar of myelomatous tissue, usually of a greyish red colour and more frequently firm than excessively haemorrhagic, although this latter form does occur. Of interest is the fact that it frequently forms a thicker layer on the posterior than on the anterior dural surface, as also occurs with the exudate of tuberculous meningitis, the tumour cells of carcinomatosis of the meninges and the dural thickening of pachymeningitis hypertrophica cervicalis. Posture is probably not a factor but an increased amount of space posteriorly is a more likely explanation, although this is by no means satisfactory.

Although on occasions, the dura mater may be invaded by myeloma cells and is thus comparable with the cranial portion of this membrane, the cord and roots are never invaded by growth. The latter however may suffer a varying degree of compression. Berblinger (1911, Case) has implied that invasion of the spinal canal can take place without

necessarily producing clinical evidence. This is no doubt correct, but his case is an unhappy example because clinical information was scanty and, on the evidence presented, some degree of neurological deficit could not be definitely excluded.

(2) The tumour tissue may grow out of the intervertebral foramina or extend out of the spinal canal by some other exit and collect in the paravertebral region. Thus it has been found on the anterior surface of the vertebrae (Gaube, 1925: Kirschbaum, 1947: Case Twelve) and this is often in the thoracic cavity. This event will be discussed later when evidence of extension from the extravertebral structures into the spinal canal is being sought. The myelomatous tissue may also spread into the paravertebral muscles and this is frequently encountered by the surgeon as he approaches the epidural space where the main body of the growth is to be found (Case Eight: Case Sixteen: Case Twenty-One). In the latter case, spread occurred around a collapsed vertebral body and formed a mass 5 cms. in diameter with a rim of calcification at its periphery; this, as is often the case, was clearly visible radiologically.

Extravertebral extension of a myeloma may cause serious diagnostic difficulties: these will be considered later. Its presence also complicates therapy, for complete

operative removal is not possible. The importance of supplementing surgery with radiation therapy is thus obvious.

(e). Collapse of the vertebra.

Bony reaction and proliferative changes are not a feature of the relentless progress of bony invasion (See Figures 26 and 27). Thus after some degree of neoplastic replacement of the vertebral body has taken place, whether by the focal or the diffuse process, it is unable to withstand the stresses and strains that the normal bone is called upon to tolerate and therefore collapse with compression occurs. Snapper et al. (1953, p.22) states that by far the commonest pathological fracture is a compression fracture of the spine for they occurred in 48 per cent of ninety-seven cases. In many patients these fractures were limited to the spine. All degrees of the process may be seen ranging from slight wedging to complete collapse and partial disappearance of the body. Case Twenty-two shows the eventual outcome of compression-collapse, for X-rays (Figure 53) demonstrate such a complete collapse of T.8 that its remains are difficult to recognise, for the adjoining bones have squeezed it out of existence. Even at autopsy it was very difficult to identify T.8 and, contrary to the usual findings, the intervertebral disc had also disappeared. Lichtenstein and Jaffe (1947, Fig.8c) illustrate the naked-

eye appearance of these events and Shapper et al. (1953, fig.38) and Raven and Willis (1949) figure similar examples. Case Thirteen, Fifteen and Sixteen of the present series are good examples of vertebral collapse; the progress of events is shown in Figures 26 and 27: 38 and 40: 33, 35 and 36. The local disease progressed in these cases, despite surgical and radiation therapy.

The collapse of a vertebral body containing myelomatous tissue is frequently a dramatic event occurring in the presence of trauma which may be slight. It is manifested clinically by the rapid appearance or the aggravation of symptoms and signs of spinal compression, a picture common to other types of malignant neoplasms of the vertebrae producing bony collapse. Extension into the spinal canal is either produced or accentuated. Case Nine is an example of cord compression produced only by collapsed bone, because myelomatous tissue was not found in the canal.

The force of the collapse, if sudden, may induce local haemorrhage and the patient of Beck (1942), dying soon after a C.5 compression fracture, was found to have a collection of blood in the spinal subdural space that had tracked down to the lumbar region. This phenomenon will be mentioned again when assessing the case of Toušek and Vertel (1947) with spinal haemorrhage.

2. Epidural Myeloma with no Adjacent
Bone Lesion.

If in a case of spinal compression due to a plasma cell myeloma the vertebrae are not diseased, the tumour must originate from one of the following sources:-

- (a). the cord or spinal roots;
- (b). the meninges;
- (c). the epidural tissue;
- (d). the paravertebral structures with extension into the spinal canal.

Each of these possibilities will be considered in turn.

(a). Cord and nerve root.

A characteristic feature of myelomas is that they never originate primarily from nervous tissue and no example is available to dispute this statement, as far as the spinal cord is concerned. In all cases the cord changes were due to pressure from outside the dura mater. Verda (1944) described a "plasmoma" attached to a nerve root, but it was probably associated with the dura rather than the nervous tissue beneath.

(b). The meninges.

The involvement of the spinal dura mater corresponds very closely to similar events in the cranium.

First of all, the membrane invariably resists the myelomatous invasion and no case where transgression has occurred is recorded. Although Stratemeyer (1950) found "neoplastic cells" on the subdural surface and in Case Twenty-two the inner layers of the dura were granular, no deeper invasion has been described. The plasma cells found by Nicholls (1927) in the transverse commissure of the spinal cord are of doubtful significance.

As in the skull, a myeloma of bone may adhere to the surface of the dura mater (Rustizky, 1873), but at operation the connection is found to be a loose one and the tumour can be readily separated. Some authors have described dural tumours in association with local bony disease but the descriptions of this association have not been recorded in detail, so that the extent of each lesion and accurate relationship could not be ascertained (Hammer, 1894: Winkler, 1900: Kaess, 1915). Warstat (1913) found that in addition to vertebral involvement the dura mater was infiltrated with tumour tissue.

The dura was carefully examined by Davison and Balser (1937) in all their cases and in Case 2 there was thickening of the membrane at the site of vertebral collapse. In Case

1, however, these authors believed that the clinical picture was the result of primary dural myelomas, despite the presence of bony tumours. Their concept of pressure by dural myelomas on nervous tissue with the production of avascular changes has been challenged already (p.51) and it seems unlikely that the dural lesions were entirely responsible for the spinal compression in this case. The fourth case of Scott, Stanton and Oliver (1933) deserves mention, for although the tumour causing cord compression was described as dural, the adjacent bones were not discussed. Therefore it cannot be accepted that this lesion was the only one present. However, Stratemeyer (1950) has reported a case of "solitary, extramedullary, plasmacytoma of the spinal dura" and it seems to be the only acceptable one in all the literature. The tumour lay mainly in the epidural space and, on account of infiltration of the dura mater, it was considered that it had arisen from this tissue. Adjacent bony lesions were absent, so the whole clinical picture was the result of this lesion. Although the author may be correct in his conclusions concerning the origins of this myeloma, his assumptions and appraisal of the literature are not entirely acceptable.

Of the cases in the present series (Appendix I) a similar lesion was suspected in Case Seventeen but the operative findings, which will be described later, dispelled

this idea. In Case Twenty there was thickening of the dura mater at the level of the cord compression; this is illustrated by Figure 48. It is worth pointing out again how effective the dural membrane is in halting the progress of myeloma cells.

Thus in a survey of myelomatous involvement of the spinal dura mater, only one acceptable case (Stratemeyer, 1950) of cord compression by a dural myeloma has been discovered. In other possible examples bone lesions have been present or pathological details have been inadequate. It can be concluded that primary dural myelomas of the spine are exceedingly rare but should be considered if bony lesions are absent. There is the possibility, of course, that the bony erosion seen on X-ray and at operation or autopsy may be secondary to a dural myeloma, for it is known (p.41) that similar lesions of the cranial convexity dura destroy the overlying bone and may eventually be difficult to distinguish from osseous tumours. There is, however, only indirect evidence in support of this and no material was available to trace the progression of such events. It seems more likely that in the large majority of cases the myeloma arises from bone and invades the epidural canal secondarily.

(c). Epidural myelomas.

The epidural space is occasionally found to contain benign or malignant lesions (Shenkin, Horn and Grant, 1945) and among the latter is the myeloma. The myeloma secondary to local bone disease has been discussed but the possibility of a "primary" epidural myeloma must be explored.

The anatomy of the epidural space has been considered by Browder and de Veer (1939) and Verda (1944), and the former suggested that although lymphoid elements may be found in this region under normal circumstances, their presence must be a very rare event. Presumably a plasma cell myeloma could arise from these or the lymphatics described by Luce (1923).

The information on this aspect of myelomatous spinal compression is very scanty and that discovered is not entirely adequate. The case reported by Browder and de Veer (1939, Case 6) purporting to be an example of epidural myeloma is not satisfactory because the tumour may have grown from the posterior spinous process of a vertebra. Klemme's (1933) four eligible cases (Case 1, 2, 3 and 4) are not described in enough detail and this is also so with Case 15 of Shenkin et al. (1945). Christopherson and Miller (1950, Case 3) reported a case where the myeloma was considered to be primarily extradural, but at operation it was thought that the bone was invaded. Stratemeyer's (1950)

case has been mentioned already, but although he compared it with other possible epidural myelomas, it is known that the lesion had arisen from the dura. Further, the other cases that he cites are not true primary epidural tumours. Probably the only acceptable case is that of Verda (1944), but here again there are doubts because part of the myeloma was adherent to a spinal root.

Among the cases in Appendix I, Case Seventeen is almost certainly a true epidural myeloma. The vertebrae were normal and the myeloma could be easily removed from the dura mater which it was compressing but not invading. Although full investigations were not carried out on this patient, the fact that she has survived thirteen years suggests that the lesion was a solitary one. Although it is known that a normal bone X-ray does not exclude myelomatous invasion (Heiser and Schwartzman, 1952), the fact that the disease has not manifested itself in any other way over a long period indicates that a bony lesion can be excluded. The second example is Case Fourteen, where again the bones were normal both radiologically (Figure 30) and at operation and an epidural myeloma was extirpated. This would seem to be another acceptable myeloma growing primarily from the epidural tissue. The presence of rib lesions, despite the dispute concerning their nature, suggests a more widespread condition than was present in Case Seventeen. Finally,

Case Twelve must be considered for an epidural myeloma without bony involvement was the main feature. It is possible that the tumour had grown from elements contained within the epidural space rather than from nearby structures.

It is thus possible to suggest that a primary epidural myeloma is a distinct pathological entity and that even in the absence of osseous lesions or evidence of myelomatosis elsewhere, spinal cord compression may be the result of a plasma cell myeloma.

(d). Myeloma extending into the spinal canal.

When sources of a myeloma within the spinal canal have been explored, it remains to consider extension of tumour material into it from outside.

The only definite case illustrating this is the one of Schütz (1914), where a myeloma in the region of the sacro-iliac joint had invaded the spinal canal with compression of the cauda equina. It has been noticed already (p.109) that myelomatous tissue may be found in close relationship to the vertebrae but outside the spinal canal, and it is usually assumed that the growth had originated in the canal and had extended out of it. In three cases (Gaube, 1925; Pines and Pirogova, 1928, Case 1: Kirschbaum, 1947) the vertebral lesions probably accounted for most of the extra-spinal tissue.

It must however be considered that the process may possibly occur in the reverse order and that the original myelomatous tissue was outside the canal, originating in paravertebral structures and then proceeding via the intervertebral foramina to compress the cord or cauda equina eventually. There is no positive evidence of this, despite the fact that the sequence of root pain and spinal compression is a frequent clinical event and may suggest this order of events. The clinical features in cases with no extra-vertebral extension are, however, identical. Cases where a rib myeloma has extended eventually to the spinal canal (p.106) have all included destruction of the vertebra.

There is thus no good evidence to support the thesis that an epidural myeloma in the absence of bony lesions could have originated outside the spinal canal.

Having considered this aspect of the pathology at length, it can be concluded that in the absence of vertebral involvement an epidural plasma cell myeloma is known to occur. The evidence suggests that it originates either from the tissue of the epidural space itself or from the spinal dura mater.

Solitary Myeloma.

As with myelomas elsewhere, it seems profitless to continue the argument as to whether cases in the literature or past cases had true solitary lesions. More precise diagnostic techniques have recently shown that a "solitary" myeloma is frequently but a part of a more widespread disease, and prolonged follow-up has usually shown the single lesion to be a fore-runner of the generalised disease. However, a lengthy period of observation, during which time no further developments are manifest, is suggestive that the myeloma is genuinely solitary. Dalgaard and Dalgaard (1952) and Rogers (1953) have recently emphasised the point that although spinal compression may be a solitary feature of myelomatosis it does not remain alone for long and after a varying length of time dissemination occurs. Unfortunately, there is no method of telling which myeloma will remain single for years and which will soon be followed by a shower of multiple lesions. The histological appearances of the two types are identical in every way.

It should first be noted that certain authors have published cases purporting to be examples of solitary myeloma but which do not comply with the usually accepted criteria (Abel, 1941).

The spinal column seems to be a favourite site for solitary myelomas, because Paul and Pohle (1940) found that of forty-five examples fourteen were in the spine. Again the difficulty arises as to whether these were true solitary myelomas, and Raven and Willis (1949) have reviewed the problem more critically. They report that, together with their cases, there are only five that can be accepted if the rigid criteria are adhered to. Only two of these patients (Walthard, 1924; Raven and Willis, 1949) had spinal compression.

Information from the analysis of the literature shows that of one hundred and forty-one cases thirty-one (almost one quarter) had no evidence of the generalised disease; but in the majority of these the investigations had been few and the follow-up usually short, so that definite conclusions cannot be drawn.

Of the sixteen cases forming the basis of the present report, ten had undoubtedly multiple lesions, and among the remaining six, three (Cases Eleven, Thirteen and Eighteen) had insufficient information. Case Twenty-three is instructive in that a spinal myeloma was treated with apparent success and three or four years later one might have thought of the lesion as a solitary one. However, eight years after the first symptom appeared the patient died of multiple myelomatosis. The cases that are left are Case Sixteen and

Seventeen, but in the latter follow-up observation has not been extensive. Thus only Case Sixteen can be considered as a genuinely solitary myeloma, probably of epidural origin, as discussed already. The patient has survived thirteen years from the first symptoms of cord compression and is still alive, thus lending support to the view of Christopherson and Miller* that a solitary myeloma does, in fact, exist but is very rare.

Amyloidosis associated with Myelomatosis.

The association of amyloidosis with multiple myeloma is a not uncommon occurrence and will be dealt with in detail shortly (pp.193-198). It may be found in the substance of the myeloma and such tumours have occurred in the vertebrae. The amyloid substance aids in the weakening of the bony structure, so that collapse may more readily take place. In addition, by increasing the myeloma's bulk it may assist in the spinal compression. Cases illustrating these complications will be discussed later. Other than supplementing the effects of the myeloma, the amyloid plays no other role in the disease involving the spinal column.

*(1950)

The Spinal Cord Lesion.

The only changes found within the spinal cord or roots are those due to direct pressure, and the histological picture is in no way different from that produced by any compressing lesion. Only a small section of the cord may be involved with few features of local pressure, but on the other hand, the cord may be extensively damaged both in its length and cross-section; for example, there was disorganisation of the spinal cord from T.2 to T.9 in Case Twenty. The alterations in the cord elements are due to compression ischaemia as well as venous obstruction. In Case Twenty there were petechial haemorrhages, due presumably to the latter process.

The amount of myelomalacia is dependent upon the degree of compression and also upon the local blood supply of the cord. Inconsistencies in cord levels have been explained by variations in spinal cord arteries. In particular, this is used to account for the not infrequent occurrence of an upper thoracic sensory level produced by a cervical compressing lesion.

Only on one occasion were tumour cells found within the cord (Nicholls, 1927) but the significance of this finding has already been questioned. Otherwise, there is no

evidence in any of the cases in the literature or in the present series that a spinal myeloma may extend through the meninges to involve the cord more intimately. Fig. 47 shows how the dura prevents trans-theecal invasion. As with the brain, a plasma cell myeloma arising from spinal cord tissue has not been described, nor would it be expected as there are no nervous tissue elements that could serve as progenitors to this tumour.

Summary of Pathology.

1. The commonest lesion producing spinal compression is extension of a vertebral myeloma into the spinal canal.
2. A primary dural or epidural myeloma exists.
3. The thoracic spine is the commonest location, and the lower nine vertebrae, but in particular T.4, 5 and 6 are the most frequently affected.
4. Osteoporosis may be the only bony finding clinically but spinal compression can still be brought about.
5. True solitary myelomas producing spinal compression are excessively rare but probably exist (Case Sixteen). Otherwise dissemination of the disease ensues at a distance of months or several years, if the generalised disease is

not already present.

6. Spinal myelomas never transgress beyond the dura mater and their effects upon the spinal cord are due solely to local pressure.

CLINICAL FEATURES.

The clinical picture can best be appreciated if a typical case history is outlined. The type of case described here is that in which spinal compression is the first manifestation of the disease multiple myelomatosis. This is the commonest and is seen most frequently by neurologists and neurosurgeons in the first instance. The other variety of case is that in which the march of events is reversed and begins with myelomatosis and ends with spinal compression.

Typical Clinical Picture.

The patient is usually a man of middle age or older, who first complains of pain in the back or the neck. This is not an infrequent event in myelomatosis, but in these cases it is very severe and, although somewhat diffuse at first, soon becomes well localised and takes on the characteristics of spinal root irritation. Thus girdle or limb pain is experienced either spontaneously or only with movement, coughing, straining or similar actions. Little relief

is forthcoming and after some months of agony he notes weakness or sensory disturbances or both in his lower extremities. These symptoms are progressive and may be associated at their onset with mild trauma. Gradually he becomes paralytic and anaesthetic and the sphincters, if not involved already, share in the dysfunction and become paralysed. He has the classical motor and sensory signs of spinal compression, the picture produced depending upon the level of the lesion. In addition there is local tenderness of the spine, perhaps with gibbus formation. He is doubly incontinent. His general condition depends upon the presence or absence of other features of myelomatosis.

If active therapy is not instituted, he will rapidly die of one of the sequelae of paraplegia or a combination of this with manifestations of the generalised disease. Even if he is relieved of spinal compression, he will probably die months or perhaps years later of multiple myelomatosis, for which no effective therapy is at present available.

It is important to point out at this stage that the clinical picture produced by the various pathological possibilities is essentially the same. Thus the osseous and the extra-osseous myeloma of the spine cannot be differentiated by the history and the physical findings alone. Differentiation must await the special investigations and surgery.

Material.

In the consideration of the clinical features of spinal myelomas with cord compression the group of cases in Appendix IA and B will be referred to (one hundred and sixty-four cases), but as the amount of information concerning them varies in quantity, it will be rarely, if ever, possible to use them all at one time. To them may be added the sixteen cases of Appendix I where the data is complete. One hundred and eighty cases are thus available. Additional clinical details are to be found under "Course and Prognosis" (p. 155).

Sex.

Of one hundred and seventy-seven patients, there were one hundred and thirty-two males and forty-five females, thus demonstrating the preponderance (3:1) of males that is seen in any large series of cases of myelomatosis.

Age.

The age was known in one hundred and seventy-five cases and the largest number of patients occurred in the sixth decade (47 patients), the fifth (42), the seventh (39) and the fourth (29). This represented 90 per cent of the total number of cases. The youngest patient was that of Zäh (1952) and was aged six, whereas the oldest (Moeschlin,

1943, Case 4) was eighty-four.

Cosacesco (1948) has claimed that the initial lesion in myelomatosis is found in the vertebrae more commonly in children than in adults. There is, however, no evidence to suggest that cord compression is also a frequent event in childhood, for in the whole series only three patients were aged less than twenty years. Although the total number of children attacked by this disease is not known, it seems reasonable to assume that if this author was correct, cord complications would be more common in this age group.

Initial Features.

To deal with this aspect of spinal myelomas, it is necessary to divide the cases into two groups:-

- (1). Those in which myelomatosis began with features of spinal compression.
- (2). Those which begin in the usual manner and spinal compression appears as a later complication.

(1). Patients presenting with spinal compression.

These are the patients dealt with initially by the neurologist or neurosurgeon, either because of apparently exclusive central nervous system involvement, or because

of rapid neurological deterioration they are in need of urgent surgical intervention. Thus Cases Eight to Twenty-three were observed in neurological departments, both medical and surgical.

In some, the spinal lesion may be the only pathological feature detectable, but if the patients are observed long enough the disease multiple myelomatosis develops and eventually proves fatal. It is thus of some importance to realise that the very first manifestation of myelomatosis may be a spinal myeloma with cord compression. If such is verified at operation, a vigorous and extensive search for latent evidence of the disease must be made. Even so, cases occur in which all the methods available at this time fail to show any abnormality other than the spinal one, yet the patient later succumbs to the widespread process. The defect here is in the investigative methods which are not yet sensitive enough to detect all varieties of the disease at an early stage.

Patients with spinal compression as the first indication of multiple myeloma can be further considered in two categories according to the outstanding clinical features:-

- (a) Patients presenting with back or limb pain followed by other signs of spinal compression.
- (b) Patients without pain but with a typical picture of progressive cord compression.

(a) Pain and focal neurological features.

This group comprises the vast majority of cases, for among one hundred and thirty-two patients (Appendix IIA) ninety-four (71 per cent) had pain as a presenting feature, and of the sixteen patients in Appendix I thirteen reported that their illness began in a like fashion. Thus about three quarters of the patients with spinal compressing myelomas complained of local pain in the earliest stages.

Their first complaint was pain in the back, limbs or in the neck, and its location gave some indication of the site of the impending neural complication. This symptom will be examined in more detail later. It was followed or accompanied by root pain and, after a variable interval, by symptoms and signs of spinal compression such as are produced by any type of compressing lesion.

From this sequence of events the pathological changes can be visualised. The back pain is a product of local bony invasion and distortion of the posterior longitudinal ligament by myelomatous tissue. Next follows pressure upon adjacent spinal roots, and finally the spinal canal is invaded and cord symptoms and signs make their appearance. This march is seen with other osseous tumours and likewise in cases of prolapsed intervertebral disc.

(b) Focal neurological features.

These patients suffered no preceding pain and were found to have a picture indistinguishable clinically from spinal compression from any cause. They were considerably rarer than those of the preceding group. Their first symptoms were referable to their limbs or sphincters and were without exception progressive in nature.

In the literature (Appendix IIA) there are one hundred and thirty-two cases where the first symptom was known and of these twenty (15 per cent) were first seen on account of painless spinal compression. Of the sixteen cases in the present series (Appendix I), three (Case Eight, Eighteen and Nineteen) gave a similar history; the incidence here is 19 per cent.

Thus it can be expected that in somewhat less than one fifth of patients with cord compression complicating myelomatosis, the disease will begin with limb or sphincter troubles before any other symptoms of the disease appear. Pain in these patients is conspicuous only by its absence.

(2). Patients developing spinal compression later in the course of myelomatosis.

Here the usual uncomplicated course of myelomatosis is witnessed, but at some time before death a myeloma of the spine produces spinal compression. It appears against a

background of the generalised disease. There are in the literature at least nineteen such cases, found among the one hundred and thirty-two referred to above (14 per cent). In some of them, it was possible to make accurate estimates of the time relationships. On an average, spinal compression appeared three or four months after the onset of the disease elsewhere in the body, but exceptions are not infrequent. In Seegelken's (1897) patient, cord symptoms developed fourteen days before death, the disease having been present for more than one year. Paraplegia appeared in Lumb and Prossor's (1948, Case 6) patient four years after the onset of the generalised disease. It was frequently observed in these patients that death rapidly followed the spinal complication, especially if this was of acute onset.

In conclusion, the commonest initial feature was pain in the back or root pain (71 per cent), and the next was evidence of cord compression (15 per cent). The remaining group (14 per cent) contains cases where the spinal compression developed after the onset of myelomatosis and therefore appeared as a late complication of the disease.

Pain.

Pain is the most prominent feature of myelomatosis for Snapper et al. (1953, p.21) found it in 92 per cent of

their ninety-seven patients. It is characteristically bone pain and its localisation to the back is a frequent occurrence. The same authors (Snapper et al. 1953, p.21) give the incidence of back pain as 75 per cent and Geschickter and Copeland (1928) quote a similar figure - 70 per cent - of patients afflicted with pain in the lumbar and sacral parts of the spine. Evans and Johnston (1949) supply some relative statistics. Of their twenty patients, twelve had backache and ten of these had collapsed vertebrae but only three of the latter group developed paraplegia. Further Lawrence and Wasserman (1950) report that eight of their twenty-four patients had backache but only one of these showed evidence of spinal compression.

First, the low back pain that is so characteristic of myelomatosis will be considered. It has usually been accepted that it is always due to an underlying bony lesion, but the statistics of Evans and Johnston (1949) and the opinions of other authors suggest that this may not always be the case. Further evidence against it is available, for whereas low back pain is very common, spinal myelomas of the lumbar region that progress to spinal compression are relatively rare. This pain varies in intensity and duration. It is usually diffuse in the lumbosacral region but may be associated with spinal root pain, and in these cases a myeloma must necessarily be present. It can be located

elsewhere in the spine and may be indistinguishable from the pain that precedes spinal compression.

The latter is localised to the area of the spine involved by the myeloma, and its site usually points to the level of eventual cord compression. Thus pain in the upper thoracic spine, frequently described as between the shoulders or more on one side than the other, is a frequent symptom in these patients and is to be expected when the high incidence of cord-compressing myelomas in this region is considered (Figure 2). Pain in the neck radiating into the arms suggests a cervical cord lesion and muchal rigidity is often present. Similarly root pain occurs frequently in the legs. However, as will be seen in the next section, root pain often exists alone without any evidence of more central neurological complications and its presence does not necessarily foretell cord pressure. There may or may not be a "girdle" type of pain especially in the thoracic region, again due to the greater frequency of lesions in this part. Another feature of this kind of pain is that it tends to be more severe and more constant (Lichtenstein and Jaffe, 1947). Thus constant and severe back pain with elements of root irritation are highly suggestive of a spinal myeloma that may at some time extend into the spinal canal to produce spinal compression.

In at least five cases (Permin, 1907, Case 3: Wall-

gren, 1921, Case 4; Davison and Balser, 1937, Case 3; Case Fourteen and Case Twenty-four), there was a long history of backache and leg pain that far antedated the present illness, the onset of which was somewhat masked thereby. It seems likely that an independent lesion, such as a prolapsed intervertebral disc, would account for these disparities and the presence of one in Case Fourteen was confirmed on myelography.

With the onset of symptoms and signs of cord compression, the back and root pain occasionally decreased, and in a few patients it disappeared entirely (Case Eleven).

The Spine.

Symptoms referable to the spinal column are almost invariable in cord compression complicating multiple myeloma, and signs are often present too.

Local tenderness of the spinous processes at the site of pain is frequent and at times these bones may be sufficiently prominent to create a small gibbus. Percussion usually produces root pain of great severity, and rigidity of the back, as an attempt to minimise the agony, is often seen (Bernard, Paget, Bera, Henninot and Samain, 1946, Case 1; Stratemeyer, 1950). Stiffness of the neck with a T.1

myeloma has also been described (Petrides, 1939, Case 1). Palpation may reveal a local mass (Davison and Balser, 1937, Case 3; Mody, 1943, Case 2) produced by extravertebral spread of the myelomatous tissue. In Case Twenty-One, such a tumour was discovered overlying L.1 and at operation this was shown to be a surface outcrop of the intraspinal myeloma.

When instead of local myeloma formation in the spine there is a diffuse osteoporosis, kyphosis with or without scoliosis rapidly manifests itself. This occurred in the patient of Gilbert-Dreyfus, Mamou and Attal (1947) and also in Case Twenty-four (Figure 58). The process, which has recently been studied in senile persons (Dent et al., 1953), effects an approximation of the thoracic cage and pelvis and is a common finding in patients with myelomatosis, without evidence of spinal compression. Thus Kahler's (1889) original patient had a pressure sore under the chin due to the foreshortening of the neck allowing the chin to rest upon the sternum; spinal compression did not occur. As has been mentioned, however, compression may be produced by this spinal change.

Features of Spinal Compression.

The symptoms and signs of this process do not differ from those produced by similar spinal lesions. Their onset,

however, is frequently dramatic and at times associated with trauma (p.137) or lumbar puncture (p.145). This is explained pathologically by sudden collapse of a diseased vertebra with the extrusion of bone and myelomatous tissue into the spinal canal. In cases where there are no such changes, sudden alteration in the blood supply of the cord would produce a similar picture, but here again pressure from an extra-osseous myeloma would be necessary to explain it. In those cases where there is an acute onset of cord compression, the prognosis is often bad because extensive and irreversible destruction of the cord takes place. The patient is rendered paraplegic, and therefore a prey to the various complications of a severe cord lesion. There is always a steady progression of symptoms and signs in these cases, and only one author (Meyerding, 1925, Case 9) thought that an improvement had taken place, although no therapy had been employed.

Other patients note a slow onset of symptoms, but whether of rapid or slow occurrence the paraplegia brings with it all the attendant infections and other consequences that usually end fatally. If in addition multiple myelomatosis progresses or appears, survival is further limited.

Relationship to Trauma.

The initial features of myelomatosis may be closely

related to trauma, an association that Geschickter and Cope-land (1928) found to be present in 20 per cent of their cases. In the cases under discussion here, it plays a definite role but, with perhaps a few rare exceptions, it acts by aggravating an already existing spinal lesion.

In all, twenty-one patients out of one hundred and thirty-one (16 per cent) showed a definite association between the onset or aggravation of neurological features and trauma.

That a pre-existing myeloma of the vertebra is necessary seems obvious, and the mechanism of the fracture is the same as in other bones of the body. In the child described by Záh (1932), an X-ray of the cervical spine taken after a fall resulting in neck pain, revealed extensive bony involvement which had obviously been present for some time although symptomless.

After noting the fragile state of the diseased vertebrae, it is not surprising that the trauma necessary to produce vertebral compression need be only trivial. Thus a sudden jerk of the head produced by the abrupt stopping of a street-car resulted in collapse of the seventh cervical vertebra and cord compression (Simmonds, 1931). Lifting was sufficient to traumatise the diseased vertebrae in at least three patients. Carrying a bag on the head (Váradí, 1937, Case 3), pulling on the arm (Codounis, 1949, Case 4),

a shoulder injury (Rosselot and Decker, 1936), reaching (Carlson, 1936, Case 3), a sudden wrench (M.G.H. Case Record No.24192, 1938) and a mild fall in four patients was sufficient to produce vertebral collapse and spinal compression. Beck (1942) describes how a simple process such as lifting a patient was sufficient to result in vertebral compression fracture. Similarly, in Case Twenty-two the patient was being lifted in bed and after this procedure rapidly developed a paraplegia. In at least two cases (Wallgren, 1920, Case 5; Dalgaard and Dalgaard, 1952, Case 2) a pre-existing paraplegia was rendered complete by a mild injury.

The patient was frequently aware of the dramatic event and that something had happened in his back. Thus the sensation was described as "a snap", "something giving way", etc. but there was rarely any increase of pain at this time.

It is only fair to point out that on the other hand, collapse of vertebral bodies diseased with myeloma has taken place at times of rest, as is exemplified by the M.G.H. Case Record No.20031 (1934) and the patient of Glynn (1914, Case 2) where spinal compression took place suddenly while the patient lay peacefully in bed.

A further aspect of this problem is the occurrence of a myeloma in an already traumatised vertebra. Thus in Case Twenty-one, the patient had suffered a crush fracture of the

body of L.1 four years before the disease began. There can be no doubt that this episode was unrelated to the myelomatosis. However, when the latter appeared it was the deformed L.1 vertebra that was first attacked (Figures 49 and 50) and spinal compression followed. The same state of affairs probably existed in the patient described by Flax (1941) in whom the first lumbar vertebra was also the affected bone, the fracture having been sustained about thirty-six years before myelomatosis began. It seems that myelomas are more likely to grow in traumatised, and therefore devitalised, tissues and this relationship is seen more frequently in other parts of the body than in the spine. Thus local trauma seemed to be closely related to the cranial myeloma in Case Seven. Various types of trauma have been incriminated, and included are such diverse influences as hypodermic injections and duodenal ulceration (Fuorste and Zuckerman, 1950). As regards chronic inflammation, it is of interest to note that in Albert's (1951) second case the spinal myeloma developed at the site of old inflammatory disease, probably tuberculous. There is no doubt that this was a genuine plasma cell myeloma, for there was other evidence of myelomatosis.

RADIOLOGICAL APPEARANCES.

The radiological changes have been partly considered

when dealing with the pathology of spinal myelomas.

(1). Plain radiographs.

According to Paul and Pohlo (1940) there are two main radiological forms of myeloma of bone. One is cystic and trabeculated, whereas the other is osteolytic and more destructive. It is the latter type that occurs most frequently in the vertebrae. There is a considerable variation in the degree of osseous change that can be demonstrated. It may range from erosion of only one pedicle (Case Eighteen, Figure 42: Sparling et al. 1947, Case 18) to complete destruction of the whole vertebral body so that its outline can no longer be discerned (Case Twenty-two, Fig. 52 and 53). M.G.H. Case Record No. 26072 (1940) showed only laminal involvement, and in Case Eleven instead of the osteolytic region being mainly in the body it was in the laminal and spinous processes but was extending anteriorly into the body. Figure 49 shows a similar appearance.

The classical type of osteolytic tumour is well-illustrated in Case Thirteen (Figures 26 and 27). The myeloma is situated in the body of L.3 and is of the so-called "soap-bubble" type. There is a complete absence of bony reaction at its edges, which distinguishes it from other malignant processes. A similar "punched-out" lesion was described by Hilton (1936, Case 1).

After the local myeloma has reached a certain size, the vertebral body collapses. This sequence of events is illustrated by Case Sixteen; first of all, there is an alteration in the texture of the vertebral body (Figure 38) indicating the presence of neoplastic tissue, but as extension continues collapse takes place (Figure 40). Case Fifteen is similar but here some of the changes may have been influenced by surgery and radiation therapy. Figure 33 shows the body still maintaining its normal shape but in Figure 35, six weeks later and following operation, compression-collapse has occurred. Eighteen months after operation considerable sclerosis has taken place and stability is being established (Figure 36), a state of affairs also demonstrated by Figure 56 which shows a sclerotic vertebral body seven years after treatment. In this regard, it is of interest to note that in myelomatosis fractures tend to heal well, and it has been suggested (Snapper et al., 1953, p.24) that this may be due to the increased serum calcium level commonly present in this disease.

Extension of the myelomatous tissue out of the spinal canal and into the paravertebral structures, or involvement of the latter by direct extension from diseased bodies or laminae, produces a soft-tissue shadow in the X-ray. This, taken in conjunction with the bony destruction so often present, immediately suggests the diagnosis of tuberculosis

of the spine. In Case Twenty-One, a paravertebral shadow was seen (Figure 50) and a shell-like calcification delineated its periphery, although this is not clearly demonstrated in the photographic reproductions.

In some cases, osteoporosis may be the only radiological finding, and this was so in Case Twenty-four where the process was so severe that photographs of the X-rays could not be obtained. As explained earlier, compression collapse of the vertebrae so affected is common. Snapper et al. (1953, pp.55-57) found that in seven of their ninety-seven cases there was diffuse demineralisation of bone, and the papers by Wallerstein (1951) and Heiser and Schwartzman (1952) discuss this aspect of myelomatosis.

On rare occasions in multiple myelomatosis no X-ray changes at all can be detected, and the latter authors found this to be the case in 13 per cent of their sixty-six patients. Nevertheless, widespread disease may be present but only found by histological study (Wallerstein, 1951). Of the present cases, in Case Seventeen there was no radiological evidence of a spinal myeloma, and the lengthy survival (13 years) suggests that myelomatosis was not present. In Case Twelve and Fourteen, however, there could be less certainty because in the latter at least the vertebrae were not examined adequately. The upper thoracic spine is a difficult region to visualise radiologically and tomography,

employed by Layaní, Aschkenasy and Nadal (1952) and in Case Sixteen (Figure 38), may be necessary.

(2). Myelography.

As in any case of spinal compression, this procedure is usually necessary to localise the lesion accurately and define its extents, especially if bony disease is absent or doubtful. In Case Fourteen (Figures 30 and 31) the column of radio-opaque material demonstrated that the myeloma lay mainly posteriorly in the spinal canal. Myelograms are also reproduced in Figures 43, 45 (Case Eighteen), 46 (Case Twenty) and 50 (Case Twenty-one).

CEREBROSPINAL FLUID.

The C.S.F. in myelomatosis will be dealt with in more detail later (pp.223-237). It can be noted here that the only characteristic finding among these cases was the classical "compression syndrome".

A complete or partial manometric block (confirmed by myelography) and a yellowish fluid containing an increase of protein, often with a high globulin content, was frequently found but was in no way distinctive. Cells were very rarely increased in number, the highest figure of forty (30 polymorphs and 10 lymphocytes) reported by Davison and Balser (1937, Case 1) being an isolated example. The second high-

est figure was sixteen (Potrides, 1939, Case 1) but in the vast majority of cases the cell count was normal. Busser and Bugaut (1937) reported an occasional mononuclear cell but plasma cells have never been mentioned. In the cases of Appendix I pleocytosis was never found. The Lange was abnormal in eight cases (see p.233) and the W.R. positive in two.

In three cases (Davison and Balser, 1937, Case 9; Browder and de Veer, 1939, Case 6; McMahon, 1951, Case 6) the lumbar puncture caused rapid deterioration in the patient's state with marked increase of neurological symptoms and signs.

DIFFERENTIAL DIAGNOSIS.

This is primarily a matter of differentiating between the various lesions that produce spinal compression. This subject may be discussed in two parts according to whether the bones are involved or not. Adequate radiological studies will readily separate the two. The cases under discussion here are all those that present with spinal compression and only later show signs of myelomatosis. It is during these early stages of the disease that the diagnosis may be difficult and this is reflected by the fact that in the cases recently reported by Svien et al. (1953) not one had been correctly diagnosed prior to operation. Likewise, with the

cases of Appendix I, a pre-operative diagnosis was unusual.

(1). Cases with involvement of the bone.

Here, the commonest mistake is to confuse a spinal myeloma with tuberculosis of the spine, and this happened on at least thirteen occasions among one hundred and forty cases, as well as during the early stages of Case Twenty-two. The picture of a locally destructive osseous lesion producing pain, gibbus formation and cord compression with a paravertebral soft tissue shadow belongs to both spinal myeloma and Pott's spine. Walch (1949) was so impressed by this similarity that he attempted, with little justification, to popularise the term "faux Pott" proposed by Delchef. Cosanescio (1948) likewise emphasised the many similarities and suggested that several cases termed Pott's disease may well have been examples of spinal myelomas. Confusion, however, should only occur at the early phases of the condition and adequate investigations usually reveal the true answer.

Other varieties of vertebral neoplasms must be considered and the most common in this age group is the metastatic carcinoma (Warstat, 1913). Search for the primary neoplasm usually resolves the problem. Lichtenstein (1952, fig.113, p.233) shows a vertebral neoplasm at first thought to be a giant cell tumour but which was proven to be a

myeloma. Paget's disease of the spine should not cause trouble, except when associated with multiple myeloma as in the patient of Hanisch (1950).

Osteoporosis of the spine occurring in myelomatosis should be differentiated from that of senility (Aegerter and Robbins, 1947).

Once collapse of a vertebral body has taken place, the primary bony process may be undetectable unless evidence of myelomatosis is forthcoming elsewhere.

(2). Cases with no bone changes.

In these cases a firm diagnosis cannot be made until a histological examination of the epidural tumour is carried out; but even then difficulties may arise, as happened in Case Eighteen where a non-specific granuloma was at first suspected.

A patient complaining of root pain followed by cord compression, in the absence of gross bony lesions, is likely to have a prolapsed intervertebral disc, and Harrington and Maloney (1950), Limarzi (1951, Case 1) and Otenaseck (1953, Case 6) have recorded this aspect of the differential diagnosis of spinal myelomas. The lesions may co-exist as has been mentioned (p.134).

(3). General considerations.

A cervical cord compressing lesion may produce an upper thoracic sensory level (Walker and Bloom, 1937, Case 5 and others) and this anomaly has caused a considerable amount of confusion in a few cases of spinal myelomas. Davison and Balser (1937, Case 12) suggested that the presence of multiple tumours of the leg bones could simulate paraplegia (cf. Sparling et al., 1947, Case 21, and hemiplegia) but this would seem to be an unlikely diagnostic hazard.

Various other diagnostic possibilities have occurred in the past. We need only mention tabes dorsalis (Jellinek, 1904; Guggenheimer, 1924, Case 1) a mistake that is unlikely to be made to-day.

The ultimate diagnosis, as in all other forms of plasma cell myelomas, rests with the histologist, and the physicians search for evidence of myelomatosis elsewhere. Direct puncture of the vertebrae as practised by Layani et al. (1952) and Dalgaard and Dalgaard (1952) may be of value in selected cases.

TREATMENT.

Of one hundred and seventy-seven cases (Appendix IIA - 140; Appendix IIB - 19; Appendix I - 16) only ninety-seven received adequate therapy and eighty-four the results

of this could be assessed.

The survival periods have been divided into groups ranging up to five years or more, and the responses to the various forms of treatment have been tabulated in Table X. The patients have been divided into those that were dead and those alive when the author published their case reports.

As it has not been possible in all cases to calculate accurately the post-therapy period, a crude and less reliable method of surveying survivals has been used. It was usually possible to determine the overall length of the disease, and all that we can obtain from Table X is an impression of the survivals occurring as influenced by therapy. Despite the statistical insufficiency of this method it points out the broad principles of therapy in this complication of myelomatosis.

Each treatment will now be considered in turn and the results of therapy in the sixteen cases from Appendix I will be analysed closely.

(1). Medical measures.

These included Coley's serum (Thomas, 1901), stilbamidine (Baker and Casterline, 1948; Bichel, 1950, Case 9; Layani et al., 1952; Greenwald, Bronfin and Auerback, 1953, Case 1: Case Nineteen), urethane (Rundles and Reeves, 1950, Case 12; Bichel, 1950, Case 9), radioactive isotopes

TABLE X. RESULTS OF VARIOUS FORMS OF THERAPY IN 84 PATIENTS WITH SPINAL COMPRESSION COMPLICATING MYELOMATOSIS.

SURVIVAL PERIODS	OPERATION		D.X.R.		OPERATION + D.X.R.		MEDICAL THERAPY	NO TREATMENT
	DEAD	STILL ALIVE	DEAD	STILL ALIVE	DEAD	STILL ALIVE		
0-5 months	8 *	-	1	-	1	4	1	26
6-11 "	4	2	-	-	-	3	-	15
12-23 "	5	3	-	1	3	3	3	10
24-35 "	-	3	1	1	3	4	1	1
36-47 "	2	1	-	-	1	4	-	2
48-59 "	2	-	1	1	1	3	-	-
5 years +	2	1	-	-	3	7	-	1
TOTALS	23	10	3	3	12	28	5	55
	33		6		40		5	

* 4 Post-operative.

(Lawrence and Wasserman, 1950) and spinal supports. They were usually used in conjunction with other remedies but occasionally they were used alone. The results (Table X) cannot be evaluated because of the small numbers. The drugs used, although uniformly disappointing, were not entirely useless and the reduction of pain with some prolongation of life has been reported by several authors. The spinal support occasionally decreased back pain owing to the immobility produced, but it was more often employed after operation to effect greater stability of the spine.

(2). Surgery.

This invariably consisted of a laminectomy to expose the tumour, and in most cases as much as possible of it was removed, thus providing an internal as well as an external decompression. At times, only a biopsy was taken because of the obvious naked eye appearances of malignancy, and it was never possible to remove the myeloma completely because of its invasive qualities, its continuity with a bony tumour or its extension through an intervertebral foramen. When bone was not involved, or minimally so, a greater degree of extirpation was possible. Occasionally spinal roots had to be sectioned to allow a better exposure. Other procedures such as a costo-transversectomy (Wright, 1937; Campbell, 1951) and various stabilising procedures did not seem to pro-

duce any additional benefit.

The results of decompressing the spinal cord or cauda equina were at times dramatic and within a few days recovery was taking place in previously completely paralysed legs or sphincters. Cases Eight, Fourteen, Seventeen and Twenty-three illustrate this gratifying recovery and there are similar examples in the literature: Snyder and Wilhelm (1948) describe the post-operative course of their patient as "spectacular". If recovery in cord function did not take place or was deficient, there was almost always a complete abolition of root pain so that the patient was much more comfortable, although perhaps still severely incapacitated. Rare exceptions to this, however, have been reported and it is important to note that although a decompressive operation did not dispel the pain of the patient described by Davison and Balser (1937, Case 2) radiation therapy did so.

Evaluation of the results of surgery in thirty-three patients (Table X) shows that, firstly, there were four post-operative deaths which occurred from a variety of immediate complications, not all of which were associated with the spinal myeloma. If these are excluded it can be seen from Table X that thirteen had died by the end of the second year of their disease and five were still alive. Only one patient lived more than five years.

(3). Radiation therapy.

This was used alone in six patients but combined with surgery in forty. Deep X-ray radiation was the usual form administered. Radium was used by Osgood (1923), Peyton (1934, Case 1), Cutler et al. (1936, Case 19), Wright (1937) and Campbell (1951) but it seemed to have no additional advantages. Details of radiation therapy in cases of myeloma with spinal compression have been given by Peyton (1934, Case 1) and Hilton (1936, Case 1). A combination of surgery with irradiation proved to be the most popular form of treatment (forty cases). Operation invariably preceded the latter because it not only verified the diagnosis histologically, but it also provided a decompression should there be post-irradiation oedema of the spinal cord.

Where radiation therapy was employed alone, four of six patients lived more than two years. Of the forty patients subjected to surgery and radiotherapy together, seven were still alive five or more years after the onset of the disease and only four had died in the first two years.

(4). Results of therapy in sixteen patients.

Accurate assessment could be made of the cases in Appendix I. The therapy used, the outcome and total survivals are indicated in Table XI.

TABLE XI. RESULTS OF THERAPY IN 16 PATIENTS WITH SPINAL COMPRESSION COMPLICATING MYELOMATOSIS

No.	PRE-THERAPY PERIOD	THERAPY *	OUTCOME **	POST-THERAPY SURVIVAL	TOTAL SURVIVAL	PRESENT STATE	MULTIPLE OR ***SINGLE
8	3 months	OP. DXR.	A	5 years	3 1/2 years	Rate unknown	M
9	-	None	D	-	6 months	-	? M
10	-	None	D	-	3 1/2 months	-	M
11	10 months	OP.	A	1 month	12 months +	Rate unknown	? M
12	6 months	OP.	D	5 weeks	7 months	-	M
13	4 months	OP. DXR.	A	2 years	2 1/2 years +	Working	S
14	12 months	OP. DXR.	A	1 1/2 years	2 1/2 years +	Working	? M
15	12 months	OP. DXR.	A	1 1/2 years	2 1/2 years +	Excellent state	S
16	6 months	OP.	A	2 1/2/12 years	1 1/2 years +	Quadrilegic	S
17	12 months	OP. DXR.	A	12 years	13 years +	Excellent state	S
18	4 months	OP. DXR.	A	1 1/2 years & then recurrence	5 years +	Working	? M
19	9 months	DXR. Drugs	D	-	2 years	-	M
20	6 weeks	OP.	D	2 days	7 weeks	-	? S
21	2 years	OP. DXR.	A	2 years	4 years +	Working	M
22	5 months	OP.	D	4 years	5 1/2 months	-	M
23	3 months	OP. DXR.	D	8 years	8 1/2 years	-	M

* OP. = OPERATION
DXR. = Radiation therapy

** A = Alive
D = Dead

*** M = Multiple
S = Single

In Cases Eight and Eleven, the patient's fate is unknown, and if these are excluded seven of the remaining fourteen are dead and seven are alive. Of the former, two had no treatment and two died very soon after operation. The rest of the seven are Cases Twelve, Nineteen and Twenty-three. The first had surgical treatment only and the second was given radiation therapy alone. The third, Case Twenty-three, is a typical example of a patient with an apparently successfully treated "solitary" spinal myeloma dying some years later of dissemination of the disease.

Of the seven survivals, Case Seventeen should be excluded because this is probably a true solitary myeloma, and although the treatment is the same the prognosis is necessarily at variance with that of other types. Case Sixteen was rendered quadriplegic on account of post-operative complications. There remain five cases, each of which was given radiation therapy after a decompressive operation. They are all alive and in excellent health, the average survival being three and one-third years. At least four of them have returned to work, which is a satisfactory measure of their rehabilitation. It is however to be noted that of these cases three were known to have the generalised disease despite their apparent good health, and in another investigations had been inadequate.

The results of therapy in this smaller series suggests

the same form of treatment indicated above - a combination of surgery and radiation therapy. It may be objected that the patients who survived had in any case the less malignant variety of the disease, but although definite statistics cannot be quoted the impression gained is that the survivals were not uninfluenced by the forms of treatment employed.

(5). Recurrence of the spinal myeloma.

Recurrences of myeloma are to be expected and a few patients had to have second operations (e.g. Ghormley and Pollock, 1939, Case 6 and Svien et al., 1953, Case 7). Altogether, seven patients had a return of symptoms and signs of cord compression after having made a good post-operative recovery. This usually occurred within a few months and often radiation therapy had not been given. A good example of these events is Case Eighteen, for an initial diagnosis of granuloma was made and deep X-ray therapy was not given. The patient returned sixteen months later with an extensive recurrence.

(6). Conclusions concerning therapy.

In the last column of Table X the fate of fifty-five untreated patients is depicted in a striking fashion. Fifty-one of them (93 per cent) were dead by the end of the second year of their disease. The equivalent figure for the

treated cases is eighteen out of forty-nine patients (37 per cent). The advantages of therapy are thus obvious.

Conclusions concerning treatment of this neurological complication of myelomatosis can be more definite than with the other varieties. While realising that the disease process has a set pattern in each individual, there is evidence to suggest that its course can at least be influenced by therapy. Pain can be relieved and there may be considerable return of function; even in the presence of the generalised disease the results may be rewarding, as has been emphasised very recently by Svien et al. (1953).

All patients, except those in the terminal stages of the disease, should be given the benefit of active therapy and from the above findings it is suggested that a combination of surgical decompression and radiation therapy is the treatment of choice. Although Svien et al. (1953) advocate surgery they do not mention the radiotherapy that was also given to all but one of their seven patients. If the patient's condition does not warrant surgical intervention, irradiation or one of the histio-toxic drugs should be used to allay pain (cf. Case Nineteen).

COURSE AND PROGNOSIS.

It will be most convenient to discuss this topic under separate headings.

(1). Interval between onset of pain and spinal compression.

The period during which the patient complained of pain alone varied considerably. Thus in Case 21 of Rundles and Reeves (1950) it was three years and in Case 15 of Shenkin et al. (1945) it was two, yet in Case Nineteen pain was the presenting symptom for only five or six weeks and in Case Nine for four. During this interval the pain was usually mounting in severity.

(2). Progression of spinal compression.

The speed with which the features of spinal compression developed likewise varied from months to days. In Case Twelve, a complete paraplegia with sphincteric paralyses became evident over a period of only two days. This rapid progression was usually seen when trauma was involved, but did not necessarily influence the post-operative prognosis. However, occasionally the neurological manifestations developed in a much less dramatic fashion and the patient noticed the gradual onset of limb weakness, sensory disturbances and trouble with the bladder or bowels. What was achieved in a few days in the previous cases took a period of weeks or months. Presumably sudden bony collapse or vascular lesions of the cord were not factors in these cases. Case 18 of Cutler et al. (1936) illustrates how slow the process of spinal compression may be, for the patient noted very

few changes in his state over a period of ten years, despite the presence of vertebral collapse.

(3). Period during which spinal compression antedated other features of the disease.

In most instances this could not be estimated because some manifestations of multiple myelomatosis, such as Bence Jones proteinuria, abnormalities of serum proteins or scattered, small bony lesions, are symptomless and their initial appearance cannot be dated. The limits, however, appear to be six years (Jacox and Kahn, 1933, Case 1) to one month (Laesecke, 1927). Dalgaard and Dalgaard (1952), describing the terminal dissemination occurring with "solitary plasmacytoma", show in their second case that symptoms of spinal compression may exist alone for several years before the disease becomes generalised. Similarly, in Case Twenty-three the patient had been successfully treated for a spinal "plasmacytoma" five years before multiple myeloma appeared and had been active and healthy during the intervening period. No recurrence of the spinal tumour had taken place.

(4). Period during which the general disease antedated spinal compression.

This has already been discussed (p.131) when it was pointed out that, although variations occurred, the average

interval between the onset of the disease and the development of cord compression symptoms was three to four months. These symptoms existed either a few days or several months before the patient died, the influence of therapy being excluded. Death was usually a rapid sequel to spinal compression when it occurred in the presence of other features of the disease.

(5). Total survivals.

The total survival could be estimated in one hundred and thirty-eight cases (Appendix IIA, 122; Appendix I, 16). All these cases, treated or untreated, are collected in Table XII, where similar survival periods as in Table X are used.

The period varied from a few weeks (Zäh, 1932 - 4 weeks: Schuppli, 1932 - 4 weeks: Kirschbaum, 1947 - 7 weeks: Case Twenty - 7 weeks: Stratemeyer, 1950 - 9 weeks: Batts, 1939, Case G.H. - 10 weeks) to sixteen years (Wright, 1937 and Campbell, 1951) or more, because this patient was still alive when his case was reported. The occurrence of a cervical cord compressing myeloma, as with other such lesions in this region, resulted in a rapidly fatal outcome (Zäh, 1932 - 0.5; Castleden, 1948 - 0.4).

A quarter of the cases died within five months of the onset of the disease and a fifth survived five years or

TABLE XII. SURVIVAL OF 138 PATIENTS WITH SPINAL
COMPRESSION COMPLICATING MYELOMATOSIS.

SURVIVAL PERIODS	CASES			
	SURVIVALS	FATAL	TOTAL	
0-5 months	4	33	37	
6-11 "	5	22	27	
12-23 "	8	18	26	
24-35 "	7	8	15	
36-47 "	5	5	10	
48-59 "	3	6	9	
5 years +	8	6	14	
	40	98	138	TOTALS.

more. Altogether three-quarters were dead two years after the first symptom.

Separate mention must be made of Case Seventeen, for the patient has now survived thirteen years and is in the best of health. It appeared that in this case the lesion was a true primary epidural myeloma and the length of survival suggests that it was a genuinely solitary lesion. Presumably if this tumour is adequately extirpated the prognosis is excellent, providing irreparable cord damage has not been incurred.

(6). Death.

The death of ninety-eight of the one hundred and thirty-eight patients is recorded. In many it was directly due to the spinal compression; broncho-pneumonia, infected bladder and bedsores were the usual terminal events in treated and untreated cases. In some patients, however, generalisation of the disease heralded the end; this was seen for example in Case Twenty-three, and death occurred eight years after the removal of a spinal myeloma.

From the cases where it was possible to detect the actual mode of death, the following information is available:-

Death due directly to paraplegia	-	13	patients
" " to multiple myelomatosis	-	7	"
" post-operatively	-	4	"
" from recurrence	-	2	"
" " incidental diseases	-	<u>4</u>	"
		<u>30</u>	patients

On the whole, it appears that the addition of spinal compression to multiple myelomatosis makes a rapidly fatal disease even more deadly. If, however, a spinal myeloma is the first indication of the disease, the prognosis is not necessarily bad and some remarkable survivals have been reported. It is in these cases that therapy is imperative.

B. NON-COMPRESSING LESIONS OF THE SPINAL CORD.

These need only be mentioned here for completeness. Ellinger (1899) describes grey degeneration in the posterior columns of the spinal cord but there is no clinical information given. Magnus-Levy (1932) however thought that this was probably due to neurosyphilis, of which there was some evidence, and further, a severe anaemia was present and this may also have been a factor. The only mention of plasma cells within the spinal cord is made by Nicholls (1927). In his patient, the vertebrae were affected but no encroachment upon the cord had taken place; yet in the transverse comm-

issure were cells identical with those that were forming the myelomas. As an isolated finding it seems of little value.

Included in this group of extreme rarities are the cases with spinal cord changes due to "toxic" influences. They are to be considered together with similar cases where other parts of the nervous system are involved (p. 199).

CONCLUSIONS

1. Compression paraplegia occurs in about 6 per cent of cases of multiple myelomatosis but probably 20 per cent represents the incidence of cord involvement of all degrees.

2. The commonest cause of spinal compression is extension of a myeloma from a vertebra, with or without collapse.

3. On rare occasions a primary dural or epidural myeloma may produce the same clinical picture. Bony disease is absent (Case Seventeen).

4. Myelomas occur most frequently in the middle and lower portion of the thoracic spine, T.4, 5 and 6 being the commonest sites.

5. In the present series, 86 per cent of patients had spinal compression as an initial feature of multiple myelomatosis, whereas 14 per cent developed this complication after the onset of the disease.

6. Pain is a presenting feature in 71 per cent of patients belonging to the former group.

7. In 15 per cent there is painless spinal compression.

8. The clinical and radiological features closely resemble spinal tuberculosis, and even paravertebral abscess is simulated by extravertebral spread of a myeloma.

9. Trauma is a significant aetiological agent in 16 per cent of cases. Usually it aggravates a pre-existing lesion, but on rare occasions the myeloma appears to be directly due to it.

10. Treatment by surgical decompression and radiation therapy is the most successful and should be employed in selected cases even if the disease is widespread. Local recurrences are few.

11. 93 per cent of patients die within two years of the first symptom if they are not treated.

12. A rapidly fatal outcome is the usual result of spinal compression occurring when myelomatosis is established, but where it is the first sign of the disease the prognosis is better.

INVOLVEMENT OF THE SPINAL ROOTS

Affection of the peripheral components of the nervous system is a common neurological complication of multiple myelomatosis.

When studying ninety-seven patients with myelomatosis, Snapper et al. (1953, pp.33-34) found that fifteen (15 per cent) showed clinical evidence of lesions of the peripheral nervous system. Most authors agree that pain, which is a characteristic feature of the disease, is often due to root or nerve irritation. Here, the spinal roots will be considered and the effects of root compression will be discussed first. Herpes zoster is a special feature of this and will be described separately.

SPINAL ROOT COMPRESSION

Encroachment of myelomatous tissue upon spinal roots has already been considered. When spinal myelomas were dealt with, those that compressed the cauda equina were described, as well as root compression occurring in conjunction with spinal cord compression. However, cases with a single root involvement without cord or cauda equina complications must now be discussed. The distinction is

perhaps artificial because the one is but a stage of the other.

INCIDENCE.

Five of the fifteen cases of Snapper et al. (1953, pp.33-34) referred to above had uncomplicated root pain, but it seems likely that the symptom is commoner than these authors suggest if the whole course of the disease is considered. It has been seen that root pain is an almost constant accompaniment of spinal compression. Following the localised back pain indicative of vertebral body invasion, it may precede other symptoms by weeks or months. A typical example is Case Twelve, where the diagnosis for some months was "spinal root syndrome of undetermined aetiology". By the localisation of the pain it is usually possible to predict the site of impending spinal compression if such is the order of events; but, in addition, neuralgic type of pain may extend into the territory of any of the spinal roots without further neurological sequelae.

PATHOLOGY.

The pathological process in these cases is one of pure mechanical compression of spinal roots - a process that was found by Jacox and Kahn (1933, Case 1) at operation and described in detail. The third lumbar root was com-

pletely encircled by tumour, and this appearance was frequently seen during operative removal of epidural masses of myelomatous tissue that had produced spinal compression. Extension into an intervertebral foramen was seen not infrequently. The basic lesion in those cases is a myeloma of the vertebra with or without bony collapse, and Fowler and Gordon (1950) recording vertebral body compression in thirteen patients found that eleven of these had root pain as a direct consequence. The sequence of back pain, root pain and finally spinal compression is readily appreciated by the order of symptoms. A myeloma may extend into the paravertebral space and nerve trunks close to the spine may be implicated. There is usually radiological evidence of this, and on one occasion the distortion was demonstrated by excretion urography. It is possible however to have typical root pain without compression of the bone, and indeed without the usual widespread destruction of vertebral structure. Lichtenstein and Jaffe (1947) mention this and Fowler and Gordon (1950) describe two patients with "sciatica" where only diffuse bony involvement without collapse occurred. The mechanism in these cases was not evident, but lesions producing pain that were not discovered radiologically and the incidental occurrence of a prolapsed intervertebral disc cannot be entirely excluded on the evidence furnished. Weber (1903) was impressed by the spinal distortion that

often developes in this disease, and he suggested that many of the pains suffered by the patients were due to pressure on the posterior spinal roots by the kyphotic spinal column.

Another pathological process has been described by Bender (1902, Case 3), for this author found that the roots forming the sacral plexus had been infiltrated by tumour cells. This has been observed so rarely that doubt may with reason be cast upon the findings and the diagnosis in this case.

Finally, Scheinker (1938) rather than explain pain by the local mechanical involvement of roots or peripheral nerves, preferred to consider "toxins" elaborated by the tumour and affecting the sensory nerves, as being responsible. This would appear to be an unlikely postulation; there is considerable evidence of root irritation but there is little to substantiate the "toxin" theory in this respect.

CLINICAL FEATURES.

The principal manifestation of root compression is pain. This may be localised to one root or occur in several according to the amount of spinal column involvement, but it is invariably intense in nature and one of the characteristics of the disease; Kahler's (1889) famous physician-patient exemplifies this. So severe was the pain in the patient of Jacox and Kahn (1933, Case 1) that he was rendered delirious

and Heuss (1929) has described a patient who eventually committed suicide on account of it. Pain may be the only feature of root irritation, but often paraesthesiae and sensory impairment as well as muscle wasting and weakness also develop in the distribution of the root affected.

The location of the root syndrome, like spinal compression, is obviously determined by the site of the spinal column myelomas. Examples from each region will be cited. Although root pain is one of the classical components of the clinical picture of myelomatosis, detailed descriptions of such events are rare and the following are the only ones available in the literature.

(1). Cervical root involvement.

A syndrome of cervical root irritation occurred in the patient of Boston (1903) but no pathological findings were discussed. Rosenthal and Vogel (1937-1938, Case 11) report a case where cervical root pain was produced by collapse and compression of the body of C.6, and Nelson (1952, Case 6) found that pain in the distribution of C.2 and C.3 was due to the same pathological process in C.3 vertebra. In both of these patients there was hyperaesthesia in the territory of the affected spinal roots. The myeloma in the patient of Petrides (1939, Case 3) had grown from a cervical vertebra and was extending into the supraclavicular

fossa, with the production of root symptoms and signs in the left arm as well as a possible Horner's syndrome on the same side. The roots of the brachial plexus were probably involved, and the same process may have explained the findings in this author's first case as well as the cervical "radiculitis" described by Batts (1939) in one of his patients.

It is difficult to evaluate the sixth case of Davison and Balser (1937). They speak of brachial plexus compression suspected clinically and verified pathologically but give no description of it. Further, there are certain features suggestive of a peripheral neuropathy and the case will be referred to later (p.179). There is similar doubt concerning the case of Torchio (1915) for a "peripheral neuritis" of the brachial plexus, not due to mechanical irritation, was described but not accounted for.

(2). Lumbar root involvement.

(a) Upper roots.

There are two cases where the third lumbar vertebral body was destroyed by a myeloma and a clinical picture of L.3 root irritation was produced. The patient, already alluded to (Jacox and Kahn, 1933, Case 1), first noticed back pain and lumbar kyphosis and only later suffered increasingly severe leg pain in the distribution of L.3 with

appropriate sensory impairment. At laminectomy, the root was surrounded by tumour tissue, and relief from pain was obtained by its removal and section of the second and third lumbar roots. Later, however, the disease spread to involve adjacent parts of the spine. Dalgaard and Dalgaard (1952, Case 3) describe a similar case where there was extra-vertebral extension of the myeloma and later involvement of more than the L.3 root.

(b) Lower roots and lumbosacral plexus - Sciatica.

Here lesions affecting the lower lumbar and sacral spinal roots and their extensions into the lumbosacral plexus are to be considered. They are involved by local myelomas with the production of leg pain which is usually of a typical sciatic type. Its resemblance to "sciatica" is indicated by the statement of Macintyre (1850): "the affection to which it bore the nearest resemblance was a severe attack of lumbago or sciatica".

Sarasin (1950) found three examples among thirty-seven cases of myelomatosis; they had been diagnosed as having sciatica because the disease presented with this clinical picture. Batts (1939) mentions four cases of sciatica in his series of forty cases, and Sloan et al. (1946) had one among twenty-one. The patient of Rundles and Reeves (1950, Case 19) had findings so closely simulating sciatica that a

laminectomy for a prolapsed intervertebral disc had been resorted to. Boston (1903) described a patient with "sciatica" and Brownell (1950, Case 20) another. In the latter, invasion of the nerve by tumour was seen at autopsy, this being one of the very few such reports.

Myelomas of the sacrum accounted for the pain in at least four cases. In the patient of Hansen (1922, Case 1) it destroyed the lower three segments of this bone on one side with the production of pain in the distribution of the sacral roots; the mass could be felt by rectal palpation. Typical sciatic pain was the result of the same localised process in the patient of Ghormley and Pollock (1939, Case 5), but here the root pain was preceded by backache, thus simulating closely a prolapsed lumbar intervertebral disc. The sciatic notch and adjacent sacrum were destroyed in Moore's (1925) third case and the pain so produced was in the distribution of the sciatic nerve. Deep X-ray irradiation did not arrest the growth of the tumour, which eventually filled the iliac fossa on one side. Petit-Dutaillis, Messimy and Pertuiset (1947), dealing only with the French literature, could find no such example other than their own. The patient presented with "sciatica" and destruction of the sacrum was found. Laminectomy revealed compression of the L.5 root and myelography had demonstrated distortion of the lumbar sac. None of these cases progressed to the extent of that of Schütz

(1914), where the sacral tumour eventually compressed the whole cauda equina.

Other cases in which sciatica was a prominent or presenting feature have been included among the spinal myelomas, and obviously any division of these cases in which cauda equina roots are involved by local myelomas will be an artificial one. Permin (1907, Case 3) described "sciatica" as being the sole manifestation of the disease for a long period, and bilateral sciatic pain preceding further symptoms (Bonhard, 1914) is not unusual when lumbar roots are invaded.

Tumours of the pubic bones, if they extend into the region of the lumbosacral plexus, also produce "sciatica". Thus myelomas of the innominate bone (Leedham-Green, Bromley and Raban, 1938) manifested themselves only by "sciatica" for years, and in the patient of Berard, Martin, Pollosson and Ponthus (1937) a tumour growing from the ilium eventually reached the size of a foetal head and compressed pelvic nerves. Similarly, a large iliac bone myeloma produced pain and then paralysis of one leg in the patient of Hoffmann (1904).

DIAGNOSIS.

It is important to emphasise that a "sciatica" syndrome may be the only manifestation of myelomatosis for months or, exceptionally, years, and the presence of a

myeloma in the early stages can only be detected by radiological or other investigations. Collapse of a body may not be present but some evidence of the disease is always forthcoming. Confusion with the common prolapsed intervertebral disc is easy (Rundles and Reeves, 1950, Case 19) but, as mentioned already, "sciatica" in a patient with multiple myeloma does not necessarily indicate root involvement by a local tumour; a prolapsed disc may be present in addition.

All other causes of root involvement are to be considered but the diagnosis can only be substantiated by histological proof, and Dalgaard and Dalgaard (1952) affected this by direct vertebral body puncture.

TREATMENT.

Treatment is only to be considered in conjunction with the disease as a whole - as in any local manifestation of myelomatosis. Laminectomy was carried out in two patients (Jacox and Kahn, Case 1, 1933 and Petit-Dutaillis et al., 1947) but the effects achieved were only temporary. In the former rhizotomy was practised, and in both radiation therapy supplemented the surgical intervention. Pain could thus be dispelled. Deep X-ray irradiation achieved good results in two patients (Moore, 1925, Case 3, and Leedham-Green et al., 1938) and in the latter calcification occurred

in the tumour after therapy. Urethane was employed by Nelson (1952, Case 6) with good relief.

It is the aim in those patients to release them from the agonising pain that above all the other symptoms of myelomatosis distresses them most. Radical measures should therefore not be shunned; root section with local radiation therapy and one of the histiotoxic drugs that frequently dull the pain must be made use of despite the poor prognosis in the majority of patients. Prefrontal leucotomy to alleviate the patient's response to pain may at times be of use.

HERPES ZOSTER

A secondary as well as a primary type of herpes zoster is known to occur. It has been described in various diseases that involve the spinal column; trauma and spinal tuberculosis (Head and Campbell, 1900), secondary carcinoma (Pendergrass and Kirsch, 1949) and Hodgkin's disease (Pancoast and Pendergrass, 1924) have been found responsible. It therefore seems reasonable to suppose that similar events should be found with multiple myelomatosis.

LITERATURE.

Bomhard (1914) mentions two authors who reported

this complication - Spiethoff and Bloch - but they have not been traced. The disorder could not be found in the case report of Conti (1911) despite the statements of Geschickter and Copeland (1928). Three or four cases had been seen by Magnus-Levy (1938), and Langdon (1939) mentioned three. There are, in addition, ten cases that have been described in some detail to be found in the literature.

Another case (Case Twenty-five, Appendix I) is added to these.

CASE TWENTY-FIVE: Male, 65. Left T.8 herpes zoster occurring one year after onset of disease and one year before death. T.7, 8, 9 and 10 vertebral bodies collapsed. No root pain. Autopsy confirmed spinal lesions: no examination of nervous system.

There is no material available to estimate the true incidence. Magnus-Levy (1938) states that it was present in "three or four cases" and we know that he was dealing with about three hundred and seventy-five cases. On the other hand, Langdon (1939) found "peripheral neuritis with herpes zoster" in three cases out of a series of twelve. These seem to be the limits of its occurrence.

PATHOLOGY.

Pathological reports describing the posterior spinal roots or their ganglia are not available in cases of myelomatosis complicated by herpes zoster. It is to be noted, however, that the skin lesion was frequently related in

location to a myeloma in the appropriate part of the spine (Bomhard, 1914; Wintrobe and Buell, 1933; Kinney, 1940, Case 2: Case Twenty-five). The state of affairs can be partially envisaged by knowledge of events in other diseases and particularly if the report of Case 14 of Head and Campbell (1900) is considered. They describe a patient with a type of sarcoma in which the herpes was due to spinal invasion of the tumour. The corresponding posterior root ganglion was surrounded by neoplasm so that it was likened to the stone of a plum. However, the ganglion was also invaded by tumour cells which would not be expected in myelomatosis. The fact that the neural tissue was surrounded by tumour would mean that some degree of ischaemia would result. Taking into account pressure on this structure by collapsed bone (which alone can produce herpes - Head and Campbell, 1900, Case 15), there is adequate cause for impairment of the ganglion's nutrition.

It has been postulated that the virus of zoster is more likely to establish itself in the ganglia with reduced vitality. In some individuals it may be present in the body without producing symptoms until the above changes take place. As with other types of secondary herpes zoster, this is the most likely explanation in myelomatosis.

CLINICAL FEATURES.

Herpes zoster of the secondary type is quite indistinguishable from the more usual primary variety. As noted above, its location is dependent upon vertebral disease. In only one case (Bing, 1936, Case 1) was there any suggestion of an associated muscular weakness, but it was indefinite.

Its appearance at various stages of the disease has been noted and it is of particular interest to observe that in at least three patients (Bonhard, 1914; Wintrobe and Buell, 1933; Kinney, 1940, Case 2) it was the very first focal abnormality of the disease. It also occurred early in the clinical course in the first patient of Anders and Boston (1903). It appeared three years before death in the patients of Levitt and Levy (1942) and Davison and Balser (1937, Case 5), whereas it was seen only shortly before death in Wallgren's (1920, Case 14) and Davison and Balser's (1937, Case 10) patients. In Case Twenty-five it was found one year after the onset of the disease and one year before death. Only one patient (Wintrobe and Buell, 1933) had it more than once, and in only one case was it treated. The latter (Case 9 of Davison and Balser, 1937) was given radiation therapy with satisfactory disappearance of the skin lesions.

As with other local vertebral lesions, herpes zoster is merely an indication of posterior spinal root ganglion

involvement and has no other significance.

CONCLUSIONS

1. Root pain is one of the commonest neurological complications of myelomatosis.

2. Any root may be involved either by myelomas of the vertebral bodies or by tumours of the sacrum or pelvic bones.

3. "Sciatica" is a feature of the latter and may be the first symptom of the disease.

4. Herpes Zoster is a manifestation of posterior spinal root irritation and it too may be the presenting feature of the disease.

INVOLVEMENT OF THE PERIPHERAL NERVES

The peripheral nerves may be involved either by compression or by a process not associated with any nearby lesion.

PERIPHERAL NERVE COMPRESSION

The first is due merely to bony tumours and need only be mentioned in passing. Any bone may be affected by myelomatosis and thus any nerve may be implicated. The third patient of Baker and Casterline (1948) had decreased sensation over the left hand and forearm, and this may have been of peripheral nerve origin. However, Fowler and Gordon (1950) describe a typical ulnar nerve palsy and Snapper et al. (1953, p.34) speak of three cases in which the only neurological abnormality was unilateral ulnar nerve involvement. In one of these latter, the nerve was definitely thickened and indurated, but only in Albert's (1951) second case could the symptoms and signs be definitely related to a bony tumour at the elbow. The aetiology in the other cases was unknown but may have been unrelated to the primary disease. Lesions in the cervical spine such as prolapsed intervertebral discs are common enough to be found coincidentally with other conditions.

As well as direct involvement by tumour, the peripheral nerves may take part in a more generalised process and the syndrome of peripheral neuropathy results.

PERIPHERAL NEUROPATHY ASSOCIATED
WITH MYELOMATOSIS

One of the rarest, but one of the most fascinating neurological aspects of multiple myelomatosis is peripheral neuropathy. The term "polyneuritis" is purposely avoided because of its inaccurate implications concerning the pathological changes.

LITERATURE.

There are in the literature reports of sixteen cases, but on close examination of these only eight can be accepted as being undoubted examples of myelomatous neuropathy.

Levison and Møller (1924) described a case that cannot be said to fit into the usually accepted clinical syndrome of "polyneuritis", and Levison's (1933) later comments indicate some confusion of nomenclature. A case of "progressive polyneuritis" is mentioned by Neel (1931) but the myeloma in the thoracic spine may have been responsible for the neurological features. Another aetiological factor in these cases is the state of the blood. The polyneuritis present in case 6 of Davison and Balser (1937) might, as the

authors suggest, have been related to the severe anaemia present rather than to the myelomatosis itself. At the other extreme, the third patient of Lawrence and Rosenthal (1949) had polycythaemia and it is possible that some of the features of this complication (paraesthesiae and weakness of the extremities, for example) produced the neuropathy-like picture. The term "neuronitis" is used by Lawrence and Wasserman (1950, Case 19) but it is not further elaborated by the authors; polycythaemia was also present.

Finally, the three cases of Kurnick and Yohalem (1948) published in the only article devoted to this subject, need appraisal. In each of them there are dubious facts and complications, so that they must all be regarded with suspicion. The first had a focal neurological lesion following operation, and this may have been due to cervical spondylitis with myelopathy rather than to the postulated "polyneuritis". The second is probably a true case but it was unfortunately complicated by spinal compression and is best disregarded. The presence of diabetes mellitus in the third case rendered the differentiation between diabetic and myelomatous neuropathy impossible.

Out of the sixteen cases, only eight remain and to these is added another (Case Twenty-six, Appendix I).

CASE TWENTY-SIX: Male, 66. One year of generalised paraesthesiae with pain and coldness of fingers and toes. Severe back pain 7 months and leg weakness for 4 months.

Picture of polyneuritis (with ?peripheral vascular occlusive disease). X-rays, C.S.F. and myelogram normal. Hyperglobulinaemia with E.S.R. 140. Bence Jones proteinuria. Abnormal pyruvate metabolism. Death. Survival c. 15 months. No autopsy.

The nine cases are collected together in Table XIII.

PATHOLOGY.

In only one case (Scheinker, 1938) was there an adequate autopsy study. The findings were of a parenchymatous nerve degeneration and the changes in the roots were described as "perineuritis interstitialis scleroticans". There was advanced disintegration of nerve fibres and most of the myelin sheaths were destroyed. The perineurium showed marked hyperplasia and proliferation of connective tissue and the changes were most severe in the distal portions of the nerves. These non-specific but unusual findings were confined to the peripheral nerves, for the abnormalities in the spinal cord - mainly anterior horn cell degeneration - were considered to be secondary. Unfortunately, the peripheral nerves are not mentioned in the well-documented M.G.H. Case Record No.32231 (1946).

It is of value to contrast the pathological events with those in similar diseases, and it is seen immediately that the invasion of the peripheral nerves occurring in carcinomatosis (Jentzer, 1930) and leukaemia (Eichorst, 1898; Alajouanine, Thurel, Castaigne and Lhermitte, 1949)

TABLE XIII.

9 CASES OF NEUROPATHY COMPLICATING MYELOMATOSIS

AUTHOR AND DATE	SEX	AGE	PRESENTING SYMPTOM	XRAY	C.S.F. PROTEIN (mgm. %)	PLASMA PROTEINS (g. per 100 ml.)	OUTCOME	SURVIVAL	AMYLOIDOSIS
SCHIMMER (1938)	M	38	Pigmented skin. Numb big toes	-	Normal	-	Death	14 months	Not mentioned
HEILM (1946)	M	64	Temperature changes and aching in feet	Spine, skull etc normal	61	Total 11.4 A 5.5 G 7.9	? c. 9 months +	Not mentioned	
E.O.H. Case No. 2231 (1946)	F	51	Aching and burning in finger-tips	Chest normal	Normal	Total 5.7	Death	6 months	Present
White & Tillingshast (1950, case 3)	M	59	Chronic diarrhoea	"Multiple granular lesions"	-	Total 9.4 A 3.6 G 5.8	? ?	Not mentioned	
LADONICK & SOLOMON (1953, case 6)	M	53	Paresthesiae of fingers and toes	-	212	Total 6.7 A 4.9 G 2.4	Death	8 months +	Not mentioned
LADONICK & SOLOMON (1953, case 8)	M	58	Shoulder pain	Hibs, skull, shoulders normal	71	Total 6.2 A 3.9 G 2.3	Death	1 year +	Of tongue
LADONICK & SOLOMON (1953, case 10)	M	53	Nodules on body	-	72	Total 6.35 A 3.3 G 3.0	Death	8 months +	Not mentioned
LADONICK & SOLOMON (1953, case 14)	F	59	Pain right arm	Clavicle normal	Normal	Total 6.54 A 4.12 G 2.42	Death	2 years +	Generalized
Case TWENTY-SIX	M	66	"pins and needles" limbs & trunk	All normal	Normal	Total 9.25 A 2.8 G 6.18	Death (No autopsy)	15 months	Not looked for

is rarely, if ever, seen in myelomatosis. Two authors mentioning it have already been noted (Bonder, 1904; Brownell, 1950, Case 2) but neither gives any details. They were dealing with symptoms referable to spinal roots and merely stated in passing that these structures were infiltrated by the neoplasm. As has been suggested already, however, (p.166) the diagnosis in Bonder's (1904) case is in doubt. The third worker to contribute to this problem is Petridos (1939, Case 1), who shows (Abb.2) infiltration of a sympathetic ganglion by "myeloblasts" from the extra-vertebral extension of a spinal tumour, probably but not certainly a plasma cell myeloma. It seems strange that, despite the frequent involvement of spinal roots and nerves, only three examples of infiltration by myeloma cells could be found. It is to be admitted, however, that full histological examination of the peripheral nervous system has never been attempted, as far as the literature reveals. Nevertheless, if this pathological change were the usual event there would surely be more evidence for it, and there is not.

Examination of the cranial nerves has been reported in a few cases and no invasion found. Thus Spurling et al. (1947, Case 21) describe how the sheath of the sixth cranial nerve had not been transgressed, despite the fact that immature plasma cells were surrounding it. These findings,

like the paucity of information concerning peripheral nerve infiltration, are in keeping with the knowledge that myelomatous tissue never extends into the substance of the nervous system.

AETIOLOGY.

The neuropathy complicating myelomatosis has in the past been ascribed to "toxic" influences (Scheinker, 1938, and others) and this topic will be discussed later (pp.199-209).

The hypothesis seems reasonable enough when one considers that similar events with other malignant diseases have been attributed to a similar process. Denny-Brown (1948) has described a primary sensory neuropathy associated with carcinoma, although this has been known to occur for many years (Auché, 1890). There is a similar process associated with Hodgkin's disease (Dogan, 1953). Actual invasion of the nerves is not included in these conditions and Denny-Brown (1948) thought that a metabolic disorder related to the tumour cells was the aetiological factor in carcinomatous neuropathy. Further elucidation of this problem, which is mainly biochemical in nature, is not at the moment forthcoming. Dogan (1953) has postulated a similar mechanism in Hodgkin's disease, but no information to substantiate or refute this claim is available.

The aetiology of myelomatous peripheral neuropathy, however, would seem to be more definite. It is to be noted from Table XIII that of the nine cases three had been found to have amyloidosis at autopsy; this was presumably the primary type found with myelomatosis and described in more detail later (p.193). In addition, the skin nodules of Madonick and Solomon's (1953, Case 10) patient and the chronic diarrhoea of the patient of White and Tillinghast (1950, Case 3) suggest that in two more also the condition was present but unrecognised. In Case Twenty-six, as well as symptoms and signs of a neuropathy, there was evidence of occlusive vascular disease (cold extremities, blue and cold left ring finger) which occurs in the primary type of amyloidosis because of involvement of small peripheral arteries and arterioles. A comparable state was found by Berlin (1946), and his patient was benefited by "priscol" therapy. Painful and weak hands made gripping difficult in Case Twenty-six, and this too is seen not infrequently with amyloidosis. Thus, among the nine cases three had amyloidosis and a further four had sufficient signs to suggest its presence. Further, it is interesting to note that of the six patients who were studied radiologically, abnormalities were found in only one, and here there was osteoporosis without local myeloma formation. This is further evidence in favour of complicating amyloidosis, because Snapper et al. (1953, p.93) have noted

the rarity of bony lesions in cases of myelomatosis associated with amyloidosis.

Although the neuropathological changes in primary amyloidosis have been described only rarely, it is known that a neuropathy can occur, and^bNavasquez and Treble (1938), Kernohan and Woltman (1942), and more recently Andrade (1952), have dealt with this topic. Changes are found within the nerves and are produced by progressive impairment of their blood supply, this being a direct result of amyloid invasion of peripheral arteries, including vasa nervorum.

It is thus submitted that in some cases the neuropathy occurring with myelomatosis is in fact due to the associated amyloidosis rather than to the primary disease itself. Unfortunately there is, at the moment, no histological verification of this thesis and the only pathological material (Scheinker, 1938) does not mention amyloidosis, although it was not specifically looked for. Nevertheless, this conception is in keeping with the known pathological events and is perhaps more satisfactory than one that invokes hypothetical toxins.

Another aetiological factor is mentioned by Berlin (1946). He noted the frequent appearance of hyperglobulinaemia and the accompanying increased blood cell aggregation in myelomatosis and inclined to the view that the clinical picture in peripheral neuropathy, and perhaps other neuro-

logical complications too, could be accounted for by intravascular clotting ("capillary embolisms") and thus infarction of nervous tissue. Furthermore, he claimed to be able to demonstrate this in the capillaries of the nail bed, and his patient's response to a vasodilator drug ("prisco") suggested a vascular defect. It is possible that this mechanism is at times responsible for the neuropathy, but the fact that only three of seven patients tested had an abnormal globulin content of their serum indicates that it is not the only one.

Associated anaemia must also be considered as a causative agent, and in the four patients in which the blood picture had been examined there was some degree to be found; in one (M.G.H. Case Record No.32231, 1946) pernicious anaemia had been excluded. It is unlikely, however, that anaemia plays a significant aetiological role for, whereas it is one of the commonest features of myelomatosis, a peripheral neuropathy is, on the other hand, one of the rarest.

Magnus-Levy (1933) originally suggested that the Bence Jones protein was produced by the plasma cells and that it might be a factor in the production of some of the "toxic" phenomena. In only four of the present series (Table XIII), however, was it present.

In Case Twenty-six, an abnormality of pyruvic acid metabolism existed but as has been shown by Joiner,

McArdle and Thompson (1950) this is not a specific defect and does not necessarily point to the causative agents.

In conclusion, several aetiological factors have been postulated but the one that seems most likely is the presence of primary amyloidosis. Future study should elucidate this point.

CLINICAL PICTURE.

In the series surveyed there were no unusual features concerning the age and sex. The onset of symptoms was gradual and as might be expected the extremities were invariably affected first. The clinical picture was not distinguishable from that of other types of peripheral neuropathy, except that hand pain and stiffness were outstanding. The paraesthesiae, often commencing in the hands and associated with muscular weakness and wasting, were constant findings. In Scheinker's (1938) patient the symptoms began in the feet and ascended so that a "Landry" type of clinical picture, as the author described it, resulted. Berlin (1946) described symptoms suggestive of peripheral vascular disease, and they were also noted in Case Twenty-six. Pain in the hands and in the back was common and the latter in Case Twenty-six took on the features of root irritation pain. Muscle pain and tenderness occurred at times. In addition to these complaints, others suggesting either multiple

myelomatosis or its localised features were at times found. Thus loss of weight, anorexia and pallor were common, and in Scheinker's (1938) patient there was myelomatous invasion of the skin as well as a sternal myeloma.

On examination the usual abnormalities found in peripheral neuropathy were present. Pain and stiffness of the hands restricted the examination of these parts but wasting and weakness were frequently discovered. Scheinker (1938) noted a striking superficial hypersensitivity in his patient and Snapper (1949, p.240-241) substantiates this finding. They both suggest that "toxic influences" are the causative agencies but Bayrd and Heck (1947) correlated it with bone pain. Scheinker (1938) goes further and states that many of the pains of myelomatosis may be due to "toxic" effects on peripheral nerves, a suggestion that has already been criticised. Other evidence of myelomatosis or of primary amyloidosis was discovered at some time in the clinical course.

The course was usually a rapidly progressive one: in the four cases where this could be estimated the patients survived six, nine and fifteen months. There was a relentless aggravation of all the symptoms and signs mentioned above with features of myelomatosis and amyloidosis superimposed. The patient of White and Tillinghast (1950, Case 3), however, had suffered from diarrhoea for eight years

before the onset of the neuropathy. This is not out of keeping with the recognised progress and symptomatology of primary amyloidosis and has been noted already.

INVESTIGATIONS.

The C.S.F. was examined in eight patients, and of these it was entirely normal in four; in the other four there was an increase of the protein content, ranging from 61 to 212 mgm. per cent. In one at least of these latter there was a markedly raised globulin figure. The Lange curve showed no change in three.

X-ray pictures were taken in six, and apart from "multiple" granular lesions and generalised demineralisation seen in the patient of White and Tillinghast (1950, Case 3), no abnormalities could be detected.

A normochromic anaemia was discovered in the four patients who had had blood counts taken. In seven the plasma protein values were reported; four were normal and in three patients there was a marked hyperglobulinaemia and a high erythrocyte sedimentation rate.

An abnormal pyruvate metabolism was detected in one case (Case Twenty-six, Fig.59). Bence Jones proteinuria could be detected in four of the six patients tested. A bone marrow biopsy confirmed the diagnosis in all of the six cases so examined.

DIAGNOSIS.

The majority of these patients presented a clinical picture of peripheral neuropathy, or one akin to it, and for a time there was no indication of myelomatosis. It was not usually long, however, before signs of the latter appeared and a definite diagnosis could be made. Until then, it was difficult or impossible to determine.

Evidence of amyloidosis may be present and the material should be looked for in all of these cases. It is interesting to note that in two cases of myelomatosis with amyloidosis (Weber, 1903, and Bayrd and Bennett, 1950) tingling in the fingers associated with weakness was among the first complaints. The first patient, however, had a normal nervous system but in the second it was not mentioned. It should be emphasised that these hand symptoms are common in amyloidosis without neuropathy, and are due to local joint or muscle involvement by the substance. Other features of primary systemic amyloidosis may simulate those of neuropathy (joint stiffness, muscle wasting, deep-seated pain and progressive weakness), and if occurring with myelomatosis may raise the suspicion of peripheral nerve involvement. The characteristic physical findings of the latter should be sufficient to differentiate it. If all three are present, the picture will be a complex one.

It may therefore be difficult to dissociate the

clinical features related to amyloidosis from those of the neuropathy. In fact, some of the cases quoted already (Table XIII) with no histological proof (e.g. M.G.H. Case Record No.32231, 1946) may perhaps be explained on a basis of amyloidosis alone without necessarily any peripheral nerve changes. As the basic aetiological factor is probably the same, however, it should not be necessary to attempt this.

TREATMENT.

There is no indication that any of these patients except that of Berlin (1946) and Case Twenty-six received any treatment. In the former "priscol" was given with some effect and the author considered that this was support for his theory of "capillary embolisms"; but as suggested above, it could be equally well explained on the basis of amyloid changes in peripheral vessels, although it is known (Van Itallie and Clarke, 1951) that "priscol" has little effect upon vessels that have undergone structural change. In Case Twenty-six a course of thiamine chloride intravenously and nicotinic acid was given, but although there was biochemical improvement (Figure 59) the clinical change was negligible and the course of the disease was not altered.

CONCLUSIONS

1. Peripheral neuropathy is a rare complication of myelomatosis.
2. There are sixteen acceptable examples in the literature and Case Twenty-six is added.
3. Pathological data is very scanty but it is suggested that primary amyloidosis occurring with myelomatosis may be responsible for the neuropathy rather than "toxins".
4. The clinical picture is not distinctive but features of amyloidosis and neuropathy may overlap.
5. C.S.F. protein may be increased.
6. Treatment is unsatisfactory.

PRIMARY AMYLOIDOSIS ASSOCIATED WITH
MULTIPLE MYELOMA, AND ITS RELATIONSHIP TO
THE NERVOUS SYSTEM.

Primary systemic amyloidosis is a condition that only recently has begun to be recognised adequately. It is widespread throughout the body and is not related to infection in any way. The blood vessels, connective tissue and muscles of organs are involved, and the heart, gastrointestinal tract (especially the tongue), joints, bones and kidneys are the most commonly invaded. The process may be a diffuse one or the amyloid material collects together to form tumours of considerable size. The Congo red test is of little clinical value in this type of amyloidosis.

The nervous system is affected by way of its blood vessels (Kernohan and Woltman, 1942), either due to perivascular deposits or amyloidosis of small arteries and arterioles. Vascular occlusion thus results and ischaemia of the nerve is produced. Many, if not all of the neurological features are dependent upon these events.

The association of amyloidosis with myelomatosis has been known since 1872 (Adams, 1872), although it is only of late that intimate attention has been directed towards it. Recent estimations (Bayrd and Bennett, 1950) show that there

are now more than seventy cases in the literature and the combination is to be found in about 15 per cent of cases of myeloma. Magnus-Levy (1933) in his extensive review of the condition, believed that the amyloid is produced by the myeloma cells themselves, but this concept has not met with universal acceptance.

It is important to consider the role of the nervous system when amyloidosis is present, and each section of it will be dealt with in turn. Either the central or the peripheral nervous system or both may be involved.

BRAIN.

Kernohan and Woltman (1942) have reviewed several cases of primary amyloid of the brain unassociated, presumably, with myeloma, but Magnus-Levy (1933) makes no reference to this in his survey of the subject and it must be assumed that it was not found in any of the thirty-seven cases he mentions. The apparent rarity is due more to the infrequency of complete autopsies than to the condition itself, and even to-day there are very few cases of amyloidosis with adequate examination of the nervous system.

Although Rubinstein (1949) has described a patient with myelomatosis who had a large frontal bone tumour that proved to be a mass of amyloid substance rather than a myeloma, no evidence of brain involvement can be found in

the literature. In Case Four, amyloid material was found within the substance of the skull myeloma but it played no role other than increasing the bulk of the tumour and thus the cerebral compression. Likewise, no cranial nerve palsy resulting from this complication is described, although such have occurred with paramyloid unrelated to myeloma (Cüppers and Krücke, 1953, Case 2). It has been suggested, however, and will be dwelt upon in more detail later (p.201), that the clinical picture in the patient described by Senator (1899) was due to amyloidosis rather than toxins (p.19). This is however merely a supposition and no direct proof is forthcoming. Similarly, the role of amyloidosis in the case of Stokvis (1883) is not clear.

SPINAL CORD.

Amyloid material is occasionally found within a myeloma, thus increasing its bulk. In the case of a vertebral body myeloma therefore, extension into the spinal canal may be produced or enhanced. Further, together with the myelomatous process, it undermines the stability of the bony structure and collapse of the body may take place more readily. These events have already been noted (p.122) and the most striking example is the case of Mandl (1924) where a "plasmocytoma" of T.3, which contained large quantities of amyloid, pursued this course. Spinal cord compression

can thus be produced as in this case and also in that of Freund (1930). Amyloid substance was likewise found within the spinal myeloma in Case Eighteen as well as in that of McMahon (1951); in each case it increased the size of the tumour. The patient "H. Det." of Magnus-Lovv (1933) is another possible example and amyloid substance was discovered in the spinal myelomas of the cases of Schütz (1914), Kempplerer (1920), Kohlmann (1921, Case 1) and Bell (1939, Case 89). There are, no doubt, other cases in the literature that have not been recognised by their authors, and that of Ophüls (1900) with extensive amyloid changes in collapsed vertebral bodies is an example. The case of Speares (1921) should also be considered to belong to this group, although the autopsy report is limited and a correlation between the amyloidosis and the myeloma was not suspected.

Thus, the only type of spinal cord complication due to amyloidosis associated with myeloma for which there is adequate evidence, is extradural compression. In all the cases mentioned above a vertebral myeloma was present, but that the amyloid material may exist alone in this region is shown by the case described by Lowe and Ross (1953). There were masses of paramyloid in the outer portion of the dura mater which was thickened. This substance was lying free in the epidural space and it surrounded the dural tube. Compression was presumably absent but no adequate account of

the nervous system is given in the report.

Changes within the cord have been due either to pressure from without or retrograde changes consequent upon peripheral nerve or spinal root involvement.

PERIPHERAL NERVE.

This is the most important feature of the association between amyloidosis and myeloma, but it has received very little attention. That it is very rare in cases of primary amyloidosis is suggested by Kernohan and Woltman, who could find peripheral nerve involvement in only one of thirteen cases that were adequately examined. As noted already (p.184), an ischaemic type of neuropathy is the end result of amyloid changes in the peripheral nerves, and there is no reason to suppose that these events cannot occur with the amyloidosis of myelomatosis.

Magnus-Levy (1933) makes no mention of it, but the nervous system had not been examined closely in any of the thirty-seven cases that he cites. Other authors likewise have made no comment upon the peripheral nerves in cases of amyloidosis complicating multiple myeloma, except Tverdy (1951). His patient had evidence of peripheral vascular occlusive disease but the nervous system was normal to the clinical investigations employed. At autopsy, however, amyloid material was found in the nerve trunks and ganglia

of the coeliac plexus as well as the autonomic nerves of various organs. It is thus possible for the amyloid substance associated with myeloma to invade nervous tissue, albeit of the autonomic type in this case. This is the only evidence so far that there is histological verification for this event.

CONCLUSIONS

Amyloidosis complicating myeloma is a very interesting problem and the effects upon the nervous system will obviously repay further study. At the moment, a lack of accurate clinical and pathological observations hampers the formation of any definite conclusions, but it is possible that certain neurological aspects of myeloma may be the product of this complication of the primary disease.

THE "TOXIC" EFFECTS OF MULTIPLE MYELOMATOSIS
UPON THE NERVOUS SYSTEM.

The ability of malignant tissue to affect the nervous system, other than by direct pressure or by invasion, has been accepted for many years, and to explain these effects at a distance "toxins" have been evoked. Thus French writers at the end of the last century described "polynévrites cancéreuses" and Boudouresques (1938) has more recently summarised this literature.

That myelomatosis should be included in this group has also been accepted but unfortunately, as in other diseases, some authors have subscribed to the concept too readily and usually when clinico-pathological correlation proved difficult. It seemed in certain cases to be a convenient explanation of events that otherwise could not be accounted for, so that at times toxic processes have been suggested too readily as aetiological agents. That they do occur in some diseases cannot be denied, but their employment as a vague concept, allied perhaps to the "miasmata imaginaria" of Osler, is to be condemned. Magnus-Levy (1938), after very extensive consideration of this disease, concluded that the existence of "toxic" processes had not been proven satisfactorily.

It is thus necessary to assess critically the contributions to the subject of myelomatous toxic effects upon the nervous system that are to be found in the literature. Various parts of this system have been thought to suffer from the effects of toxins and these will be dealt with in turn.

BRAIN.

The terminal delirium, coma and other mental changes seen with myelomatosis are due, no doubt, to a variety of causes, the chief being anaemia and uraemia (p.52). A specific toxic effect of the malignant tissue has been suggested, but only in the vague manner in which this term is often employed in other "toxic" states. Its effect is presumably a generalised one and it may be the sum of several components which have not yet been detected. Aronsohn (1931) thought that the diabetes insipidus present in his patient could be the result of toxic processes but also considered local pressure upon the pituitary or para-pituitary structures (p.48) as a possibility. Kalischer (1928), on the basis of his first case with cranial involvement, was also prepared to accept the concept.

No changes in cerebral tissue have been demonstrated at autopsy and none presumably will be by the methods of study at the moment available. The lesion is probably a

biochemical one, and more refined techniques such as histochemistry will be necessary to demonstrate it.

CRANIAL NERVES.

At least two authors have suggested that the function of the cranial nerves may be influenced by toxic processes in myelomatosis.

The first mention of toxins in myeloma is, in fact, made with reference to the cranial nerves, and centres on the much-quoted case of Senator (1899) referred to already (p.19). The patient was woman of thirty-six with bilateral tongue weakness, paresis of the arytenoideus and sensory impairment over the third trigeminal area. The clinical impression was one of pseudo-bulbar palsy but at autopsy there was clear evidence of multiple myeloma. The brain stem was carefully examined by Oppenheim and the nuclei of the cranial nerves in particular were found to be normal. No clear evidence of compression could be found but, as Antoni (1936) pointed out, the nerve foramina of the skull were not described. In the absence of any obvious aetiological agent, it was suggested that the cranial nerve dysfunction was a product of toxic influences and Oppenheim quoted a similar patient who was found to have a lymphosarcoma of the anterior mediastinum. A myasthenic type of muscle palsy was visualised in Senator's (1899) case and the

term "asthenic bulbar paralysis", applied by Strümpell (1896) to cases of myasthenia gravis, was suggested. The case cited by Oppenheim no doubt had this disease and a thymoma. Although Senator's (1899) case must still remain a mystery and the only one of its kind in the literature, it is of some interest to note that there was amyloid material in the kidneys. It is not uncommon to find dysphagia and dysarthria with primary systemic amyloidosis, and it is possible that the clinical picture could be explained on this pathological basis, or that the cranial nerves themselves were affected by amyloid changes which are known to occur in peripheral and some cranial nerves (Cüppers and Krücke, 1953)(pp.193-198). It seems preferable to attempt an explanation on the grounds of a known pathological process rather than on a vague theoretical concept.

The second author to incriminate toxic effects is Langdon (1939), who maintained that the cranial nerve palsies in his patient were produced by "toxins" from a basal myeloma rather than by direct pressure (p.29). The clinical picture was identical in every way with that occurring in the other cases of basal myeloma with cranial nerve palsies, and to advance such a postulation seems unnecessary in the light of this experience. Langdon (1939) was perhaps influenced in his conclusions by the ocular changes (p.86), for the visual impairment, the central scotoma (first apparent to colours)

and the optic atrophy were all reminiscent of a toxic type of amblyopia as, for example, occurs with tobacco or methyl alcohol intoxication. It is possible, however, for pressure on the optic nerve to produce such features, and Kurnick and Yohalem (1948) among others have rejected the authors' claims.

Both these cases are therefore under suspicion and should not be used as evidence in favour of a theory of myelomatous toxins.

SPINAL CORD.

The majority of the literature on the subject of the toxic neural influences of myelomatosis concerns their effects upon the spinal cord.

There are two cases that are repeatedly referred to and they will be dealt with first. Nonne (1921, a and b) described a man aged fifty-seven who had several clinical features in keeping with a myeloma of T.1 vertebra and X-rays showed rarefaction of the body. A cord compressing lesion was considered but apparently could not be verified at autopsy, and microscopically the spinal cord and dura mater were normal. It is interesting to compare this case with Case Nineteen where a similar state of affairs existed but unfortunately an autopsy was not carried out. On the basis of these findings, the author suggested that, as in carcinomatosis toxic effects might produce a similar clinical pic-

ture, so they could be responsible in myelomatosis. It seems, however, that in the presence of focal neurological signs pointing to a specific region of the spinal cord and X-ray evidence of change in the same area, even though no cord compression can be detected, one is not justified in postulating an entirely new pathological process.

The case described by Kreuzer (1926) is also suspect. Here again there was clinical evidence of a focal spinal cord lesion in the cervical region and at autopsy a spinal myeloma had extended into the spinal canal, but it was thought that it could not explain the cord changes. Some confusion may have been produced by the presence of an upper thoracic sensory level, indicating a cervical rather than a thoracic cord lesion (p.148). The histological appearances in Kreuzer's (1926) case would not be incompatible with pressure, for the petechial haemorrhages and dilated capillaries found in the lateral columns of the cervical cord were also present at the site of compression in Case Twenty (Appendix I).

On the evidence presented by those authors therefore, it is impossible to accept their cases as examples of toxic effects of myelomatous tissue upon the cord. In each, potential cord compressing lesions were present and cannot be dismissed lightly.

Other authors have published cases in which they

believed toxic influences were affecting the function of the spinal cord. Although adequate evidence of spinal compression was found by Pines and Pirogowa (1928, Case 2), they thought that a toxic effect might also be present. The reason for this deduction is not clear and the same confusion exists with Schuppli's (1939) case, where adequate spinal compression could not be found to account for the clinical picture. The clinical findings of cauda equina compression in Hallermann's (1929) eighth case were thought to be due to toxins and the large pelvic myeloma was considered to have played no part, despite its probable invasion of the spinal canal.

Sjögren and Wohlfahrt (1933) described a patient with a transverse cord lesion, and although no compressing lesion could be discovered (investigations were however limited) changes akin to subacute combined degeneration were found in the spinal cord. It is germane to the present discussion to consider for a moment the identical problem with regard to Hodgkin's disease. Shapiro (1930) claimed that the cord changes in his patient simulated those of subacute combined degeneration and were due to toxins rather than local compressing epidural tumours. Weil (1931) on the other hand, supported by Hassin, attacked the theory of hypothetical toxins and showed that the cord findings described by Shapiro (1930) were probably those of pressure.

The same was also probably true in the case of Sjögren and Wohlfahrt (1933). A further case, reported by Lindbloom and Mulder (1941) completes this collection. Again, however, there was clear evidence of a focal spinal cord lesion produced by spinal compression, and the reason for postulating toxic effects is not apparent. The histological changes were to be found in most parts of the cord in section but mainly in the lateral columns - a point perhaps in favour of compression.

We may thus conclude after surveying the literature that there is no clear evidence in the cases so far described to allow of the assumption of a toxic process affecting the spinal cord in myelomatosis. Consideration of its pathology indicates that its influence upon the nervous system would not be expected to be the same as in other malignant and allied diseases. It does not invade the meninges or nervous tissue in the manner of carcinomatosis or leukaemia, nor does it behave in the manner of the other malignant lymphomata, for Hodgkin's disease, for example, infiltrates the neural tissue (Winkelman and Moore, 1941) but myelomatous material only very rarely advances beyond the dura mater and never invades the brain or spinal cord. These fundamental differences are illustrated by the fact that cord changes are well recognised in association with carcinoma (Lubarsch, 1897), Hodgkin's disease (Pakesch and Vinazzer,

1952), leukaemia and chloroma (Critchley and Greenfield, 1930). The role of amyloidosis in the spinal cord has not apparently been investigated in any detail but vascular changes might be expected.

That similar events may, however, occur with myelomatosis is not absolutely denied and Snapper et al. (1953), an authority on myeloma, mentions a case of "non-specific type of degeneration of the spinal cord". If such a condition did definitely occur it would be reasonable to expect more unequivocal evidence of it in the literature, particularly in view of the recent increased interest in the neurological complications of malignant diseases and in myelomatosis.

Finally, mention must be made of some puzzling cases recorded in the Scandinavian and Swiss literature. A group of authors (Bing and Neel, 1936: Bing, Fog and Neel, 1937: Bichel, Bing and Harboe, 1950: Wührmann and Wunderly, 1947) have together published five similar cases. They all had hyperglobulinaemia with "toxi-infectious" involvement of the central nervous system, as well as C.S.F. changes. The spinal cord and roots were mainly affected and inflammatory changes were found here as well as in other organs. There were plasma cells in the medulla and cauda equina roots in one patient (Bing, Fog and Neel, 1937), and another (Bichel, Bing and Harboe, 1950) had an increased number of plasma

cells in the sternal bone marrow. It was thought, however, that myelomatosis could not explain all the findings, and the nervous system features would tend to confirm this view. Toxins were discussed but for the moment these cases must remain an enigma, unless one suggests that they are examples of macroglobulinaemia to be described shortly (p.219). They do not help in the elucidation of the present problem.

PERIPHERAL NERVES.

When the peripheral neuropathy associated with myelomatosis was under discussion, the various aetiological factors were considered. It was thought that the theoretical concept of "toxins" might have a measure of truth, but that involvement of the nerves by the amyloidosis co-existing with myeloma was more likely. The subject is adequately dealt with on pp.183-187.

CONCLUSIONS

1. The literature concerning the so-called "toxic" effects of myelomatosis upon the nervous system reveals very little evidence in favour of their existence in a form comparable with that seen in other malignant diseases. The known differences in pathology would perhaps predict this variation in behaviour.

2. The cases of "toxic" changes in the cranial nerves

and in the spinal cord are not convincing but a type of "toxic" neuropathy is recognised.

3. It is suggested that amyloidosis may be the common factor underlying the "toxic" complications described and also responsible for the peripheral neuropathy.

VASCULAR LESIONS OF THE NERVOUS SYSTEM
IN MYELOMATOSIS

A. HAEMORRHAGE

A haemorrhagic tendency is not uncommon in myelomatosis for Snapper et al. (1953, p.19) found it in 35 per cent of their cases. It usually manifests itself by way of epistaxis, bleeding gums, haemoptysis, gastro-intestinal haemorrhage or skin petechiae, but involvement of the retina or central nervous system may occasionally occur. The retinal manifestations have already been discussed (pp.75-81) but the latter will now be considered.

LOCATION OF HAEMORRHAGE.

These haemorrhagic findings may be grouped according to their location within the nervous system. They are all very rare but, as neurological complications of myelomatosis, must be mentioned. A convenient subdivision is:-

- (1). Subdural haematoma.
- (2). Intracerebral haemorrhage.
- (3). Spinal haemorrhage.

(1). Subdural haematoma.

Hoffmann (1904) cites a case of Spiegelberg where "pachymeningitis externa" was discovered at autopsy, but as the original article (Inaugural-Dissertation: Freiburg) could not be consulted, there was no means of telling whether the author was referring to a subdural haematoma or not. Certainly, this finding was thought to be incidental, as was also so in the seventh case of Wallgren (1920) where a small subdural clot found at autopsy did not seem to have contributed to the clinical picture. On the other hand, the haematoma found in the patient of Donhauser and de Rouville (1941, Case 5) appeared to be directly responsible for his death, because this occurred in coma after increasing headache and vomiting. The account, however, is somewhat confusing and the nervous system was not described in detail. Case 14 of Lumb and Prosser (1948) was of interest, in that the subdural collection developed rapidly and the patient died from its effects two days after entering hospital; the brain itself was normal. The only other reference in the literature to this event is by Brownell (1950) who, when discussing bleeding incidents in myelomatosis, mentioned a patient with a subdural haematoma but gave no details.

Clinically, this lesion differs in no way from the more common traumatic variety but in the terminal stages of myelomatosis, when it seems to be most likely to appear, it

may be difficult or impossible to differentiate it from other pre-mortem events. However, its diagnosis in the presence of an advancing incurable disease appears somewhat academic. There seemed to be no relationship to head injury in any of the quoted cases and they thus belong to the non-traumatic or spontaneous variety of subdural bleeding. Myelomatosis as an aetiological factor in subdural haematoma has not, however, been recorded previously (Scott, 1949).

There is no pathological material concerning this complication and it is impossible to deny the possibility of the subdural haemorrhage being a complication of myelomatous invasion of the dura mater, as occurs in carcinomatosis and sarcomatosis (Russell and Cairns, 1934). The absence of this phenomenon would further illustrate the fundamental differences between myeloma and similar malignant diseases.

The occurrence of a subdural haematoma with myelomatosis should at least be recognised, for it may conceivably complicate the earlier picture of the disease, and treatment, if not successful in the long run, will relieve the patient of distressing symptoms.

(2). Intracerebral haemorrhage.

Information concerning this occurrence is scanty. The patient of Canestro (1927) is said to have died of a

corebral haemorrhage but no details are available, and the information is likewise limited in the case recorded by Satanowsky, Lascano Gonzalez and Valezquez (1934). Here death was due to intracerebral bleeding which had inundated the ventricles. If the case of Cosin (1935) is accepted as an example of myelomatosis (and this seems highly probable) it is to be noted that multiple subcortical haemorrhages were found, as well as more deeply placed extravasations, one of which had reached the ventricle.

The findings in Case 1 of Eskelund and Noring (1953) are, however, open to doubt. The patient had headache with vomiting and died in coma, and in the pons were found two areas of haemorrhages (the specified diameters were 2.0 cm., which seems unlikely). The authors thought these were primary in nature but it is also possible that death was due to raised supratentorial pressure and that the pontine lesions were due to this, occurring as a terminal phenomenon, as is known to take place (Poppen, Kendrick and Hicks, 1952). The brain was described as oedematous but unfortunately neither it nor the skull was dealt with in detail.

The first patient of Wallerstein (1951) died of a subarachnoid haemorrhage, but this was probably due to the rupture of a mycotic aneurysm consequent upon acute bacterial endocarditis rather than to the primary disease, myelomatosis. Other than this case and subarachnoid bleeding

accompanying intracerebral haemorrhage, this finding has not been described.

Cerebral haemorrhage occurring as an incidental event is possible.

(3). Spinal haemorrhage.

There is in the literature only one case illustrating this event. It is that of Toušek and Vortel (1947) and concerns a patient with myelomatosis who developed spinal compression suddenly. At autopsy an epidural haemorrhage was discovered in the cervical region and the question of whether the compression was due to haematoma or diseased vertebra has been discussed already (p.91-92). Probably both factors were involved. Although the features of a bleeding tendency were present, the patient also had evidence of a hyperproteinaemia which we shall now see is equally important, if not more so, than the haematological findings.

B. THROMBOSIS.

Evidence of thrombosis within the central nervous system receives less support from the literature, although retinal venous thromboses have been considered already (p.76).

The patient of Venturi (1901) is said to have had thrombosis of intracranial sinuses, and in Case 7 of Wallgren

(1920) there was thrombus formation in the sagittal sinus. The significance of these findings is not clear, and although the latter is frequently quoted in the literature as one of the neurological aspects of myelomatosis, there was no clinical evidence of it. Wallerstein's (1951) second case is likewise of small value; there was a cerebrovascular lesion, thought to be thrombotic in type but not verified histologically, which occurred in relation to acute heart failure due to amyloidosis. The heart failure may, by a state of hypotension, have produced the clinical events rather than a primary intravascular lesion, a concept that has recently been elaborated by Corday, Rothenberg and Putnam (1953).

The case of Schumacher, Williams and Coltrin (1937) is, however, more helpful. At autopsy there were signs of antemortem clotting in the right auricle but changes were also found in the smaller cerebral vessels. Many were plugged and thrombosed and had areas of degenerating brain tissue surrounding them.

AETIOLOGY.

The aetiology of the various vascular complications of myelomatosis may now be reviewed. Included here are the cases of retinal haemorrhage and thrombosis (pp.75-81), the six definite cases of haemorrhage implicating the nervous system and the one example of cerebral thrombosis just

detailed.

Taking first of all the haemorrhagic manifestations, of the sixteen cases (retinal and intracranial and intraspinal) there was an account of bleeding elsewhere in the body in ten of them, and of the remainder several had inadequate clinical data. Thus the neurological aspects are part of a generalised haemorrhagic tendency in many, if not all, of the patients. It is natural that a search for evidence of a bleeding tendency should have been made in most of these cases. In only a few, however, was this forthcoming and authors were at a loss to explain otherwise typical purpuric features. Ellinger (1899) and Toušek and Vortel (1947) found a lowered platelet count and Satanowsky et al. (1934) described disturbances of the clotting mechanism. The paucity of these findings thus suggests that some other factor is responsible for the vascular changes that have been described.

A survey of these cases reveals that the common factor is an increase of serum proteins, with a specific rise in the gamma globulin fraction. An estimation was carried out in eleven of the seventeen cases (retinal - ten, nervous system haemorrhages - six and thrombosis - one) and it is interesting to note in passing that Ellinger (1899), whose case belongs to this group, has been credited with the first report in the literature of hyperproteinaemia associ-

ated with multiple myeloma. In each of these ten cases there was an excess of globulin, and the markedly elevated erythrocyte sedimentation rate in the patients of Cosin (1935) and Toušek and Vortel (1947) are probably a reflection of this abnormality. It seems probable therefore that hyperproteinaemia, and more specifically a hyperglobulinaemia, is a factor common to most of these cases and its role in aetiology must next be considered. This conclusion has also been reached by Snapper et al. (1953, p.19).

The abnormal proteins in myelomatosis form an attractive but complex subject, a comprehension of which may lead us to the elucidation of the disease itself. All advances in our knowledge have been made in the last ten years and Waldenström (1952) has recently summarised the known facts. Hyperproteinaemia encourages auto-agglutination of the blood indicated by abnormally rapid rouleaux formation and the greatly accelerated erythrocyte sedimentation rate. If these events occur in vitro, their presence in vivo is not altogether unlikely, and their role in the production of the vascular complications can best be studied in the retina.

Here the various clinical findings are stages in the development of blood vessel occlusion, which is determined initially by the state of blood and its high protein content. Thus the first indication is a sluggish flow of venous blood in the retina, induced by pressure on the eyeball (Foord,

1935). The next stage is occlusion of small veins and venules with retinal haemorrhages, and the ultimate product is obstruction of the central retinal vein (Wintrobe and Buell, 1933: Walsh, Case No.277179, pp.1052-1054, 1947). Bleeding into the retina is due to increased venous pressure with the passage of blood cells across the vessel walls.

It seems reasonable to consider similar happenings in the brain and some support for intravascular thrombosis is gained from the case of Schumacher et al. (1937) described earlier, where cerebral thrombosis was suspected. In this patient the plasma protein content of the blood was extremely high, for the level of 23.27 gm. per 100 ml., of which 16.02 gm. was globulin, is probably one of the highest ever recorded in this disease.

That other factors are involved is not excluded, and multiple aetiological agents may explain all the vascular complications rather than only one. This is suggested by the fact that there are other forms of hyperproteinaemia, where these events do not occur. Some affiliation with sarcoidosis has been suggested recently (Gautier and Maurice, 1953). A haemorrhagic diathesis associated with the almost universal anaemia cannot be invariably excluded although we have seen it to be rare. Another factor not considered previously is the effect of amyloidosis. The primary systemic type is associated with petechiae of the skin

(Goltz, 1952) due to involvement of small blood vessels and, although it is not mentioned in any of the cases described in this section, it is very unlikely that it was sought after. Its role must await further investigations.

DIFFERENTIAL DIAGNOSIS.

It is of great importance that the more benign disorders of the serum proteins should not be confused with myelomatosis.

Among other features in common, they both have haemorrhagic tendencies, evidence of which may be manifested in the nervous system.

There is a group of disorders embraced by the term "macroglobulinaemia" (Waldenström, 1952, pp.414-423). They all have as a basic defect a serum component isolated only by ultracentrifugation, and the disease is a diffuse one akin to the plasma cell type of leukaemia which in the past may have been confused with one of these syndromes. (Note Case 14 of Lumb and Prosser, 1948 where spinal complications occurred in the presence of a disease styled plasma cell leukaemia). They are characterised by haemorrhagic manifestations, severe anaemia, general decalcification of bones and a very high erythrocyte sedimentation rate.

Waldenström (1952) recognises among this group an "essential" type of hyperglobulinaemia which is alike in

many ways to myelomatosis but, because of its favourable prognosis, should be recognised as a distinct entity. He describes a patient with central retinal vein thrombosis, back and limb pain and other features suggestive of multiple myelomatosis, but no signs of this disease could be detected despite a careful follow-up of the patient for fifteen years.

Another member is "purpuric hyperglobulinemica" (Waldenström, 1952, pp.417-419) and it should be considered in the differential diagnosis of myeloma with haemorrhagic manifestations. Its course is also a benign one and its recognition is therefore especially important. The high serum globulin content is associated with chronic purpura and can only be distinguished by bone-marrow studies. It seems possible that the cases described by Lindeboom and Mulder (1941) may belong to this group and the mysterious cases detailed already (p.207) may also be associated.

Finally, cryoglobulins associated with purpura (Waldenström, 1952, pp.420-423) must be mentioned. Although this disturbance of serum proteins most often accompanies multiple myeloma, on rare occasions it may be an isolated phenomenon. The differential diagnosis, however, is a difficult one and must be left in the hands of the protein chemist.

Despite their rarity, these conditions should be considered when myelomatosis with purpuric manifestations is

encountered. Firstly, because the prognosis may be profoundly affected and secondly because they are opening up a fruitful field of investigations in a subject that at the moment is very obscure but promises to be of no little value.

TREATMENT.

Treatment of the vascular complications of myelomatosis has never been considered. The neurological events have usually occurred at a stage of the disease when therapy was patently valueless.

However, in certain cases, therapeutic measures may be considered. Surgery for the intracranial or spinal haemorrhage, vasodilators such as "priscool" for the retina, and carbon dioxide for the brain to combat local ischaemia as well as anticoagulants may be of some value. However, these procedures are dealing with the products of a basic disorder and the possibility of affecting this by therapy, at the moment, seems hopeless.

PROGNOSIS.

The haemorrhagic intracranial episodes have been uniformly fatal, whereas retinal haemorrhages, as seen already (p.77), do not usually contribute in themselves to the progress of the disease. Vision may be temporarily impaired if the macular region is involved but some recovery

is to be expected. The course of the disease as a whole determines the ultimate prognosis.

CONCLUSIONS

1. Haemorrhagic and thrombotic manifestations in the central nervous system and retina are rare complications.

2. Subdural haematoma, intracerebral and retinal haemorrhage and thrombosis have been described.

3. The basic mechanism appears to be auto-agglutination due to hyperglobulinaemia, but other agents such as amyloidosis and defective blood factors are possibly involved.

4. Benign types of hyperproteinaemia must be differentiated from myelomatosis on account of prognosis, and possible contributions to an interesting and complex subject.

THE CEREBROSPINAL FLUID IN
MULTIPLE MYELOMATOSIS

Some of the changes in the cerebrospinal fluid have already been indicated but they will now be collected together with additional observations incorporated. The abnormalities will be discussed under headings related to the physical, cytological and chemical properties of the fluid.

Only on a few occasions has the C.S.F. been examined in patients who had no evidence of nervous system involvement. Our appraisal of its changes therefore deals almost exclusively with cases where abnormalities were present, and unfortunately it is not possible to indicate the frequency of the changes to be detailed. However, the presence of some influence upon the nervous system, albeit silent, cannot with confidence be excluded in patients in whom the nervous system is otherwise intact.

GENERAL APPEARANCES.

Only in the C.S.F. from patients with spinal compression produced by a spinal myeloma has a colour change been detected. Occasionally, a yellow discolouration was noted, which was merely part of Froin's syndrome and indicated a

spinal block. The xanthochromia was probably produced by lipid-like substances resulting from the destruction of spinal cord tissue, as occurs with any type of spinal compression (Crosby and Weiland, 1953), and gives no indication of its aetiology.

PRESSURE.

There are only two changes that need be mentioned. The first is an increase of C.S.F. pressure indicating increased intracranial tension and a space-consuming lesion. Other evidence of this is usually present and illustrative cases have already been referred to (p.43 and p.82).

Secondly, manometric examination in patients with spinal myelomas frequently demonstrated a block of the spinal subarachnoid pathways, which was either partial or complete, depending upon the degree and site of spinal compression.

CELLS.

It is very rare to find an excess of C.S.F. cells in myelomatosis. In cases without neurological complications the data is quite inadequate. Degenhardt and Sheehan (1949) reported three cases where there were no neurological features and the cell count was normal, whereas Madonick and Solomon (1953, Case 2) in a similar case found sixteen lymphocytes.

There are four cases that must be discussed. The patient described by Durman (1928) had "symptoms suggesting an early meningitis", but no more information is given and the report on the C.S.F. is not included. Although Case 5 of Madonick and Solomon (1953) had "nuchal rigidity", there was no other evidence, either clinically or in the C.S.F., of meningitis, and it should be noted here that a myeloma of the cervical or upper thoracic spine will produce rigidity of the neck closely simulating that due to meningeal irritation. A more interesting case was that of Laurentius (1938) mentioned already (p.61) in connection with myeloma of the dura mater. The case was that of a child with myelomatosis who had presented with signs of a low-grade meningitis. At first, the C.S.F. cell count was normal and a few days later it was increased to forty-four (equal numbers of polymorphonuclears and lymphocytes). The other constituents were normal, except a positive Pandy test and a slight first zone curve in the mastix and gold sol reactions. The author thought that a myeloma extending through the meninges could have produced a serous meningitis, but he had no autopsy verification of the suggestion. As was postulated earlier (p.62), this was probably a coincidental phenomenon, a conclusion that is supported by a very similar case reported by Turner and Smith (1949). The patient was a child and the presenting features of myelomatosis were mild

signs of meningism with 240 un-named cells in the C.S.F. Unfortunately, this aspect of the case was not discussed and no definite opinion was given. That both these patients were children is of note, but further elucidation does not appear to be profitable. However, from the knowledge of the manner in which myelomatosis imposes itself upon the nervous system, it is known that extension of tumour tissue through the dura is extremely rare despite its frequent proximity to it. Further, in patients where such extension has been proven (M.G.H. Case No.20031: Case Five: Case Seven) the C.S.F. has shown no pleocytosis.

Other cases, however, have been described with an increase of cells. Of the cases with basal myelomas, the patients of Riser and Sorel (1929) and Gros (1945) had ten and nine lymphocytes respectively. There seems to be no correlation between this and either the pathological findings or the rest of the fluid's properties.

The spinal myelomas provide a useful group because in many of them the C.S.F. was examined. Taking first the series of cases presented above (Appendix I, Cases Eight to Twenty-four), it was found that of fifteen not one had an abnormality of the cell content. The opportunities for an increase of cells in these cases are greater than in other types of myelomatosis, because there is always tumour tissue growing in intimate relationship to the dura and concentration

of the fluid, produced by a subarachnoid block, would tend to increase the number of cells in the lumbar sac. The absence of a pleocytosis is a striking tribute to the dura mater's role as a barrier against the advance of myelomatous tissue. In cases from the literature, however, (Appendix IIA) an excess of cells is occasionally reported. Thus Davison and Balser (1937, Case 1) found forty cells (30 polymorphs and 10 lymphocytes), and as dural invasion had taken place it is possible that they had resulted from this. But of the sixty-two cases (Appendix IIA and B) this is the only example of a pleocytosis, the next lowest figure being sixteen (Petrides, 1939, Case 1), despite the occurrence of dural myelomas in some other patients. This one case report therefore should be accepted with reserve.

If myelomatous tissue grows through the dura mater or if infiltration of this membrane occurs, it might be expected that some of the plasm cells would eventually find their way into the subarachnoid space and be found in the C.S.F. It is doubtful, however, whether this ever occurs. Busser and Bugaut (1937) found an occasional monocyte, but only Khondkarian (1950) alludes to plasma cells in the C.S.F.

In conclusion, it can be stated that for all practical purposes a C.S.F. pleocytosis in myelomatosis does not occur, thus emphasising again the inability of this disease to invade the nervous system in a manner that is seen with the

other malignant lymphomas (Sparling et al., 1947), leukaemia (Critchley and Greenfield, 1930) and carcinoma (Jacobs and Richland, 1951). It is interesting to note that Schwab and Weiss (1935) found that five out of sixty-nine patients with leukaemia had meningeal signs.

PROTEIN.

The protein of the C.S.F. in myelomatosis is one of the most interesting aspects of this problem. It has not however been studied in as great detail as its serum counterpart, and Waldenström (1952) when reviewing the present knowledge of protein disturbances in myeloma does not mention it. Unlike the cell count, it is frequently abnormal.

(1). Observed abnormalities.

First of all, the protein abnormalities found with neurological complications of myelomatosis will be noted. As the normal C.S.F. protein content varies in different laboratories, it is difficult at times to evaluate the figures that appear in the literature. A value of 50 mgm. per cent has been accepted as the upper limit of normal. Thus, considering the myelomas of the skull base (pp.17-37), four patients (M.G.H. Case Record No.20031, 1934: Gros, 1945: Sparling et al., 1947, Case 20: Delmas-Marsalet et al., 1951) had an increased amount, the highest quantity

being 95 mgm. per cent. In four others it was normal and there seemed to be no correlation between the size of the basal lesion and the protein level; an excellent example of this is the huge myeloma in Case One, where the C.S.F. was normal to the usual tests.

Involvement of the skull vault rarely leads to an alteration in the C.S.F. per se, but information on this matter is scant because a lumbar puncture has rarely been carried out on these patients nor on those with no neurological features. In Case 1 of Denker and Brock (1934), however, an increase of C.S.F. protein was seen to occur as the calvarium became diffusely diseased. Here again there was no relationship between the degree of skull involvement and the protein level. It was normal in Cases Four and Five.

In the presence of a spinal myeloma, the additional factor of spinal compression is introduced and the height of the protein content is, in these cases, determined by the size of the lesion and thus the severity and the chronicity of the subarachnoid block. Levels exceeding 1,000 mgm. per cent (M.G.H. Case Record No.24192, 1938: Flynn and Sailer, 1941: Bernard et al., 1946, Case 1) are found and a considerable increase is not uncommon.

Finally, in myelomatous peripheral neuropathy an increase of spinal fluid protein was found in half of the

reported cases (p.189). This finding suggests that the pathological changes are not restricted to the peripheral nerves but involve the spinal roots also. A close comparison can therefore be made with diabetic neuropathy (Rundles, 1945) and other forms of this disease.

(2). Aetiology of the protein changes.

Excluding the cases with spinal compression, the origin of the increased C.S.F. protein is obscure. Electrophoresis has greatly added to our knowledge but evidence deduced without its use will first be presented.

Degenhardt and Sheehan (1949) indicated that the C.S.F. rather than the serum protein might be a more sensitive index of a disturbed generalised protein relationship in the body, whereas Madonick and Solomon (1953), extending their work, could find no relationship between the total serum and the total spinal fluid protein concentration. That much of the protein is made up of globulin can be detected by the frequency of a strongly positive Pandy test and marked changes in the Lange reaction.

However, it has been possible to elucidate further these conflicting views by employing electrophoresis. Wallonius (1952) and others have shown that the C.S.F. proteins are normally identical with those of the serum and in myelomatosis the high serum globulin is also to be found in

the spinal fluid (Labhart, Schweizer and Staub, 1951), as was already known from the cruder tests noted above (Pandy and Lange); this process is effected presumably via the blood-brain barrier. However, Kabat, Freedman, Murray and Knaub (1950), investigating cases of disseminated sclerosis, demonstrated a high C.S.F. globulin although the total protein content as determined by the usual laboratory procedure revealed a normal fluid. This can also occur in myeloma and would explain the disparity between C.S.F. and serum findings in the patients of Madonick and Solomon (1953). If the serum globulin is normal and the C.S.F. content is increased, some other mechanism than transfer across the blood-brain barrier must therefore be postulated. Kabat, Moore and Landow (1942), using electrophoresis in examination of the C.S.F. in patients with neurosyphilis, and more recently Wallenius (1952), have shown that a localised synthesis or release of globulin may occur in the meningeal spaces. As it is known that the hyperglobulinaemia of myelomatosis is produced by the plasma cells (Waldenström, 1952), it would be necessary to suggest that the same events take place in the C.S.F. if an increase in globulin is found only in the latter. However, it has been seen that only on very rare occasions, if ever, does myelomatous tissue reach the nervous tissue of C.S.F. pathways. Here, therefore, for the first time there is evidence suggestive of myelomatosis extending its influence into the

central nervous system other than by direct pressure. However, the possibility of a globulin-like substance produced by the myeloma cells outside the nervous system finding its way across the blood-brain barrier is not excluded. The Bence Jones protein can be excluded as a possibility, as will be seen shortly. The mechanism is, at the moment, quite unknown but offers an interesting field of research.

One further aspect of this problem must be mentioned, and this is that Madonick and Solomon (1953) could not establish a correlation between the C.S.F. protein content and nervous system involvement. Thus patients without neurological complications might have an increased C.S.F. protein (as was also shown by Moeschlin, 1943) and we have noted already that the reverse also occurs. This is obviously a very important consideration, because an abnormal C.S.F. does not therefore indicate nervous system complications although whether they will develop later in some of the cases is not determinable. Madonick and Solomon (1953) found that out of twenty-one cases of multiple myeloma eleven had an increased C.S.F. protein content, and of these four had no neurological signs. Further correlation with electrophoretic studies is obviously needed.

Using the same series of cases, Madonick and Solomon (1953) could find no relationship between Bence Jones pro-

teinuria and the C.S.F. protein. The C.S.F. in eight cases was examined for Bence Jones protein but in only one was it definitely present and in another the test was doubtful. Degenhardt and Sheehan (1949) looked for it in three cases but found it in none, whereas both Magnus-Levy (1931) and Müller (1931) were successful with individual cases. The whole subject of the Bence Jones protein is still obscure (Snapper et al., 1953, pp.58-63) and the significance and mechanism of this finding is likewise problematical. The fact, however, that this abnormal protein may be produced by the plasma cell (Magnus-Levy, 1931) which is known to be excluded from the C.S.F. is an additional unelucidated problem worthy of further attention. A possible explanation is its passage across the haemato-encephalic barrier, a mechanism also invoked for the presence of increased C.S.F. protein in such diverse conditions as myxoedema (Thompson, Thompson, Silveus and Daily, 1929) and chronic nephritis (Lyttle and Rosenberg, 1927). Moeschlin (1943) thought, however, that there was some correlation between albuminuria and C.S.F. globulin for, whereas in the only case where the latter was absent Bence Jones proteinuria occurred, in each of the other four the reverse was found.

LANGE REACTION.

The various tests employed (mastix, gold sol, etc.) are very delicate and tend to vary somewhat in the hands of

different workers and in different laboratories. This may occasionally account for the variations found in the literature. As this test is dependent upon globulins in the spinal fluid, it seems that these findings are merely a reflection of the hyperglobulin-liquor dealt with in the preceding section.

Firstly, it is necessary to exclude the abnormal Lange curve seen in cases of spinal compression due to a myeloma. As in cases with other aetiological factors, this finding, like the xanthochromia, is but a part of the compression syndrome of Froin. It was seen frequently in the cases of spinal myeloma; occasionally there was a strongly paretic reaction (Denker and Brock, 1934, Case 2; Snyder and Wilhelm, 1948; Case Twenty-one) and sometimes a mid-zone type (Davison and Balser, 1937, Case 2; M.G.H. Case Record No.26072, 1940), but three times the change was of the meningitic variety (M.G.H. Case Record No.24192, 1938; Petrides, 1939, Case 1; Moeschlin, 1943, Case 4). A manometric block was found in all these cases and the W.R. was invariably negative when reported. In six cases of the present series (Appendix I), an abnormal curve was found in one.

That these changes can also occur in patients without central nervous system involvement is indicated by Degenhardt and Sheehan (1949, Case 10) and also Moeschlin (1943,

Cases 1, 2 and 3).

There are in the literature four cases with neurological changes but no obstruction to the spinal C.S.F. pathways, where a very strongly paretic curve was recorded (Durman, 1928: Bross, 1931, Case 2: M.G.H. Case Record No.20031, 1934: Sparling et al., 1947, Case 21). In some, the curve represented both a first and second zone displacement (5555554332 - Sparling et al., 1947, Case 21) and in at least one the distortion was present in all zones (5555555554 - M.G.H. Case Record No.20031, 1934). In each of these cases, except M.G.H. Case Record No.20031 (1934) where it is not recorded, the blood W.R. was negative and neurosyphilis could be excluded with confidence. Although the patient of Bross (1931, Case 2) had bilateral ptosis, an abnormal pupil and a patch of old choroiditis, the C.S.F. W.R. was negative and the fluid was normal except for the paretic Lange and mastix reactions and a positive Pandy and Nonne-Apel't test. The absence of cells suggests that the spinal fluid changes were not due to syphilis but probably to the myelomatosis.

Moerschlin (1943) has examined this phenomenon in five cases, one of which (Case 4) had spinal cord compression and has been referred to already (p.127). In four of them (including Case 4) first zone curves were found. He correlated these changes with the marked increase of

globulin which occurred in them but which was absent in the only normal one (Case 5). The cell content of the fluids was normal. In Case 4 with spinal compression, he noted a double curve obtained by the mastix test.

As Moeschlin (1943) has suggested, in the absence of neurosyphilis the finding of a paretic Lange curve in the C.S.F. may be a useful point in favour of the diagnosis of myelomatosis in an otherwise difficult case. Its presence, however, does not necessarily imply nervous system involvement. It is interesting to note in passing that Schwab and Weiss (1935) describe the occurrence of a paretic Lange curve in the C.S.F. of a patient with acute myelogenous leukaemia.

OTHER CHANGES.

The W.R. in the C.S.F. was described as "weakly positive" in Case 1 of Guggenheimer (1924) but no other C.S.F. findings are given, and as in Peyton's (1934, Case 1) patient where the reaction was positive, no conclusions are possible on the evidence available. Presumably syphilis occurred as a coincidental disease or the result was false.

The chloride and glucose content of the C.S.F. has only occasionally been estimated but no abnormalities have been reported. Studies on other electrolytes have not been carried out.

CONCLUSIONS

1. In cases of myelomatosis with spinal compression the C.S.F. findings are of considerable diagnostic value. However, as the C.S.F. is abnormal with and without neurological complications, its use in diagnosing other forms of nervous system involvement is obviously limited.

2. Intracranial encroachment may increase the fluid pressure, but a marked pleocytosis probably never occurs.

3. The protein is often increased, the globulin portion being prominent, as shown by the electrophoretic pattern and a strongly positive Lange curve. These latter alterations in the properties of the C.S.F. are the most important, both as regards elucidation of the nature of myelomatosis and its effect upon the nervous system, as well as a help in the diagnosis of the primary disease.

CONCLUSIONS

The neurological complications of multiple myelomatosis are an important aspect of its clinical picture.

They can be grouped on an anatomical basis according to the region of the nervous system involved. The following classification is a useful one:-

1. Involvement of brain, cranial nerves, cranial dura mater and orbit. It is possible to subdivide this further into clinical sub-groups:-

Group I. Cranial nerve palsies. A myeloma of the basal bones, especially the sphenoid and petrous temporals, can produce one or several cranial nerve palsies.

Group II. Intracranial tumour syndromes. Here are included such features as increased intracranial tension, focal neurological abnormalities, epilepsy, diabetes insipidus and mental changes. These cases all have myelomas of the skull vault but, very rarely, a tumour may grow from the intracranial dura. If the latter develops from the convexity membrane it produces the effects of its osseous counterpart, but if it grows from the dura elsewhere (e.g. tentorium) it cannot be identified clinically. Diffuse invasion of the dura mater produces no recognisable features.

Group III. Intra-orbital tumour syndromes.

The myeloma grows either from the orbital structures or walls and is therefore primary, or it arises from para-orbital structures and invades the orbit later and is secondary.

2. Ophthalmological manifestations include retinal thromboses and haemorrhages, papilloedema, ocular nerve palsies and encroachment upon the optic pathways.

3. The spinal cord is involved in about 20 per cent of cases of myelomatosis but only 6 per cent reach a stage of compression paraplegia. The lesion is most commonly in the bone (lower nine thoracic vertebrae, especially T.4, 5 and 6) but a primary epidural and dural myeloma occurs. The clinical picture is a constant one of back pain and root pain, followed by symptoms and signs of spinal compression. The onset is associated with trauma, often mild, in 16 per cent of cases.

4. Spinal roots are frequently affected with the production of pain which is a characteristic feature of this disease. On rare occasions "secondary" herpes zoster may occur.

5. Peripheral nerves may be compressed but peripheral neuropathy is a distinct clinical entity. It is submitted that primary amyloidosis associated with myelomatosis may play a role in the aetiology of this condition.

There are other complications which are not due to direct pressure by myelomas:-

1. Primary amyloidosis may also affect other parts of the nervous system, usually by compression.

2. "Toxic" effects of myelomatosis upon the nervous system have been postulated but there is no conclusive evidence of their existence.

3. Vascular events accompanying myelomatosis may involve the nervous system; cases of cerebral thrombosis and haemorrhage, as well as retinal changes mentioned above, have been described. One of the factors in their aetiology is hyperglobulinaemia.

4. Cerebrospinal fluid changes are uncommon, the only one of note being an increased protein content, usually with increase of the globulin fraction. Electrophoresis shows that this is not a direct product of the serum content.

Any one of these complications may be the first indication of the disease multiple myelomatosis, or it may appear during the course of the condition. It may precede other evidence of the disease by months or years; there is, however, strong evidence to suggest that a genuine solitary myeloma exists. On the other hand, neurological complications may occur in the presence of the generalised disease.

Treatment is unsatisfactory and the eventual course

of the disease is rarely if ever altered by it. A careful combination of radiation therapy, surgery and histiotoxic drugs is recommended as the therapy of choice. Results are best with spinal compression where treatment should be employed despite the presence of the generalised disease in some cases.

A study of the reactions of the nervous system to multiple myelomatosis reveals a very interesting and significant finding. Unlike other malignant diseases, the other lymphomata and the leukaemias, invasion of nervous tissue rarely if ever occurs. Investigation of the cause of this phenomenon would add not only to our knowledge of myelomatosis but also to our understanding of the nervous system. This problem would seem to be but a small part of a much more extensive undertaking to evaluate the response of the nervous system to non-neurological diseases of all kinds. Exploration of the borderland between general medicine and neurology is a profitable and necessary field of research for the future.

SUMMARY

With the aid of twenty-six cases and a review of the world's available literature, the neurological aspects of myelomatosis have been studied.

First of all, conditions produced by local pressure upon nervous tissue are described and can be grouped according to the anatomical region involved. Thus, brain, cranial nerves, cranial dura mater, orbit, eyes, spinal cord and roots and finally peripheral nerves are considered in turn. Each complication is dealt with in detail and with adequate reference to the literature and illustrative cases.

Next, certain conditions which accompany myelomatosis and influence the nervous system are detailed. They produce their effects other than by pressure and include amyloidosis, vascular manifestations and "toxic" effects. It is suggested that amyloidosis plays a role in the latter.

Finally, the changes in the cerebrospinal fluid are mentioned.

The reaction of the nervous tissue to myelomatosis is an interesting one because invasion probably never occurs.



i.e., 126 lb (570 g) per child per week. If the rate of contamination was 1 p.p.m., a meal containing 100 g of groundnuts would result in a dose of 0.1 mg, which would be 0.0025 mg per kg body-weight in a 40 kg (88 lb) child. The lethal dose (LD₅₀) in 50% of ducklings is 0.4 mg per kg, to attain this a 40 kg child would need to eat 16 kg of nuts, which is unthinkable. However, if the nuts contained 10 p.p.m. it would require little more than 2 weeks for a child to total an LD₅₀ duckling dose. From the data presented here on the state of the nuts in relation to aflatoxin content (tables II, III, and IV) it would seem difficult for a level of contamination of 10 p.p.m. or more to escape unnoticed, many would discard groundnuts if there was an obvious growth of mould. However, at a level of 1 p.p.m. the fungal growth may not be sufficient to make it obvious to casual observation (fig. 1). At this concentration the description of the nuts was predominantly "many with broken testa".

There is, however, a real danger that the mould may grow on the nuts during a damp period followed by an arrest in growth with a change in climate or storage conditions. The nuts may then appear relatively free from mould, although they may be dirty. This may well have been the case in sample 25 which was classified as in a fair condition, but had a high aflatoxin content. With this last reservation, it is probable that groundnuts could be regularly eaten with an aflatoxin content of up to 1 p.p.m. Whilst on the one hand it would take a considerable period of time for an LD₅₀ dose to be consumed, it should also be pointed out that the sample examined by us was free of *A. flavus* species. It is difficult to predict the cumulative effect at such a low dose, but as the effect of aflatoxin is so specific, it is sufficient to know about the cumulative effects of low doses to reach a conclusion regarding its implications to human hepatoma in Uganda except to say that if it does play a role it is most likely to be intermittent and chronic. The probability of a toxic dose being consumed at one meal is almost negligible, and at 1 p.p.m. it would require something like 6 months to total such a toxic dose.

An analogy with current views on radiation hazards may provide some guidance to the situation. The maximum accepted safe cumulative dose throughout any given year is approximately 1/100th of a single lethal dose (Adrian Committee 1966). If the analogy is valid, it might provide a basis for considering the possible harmful effects of aflatoxin in foodstuffs.

The obvious speed with which the aflatoxin can accumulate in groundnuts, given the right conditions, the nature of cropping, length of storage, humidity, and rainfall in areas where the groundnuts are grown, recommends a more detailed inquiry than was possible here. Furthermore, the report by Coady (1965) on the isolation of aflatoxin-producing fungi from other food sources in Malawi indicates that attention should not be confined to groundnuts.

We thank Dr. J. Nabney for supplying us with details of his method for estimation of aflatoxins before publication, the British Empire Cancer Campaign and the East African Medical Research Council for supporting this research, and Dr. Y. M. Clayton for assisting us with the identification of the species of fungi.

Requests for reprints should be addressed to M. A. C., Nuffield Institute of Comparative Medicine, Zoological Society of London, NW 1.

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Before Our Time

SOME ASPECTS OF THE FIRST RECORDED CASE OF MULTIPLE MYELOMA

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IN an important series of papers published between 1846 and 1850, John Dalrymple,¹ Henry Bence Jones,²⁻⁴ and William MacIntyre⁵ described all the essential features of the disease now known as multiple myeloma. These papers covered the clinical aspects of the disease, the properties of Bence Jones protein, the postmortem findings, and the histological appearances, and left no doubt that the authors considered this a hitherto undescribed disease "essentially malignant in nature" affecting the "nervous system".

WILLIAM MACINTYRE

William MacIntyre was perhaps the most remarkable member of this outstanding trio. He was, at the time he saw the patient in 1845, 55 years of age and physician to the Metropolitan Convalescent Institution and to the Western General Dispensary, St. Marylebone. On Friday, Oct. 30, 1845, he was called from his rooms at 84 Harley Street, to see a patient who had been under the care of Dr. Thomas Watson for several months. From the history and examination, MacIntyre noted many important clinical features of the disease, including the severe bone pains and could later assess the significance of the pathological fractures. Equally remarkable was the care with which he observed the colour of the urine. In view of the history of oedema, one of the first acts when he saw the patient had been to carry out this examination. He thereby noted and later described all the important characteristics of the protein that subsequently and with little justice became known as Bence Jones protein. The ability of the precipitated protein to redissolve with a rise in temperature of the urine, only to reprecipitate as the urine cooled, was clearly described. MacIntyre was also aware of the other property of this protein—namely, its tendency to precipitate at temperatures considerably lower than those of other proteins. Thus, he noticed that the protein redissolved at the "coagulating point" of albumin, namely, 160–170°F (71–77°C)—the inference being that the protein had precipitated at a temperature well below this.

Dr. Watson had evidently not examined the urine during the time that the patient had been under his care. But he appears to have been present during the discovery of this unusual protein or else MacIntyre discussed his perplexing findings with him, since both physicians quite

1 Dalrymple, J. *Edinb. J. Med. Sci.* 1846, ii, 85.

2 Bence Jones, H. *Lancet*, 1847, ii, 88.

3 Bence Jones, H. *Trans. R. Soc.* 1847, 5, 673.

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5 MacIntyre, W. *Med. Chir. Trans.* 1850, 33, 211.

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independently sent a specimen of urine to Bence Jones. It was customary then for the specialist services to be provided by practising physicians and surgeons, and Bence Jones had already established a reputation as a chemical pathologist.

BENCE JONES

Henry Bence Jones, of 50 Lower Grosvenor Street, was at this time only 31 years of age and was physician to St George's Hospital. He was able to confirm MacIntyre's findings and then proceeded to examine the urinary protein in some detail. His papers were therefore concerned with the properties, analysis, and significance of this protein, whereas the paper by MacIntyre dealt mainly with the clinical features of the disease. For this reason, Bence Jones became credited with the discovery of the protein. Further confusion arose over the part played by Dr Thomas Watson, since Bence Jones quotes the letter from Dr Watson which accompanied the urine: "The tube contains urine of very high specific gravity. When boiled it becomes highly opaque. On the addition of nitric acid it effervesces, assumes a reddish hue and becomes quite clear, but as it cools assumes the consistency and appearance which you see. Heat reliquesfies it. What is it?" Nevertheless, the fact that the urine specimens were sent on Saturday, Nov. 1, 1845—that is, the day after Dr MacIntyre had been called in for consultation—supports MacIntyre's claim to the discovery, and this is established by the statements made by Bence Jones in his papers. In the first² he writes: "On the last day of October, a peculiar state of urine was discovered, through the carefulness of Dr MacIntyre", and in the second,¹ "He [Dr MacIntyre] being in attendance on the case with Dr Watson, had two days previously first observed the peculiar reactions of the urine."

DALRYMPLE

MacIntyre³ also described the postmortem examination carried out by Mr Alexander Shaw, surgeon to the Middlesex Hospital. The significant findings were in the bones, particularly the ribs and sternum, and the cervical, thoracic, and lumbar vertebrae. The affected bones were softened, fragile, and easily cut, with the interior replaced with a soft, "gelatiniform", blood-red substance. Some of this material taken from two of the lumbar vertebrae and a rib was referred for histological examination to John Dalrymple, surgeon to the Royal Ophthalmic Hospital, Moorfields, and a member of the Microscopical Society. He described the nucleated cells which were present in great numbers and which formed the bulk of this gelatiniform mass. These cells were said to vary in size and shape but the majority were round or oval with the smaller cells "one and a half to twice larger than the average blood cell or blood disc" (red blood-cells).

TABLE I—DETAILS OF PATIENT WITH MULTIPLE MYELOMA DESCRIBED BY WILLIAM MACINTYRE AND HENRY BENCE JONES

	MacIntyre ³	Bence Jones ^{1,2}
Name	Mr M—	No details
Address	London	London
Age at death	45	45 ¹ 47 ²
Date of death	Jan. 1, 1846	Jan. 2, 1846
Occupation	Tradesman	Tradesman ¹ Grocer ²
Social details	Married early Numerous offspring "Holiday in Scotland"	Wealthy

Dalrymple also noted that the larger and more irregular cells frequently contained two and often three nuclei. These descriptions would be consistent with malignant plasma cells with some multinucleated forms. Dalrymple's paper was illustrated by two woodcuts which were credible drawings of these cells. Both Dalrymple and MacIntyre believed that this disorder was principally a malignant disease of bone. They were puzzled because the tumour had not extended outside the bone, and thus they explained by the limited duration of life of the nucleated cells and therefore limited production of bulk by the tumour.

THE PATIENT

The identity of the patient has so far been unknown. It would also be interesting to know the cause of death that appeared on the death certificate of this first recorded case of multiple myeloma. In order to trace this case therefore, the personal details of the patient were taken from the various papers (table 1). Unfortunately, the index of deaths for the first quarter of 1846 gives only the names in alphabetical order, the district of registration, and the volume and page number of the entry in the Register of Deaths. The initial step in the search was therefore to extract from the index the names beginning with M, of all males who died in the London area. In the first quarter of 1846, of the 45,941 males who died in England and Wales, 7259 had names beginning with M, and of these 437 died in the London area. These names were then arranged according to volume and page number to facilitate the search of the Register of Deaths by officers of the General Register Office. The search instructions were to note all names of men aged 45, 46, or 47 years, who died on Jan. 1 or 2, 1846. The expected number of such men can be calculated. Thus, 437 names will represent all deaths from birth onwards, and from the figures in the Annual Report of the Registrar General for that year about 20 of these would be aged 45 to 49 years. Assuming that the death-rate is equal over this age-span, then only about 12 of these men would be aged 45, 46, or 47. These 12 men would have died over the period from Jan. 1 to March 31, and therefore no more than one of these can be expected to have died on Jan. 1 or Jan. 2.

TABLE II—DETAILS OF DEATH CERTIFICATE

When and where died	Name and Surname	Sex	Age	Occupation	Cause of death	Signature, description and residence of informant	When registered	Signature of Registrar
First of January 1846 at No. 37 Devonshire Street	Thomas Alexander McBean	Male	45 years	Grocer	Atrophy from Albuminuria Certified	Mary Davidson present at death No. 22 Devonshire Street	Eighth of January 1846	William Clapp Registrar

The search agreed with this prediction, since only one man was found who fulfilled all the particulars and this person must therefore be the patient seen by Watson, MacIntyre, and Bence Jones (table II). It is gratifying to find that the death certificate is consistent with the known personal details, including the holiday in Scotland! Not unexpectedly, the details of the patient given in MacIntyre's paper are correct, in contrast to some of the details given by Bence Jones. The cause of death is given as "atrophy from albuminuria". This was a reasonable diagnosis, since the term albuminuria was used in those days quite non-specifically to mean proteinuria. Alternatively, the cause of death might have been given as "McBean's disease with MacIntyre's proteinuria".

I should like to thank the officers of the General Register Office for their kind cooperation.

Round the World

U.S.A.

The growth of the Citizens League Against the Sonic Boom, based in Cambridge, Massachusetts, has been striking. Founded only nine months ago (March 9, 1967) by nine charter members, it has today over 2000 members from the U.S.A., Canada, the United Kingdom, and Sweden. The director, Dr. W. A. Shurcliff, is a physicist at Harvard University, and the deputy director, Prof. J. T. Edsall, is a biochemist, also at Harvard. The League includes many other eminent professional men— aeronautical and acoustical engineers, biologists, doctors, law vers, economists, architects, teachers, and musicians.

The League takes up no position about military planes and their sonic booms, but vigorously opposes the development of commercial—i.e., civilian—supersonic transport planes (SSTs). Using facts gleaned from deep within Government reports on sonic-boom tests, and some wrung from the U.S. Federal Aviation Administration (monolithically for the SST) the League has prepared an impressive array of moderately written fact-sheets, recording firm evidence that sonic booms of intensity 1 lb per sq ft are intolerable—both to people and to property—and concluding that the 2 lb per sq ft booms predicted for the SSTs would be "doubly intolerable".

The League has moved fast. It has collected a library of technical reports and clippings about sonic booms, drafted and published advertisements in many magazines and newspapers, including several half-page advertisements in the *New York Times*, and raised more than \$20,000 through voluntary contributions. It has created a national committee, it has taken part in many TV and radio programmes, it is in touch with conservation groups in several countries, including the Anti-Concorde Project (give or take an e) in the United Kingdom.

The response has been enormous. Before March, 1967, only a few people had spoken out against the boom, noteworthy among these was Bo Lundberg, then director general of the Aeronautical Research Institute of Sweden. Since March, more than 900 newspaper articles and 40 magazine articles against it have been published in the U.S.A. Nearly every major newspaper has carried an article expressing alarm that Governments propose to subsidise the construction of a machine that, while saving a little time for an élite few and perhaps yielding a small profit for aviation, will destroy the peace and quiet of millions of people.

The League says that its educational campaign is to be intensified until the Governments are forced to admit that the sonic boom is more than a small defect in the SST programme, more than a mere annoyance, but is an outrage to civilised living. The League is not satisfied with Government protestations that, at the start at least, the SSTs would be operated only over oceans, it is convinced that, once loosed on the world, they will encroach on assured quiet until uninterrupted sleep will become a historical curiosity.

Very Special Articles

THE BOAT

"Well", said the Boatman, "so ye've wakened up at last."

"Yes", I said, "where am I?"

"In a boat", said he.

"Thanks", I said, "I can see that. Where is the boat?"

"I don't rightly know", answered the Boatman.

"Do you mean to tell me that you sit there steering this craft, and by the look of you, have been doing so for a long time, and don't know where we are?"

"That's what I said", he replied.

"Do you perhaps know where we are bound, then?"

I asked, with a touch of sarcasm.

"No", he said.

"But" I began.

"Look, young feller", he answered, "when you was a-sleepin' in the bilges there, I thought ye'd the look of a sensible lad wot I could have a sensible talk with. Seems yer like all the rest of 'em, askin' a mort o' questions wot nobody knows answers to. I give up askin' questions afore yew was hatched, an' I only asked one then."

"What was that?"

"Same as yew, young man. When the owner give me this ol' boot, he say to me, 'George', he say, 'I'm hully sorry ter give yew this leaky old craft ter be master of, but es yew can see, I've nothin' else'. 'Where do I steer for?' sez I. He give me a queer ole look an' a wink, an' then sez he, 'Dew yew steer afore yer own nose, bor, an' some day happen yew'll git somewhere'. I could see he wuz a Suffolker, like me, so there warn't no use pesterin' him with talk an' questions, so I kep' me mouth shut. 'Dew yew keep 'er afloat, an' into the wind, bor', sez he, 'an' yew'll find yer time well occupied', an' with that he went off, slow-like up the hard, an' I never see him since."

"There seem to be lots of people on board", I said.

"Too many. The cussedest lot yew ever did see. When they ain't fightin' each other an' lightin' fires fit to burn the bottom out of her, they're arguin' about wot none of 'em don't understand. See that lot up in the bows there", he said, suddenly becoming more communicative, "clever dicks if ever there was any. Always shoutin' back that they can see lights or land or summat, and tellin' me how to run this ship. If it ain't them, it's them others to port and starboard—different colour skins and talk, but the same ideas, more or less. All on 'em know my job better 'n I do, and jumpin' about so's yew can't keep 'er on an even keel. All the same, I'd rather 'ave them than this bunch in the stern, moanin' an' gripin' an' sayin' we're sinkin'—not but wot we aren't, 'alf the time. But we ain't done it yet", he finished with a note of triumph.

"Where are you from?" I asked.

"I'm out of Lowestoft", he said, "an' if ever I get back, you'll not find me at sea again, once I get this cargo of lubbers ashore. Gawd knows wot the owner wants 'em for."

"When are we supposed to arrive?" I asked.

"More bloody questions", he replied. "I've been sailin' this ole bitch of a boot some thousands of years now, young feller, an' I don't know when we're goin' to get into port, no more than when we started."

"What do you suppose I should do?" I asked him, rather diffidently.

"Yew do what yew please, young feller", he said. "I've got to steer this ol' boot till I get callouses on me backside, but yew please yourself. Some write books about the journey, some read 'em, some fight, or preach, or talk politics, or go whorin'. Not many get near an idea of wot the trip's about, an' they're usually the quiet sort wot 'ear songs in the wind an' see somethin' lovely in a gull's wing."

"Perhaps I could do something, as well as listen to the wind", I said, but the Boatman was gazing into the mist, and did not answer.

And that is roughly how I came to be a surgeon.

Previous therapy slows myelomatosis study

LEARNING the natural history of myelomatosis — which usually occurred in the eighth decade of life—was complicated by the treatments so many patients had already had before their true condition was diagnosed, a Kent Post-graduate Medical Centre meeting was told.

Visiting Canterbury, centre of a research project into the disease, Professor Jan Waldenström, of the University of Lund, Sweden, said that between 1950 and 1966 there had been 128 cases in the city of Malmö, which had a population of a quarter of a million. There was an equal sex distribution—compared with the 2:1 male-female incidence of lymphatic leukaemia — and none of the patients was under the age of 40.

Osteolytic changes on the X-ray, especially of the skull, were characteristic, but spinal X-rays were not so helpful because old people already had osteoporosis.

Plasma cells in the bone marrow, anaemia, an abnormal gamma-M-globulin (a narrow band on the electrophoretic strip compared with a broad band in autoimmune disease) and Bence Jones proteinuria were all diagnostic.

The prognosis was bad, Professor Waldenström said, if there was a pronounced anaemia

or if there was uraemia only six of 34 uraemic patients lived for a year.

He encouraged his patients to be ambulant and preferred to give melphalan (Alkeran) 5mg daily for 25 days, with an interval of 10-14 days before going on to a maintenance dose of 2mg daily.

It was essential to follow the blood picture, a WBC count of 2,000 with 100,000 platelets being the lowest limit of safety even when drug therapy was stopped, the WBC and platelet counts might continue to fall. Although the patients showed biochemical improvement the disease might progress.

The disappearance of bone pain was the most important clinical benefit from treatment. Healing of the osteolytic lesions was very rare.

The eventual causes of death were usually uraemia with lowering of urinary volume, hypercalcaemia, increasing anaemia and loss in weight.

Med. News

- 13 Oct. '67 -

WITH A WILL!

When you are consulted about bequests for medical work that deserves support, please remember the work of the Imperial Cancer Research Fund. Founded on the initiative of the Royal Colleges of Physicians and Surgeons, the I.C.R.F. is fighting all forms of cancer, including leukaemia, with every weapon of modern science in its own up-to-date laboratories. It has no official grants and is entirely supported by voluntary contributions. Will you please help—now?

How to word your Will

'I hereby bequeath the sum of ——— pounds free of duty to the Imperial Cancer Research Fund, Lincoln's Inn Fields, WC2 for the purpose of scientific research, and I direct that the receipt of the Honorary Treasurer or Secretary shall be a good discharge for such legacy.'



Patron:
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A. DICKSON WRIGHT, ESQ., M.S., F.R.C.S.,
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The I.C.R.F. Laboratories in Lincoln's Inn Fields and Mill Hill rely entirely on public support. Over £1 million is needed annually. Please help us to fight cancer with modern equipment and trained minds.