

Systemic amyloidosis and malignant disease

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SYNOPSIS Among 8,758 necropsies there are 93 cases of systemic amyloidosis. Of these, 14 are associated with malignancy: seven with myelomatosis or malignant lymphoma, and seven with carcinoma. The incidence of amyloidosis in myelomatosis is at least 10%. Attention is drawn to the presence of amyloid in the tubular casts of 'myeloma kidney'. In Hodgkin's disease the incidence is about 4% but it may be higher in patients receiving chemotherapy. In lymphosarcoma it is of the order of a fraction of 1% but in macroglobulinaemia, essential or associated with malignant lymphoma, the incidence is considerably higher. Systemic amyloid is found in one in 375 of patients with carcinoma and in only a single patient among 1,500 'control cases'. Renal carcinoma accounts for one-quarter of all carcinomas associated with systemic amyloid. The other carcinomas originate in a variety of organs.

In myelomatosis, amyloid may be found in the tumour deposits. In Hodgkin's disease and in lymphosarcoma there appears to be greater amyloid deposition in neoplastic tissue than hitherto realized. The carcinomas provide a striking example of topographical association of amyloid and tumour, the two being closely related in six of seven cases.

Systemic amyloidosis associated with malignant disease has received some attention in the recent literature but many of the problems arising from the association remain unsolved. This investigation was undertaken in an attempt to clarify some of the controversial points. We are not concerned here with amyloid deposited purely locally within tumours, a remarkable occurrence in a special type of thyroid carcinoma (Hazard, Hawk, and Crile, 1959), in pancreatic insulinomas (Porta, Yerry, and Scott, 1962), and in certain calcifying odontogenic tumours (Vickers, Dahlin, and Gorlin, 1965).

MATERIAL AND METHODS

This study is based on an analysis of 8,758 necropsies at Hammersmith Hospital between 1935 and 1962 inclusive; neonates up to 1 month old are excluded. The methods used to confirm the presence of amyloid consisted of metachromatic staining with methyl violet, staining with Congo red with resulting birefringence and dichroism, and the demonstration of pale green fluorescence in ultra-violet light after staining with thioflavine-T. Where hyaline collagen gave rise to difficulty, Van Gieson staining and the thioflavine-T method proved invaluable in distinguishing this from amyloid.

RESULTS

There were 93 cases of systemic amyloidosis, a figure that does not include minor degrees of senile (cardiac) amyloidosis. Twenty of these 93 cases were associated with malignant disease but after the clinical and necropsy protocols and the sections had been scrutinized, six cases were excluded because of coexistent disease that was probably or potentially responsible for the development of amyloid. There remain 14 patients in whom assessment of all data led to the conclusion that the malignant disease was responsible for the amyloidosis (Table I). In 10 of

TABLE I

AMYLOIDOSIS AND MALIGNANCY

Total number of cases of systemic amyloidosis	93
Systemic amyloidosis with malignant disease	14 (15%)
Systemic amyloidosis with myelomatosis or malignant lymphoma	7 (7.5%)
Systemic amyloidosis with carcinoma	7 (7.5%)

these there were no complicating factors, in four a recent or old infection was deemed unrelated to the amyloidosis for reasons given later. These 14 cases of systemic amyloidosis associated with malignancy represent 15% of all patients dying with amyloid

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disease: seven had myelomatosis or malignant lymphoma and seven were associated with a carcinoma.

The main clinico-pathological findings are summarized in Table II. Two reports illustrate the development of amyloidosis in different types of malignant disease.

ILLUSTRATIVE CASES

CASE 7 A 65-year-old man complained of increasing lassitude and shortness of breath since 1955. Ankle swelling developed and he was admitted to hospital in 1961. He was a thin man with a pulse of 80/minute. Jugular venous pressure was raised 4 cm. Blood pressure was 110/70 mm. Hg. The apex beat was in the fifth intercostal space, 4 in. from the midline. There was a loud third sound at the apex. The liver was palpable 2½ in. below the costal margin. Leg oedema was present. He had had suppurating wounds in 1916, and suffered from gout.

A chest radiograph showed generalized cardiomegaly, and an E.C.G. ventricular extrasystoles with flattened or inverted T waves. Haemoglobin was 10.2 g. %, W.B.C. 8,000/c.mm. The sedimentation rate was 120 mm./hr. Serum uric acid was 9.0 mg. %. Serum protein was 9.3 g. % (albumin 3.3 g. %, globulin 6.0 g. %). Electrophoretic analysis showed a very high narrow peak in the gamma globulin region; ultracentrifugal analysis showed an excess of macroglobulin, calculated to be about 25%, with a gross excess of the 19S component. There was no albuminuria or Bence-Jones proteinuria. Bone marrow aspirate showed a marked increase of lymphoid cells, mostly mature with some more primitive forms. Some plasmacytoid cells were present but few typical plasma cells. The appearances were consistent with a diagnosis of Waldenström's macroglobulinaemia. Heart failure responded transiently to digitalis, mersalyl, and a low-salt diet. Large numbers of atypical lymphocytes appeared in the peripheral blood terminally.

Necropsy Cervical, axillary, thoracic, and abdominal lymph nodes were enlarged. The para-aortic nodes were confluent and formed invasive masses infiltrating the thoracic wall and psoas muscles. Microscopically, the nodal structure was destroyed and replaced by cells intermediate between lymphocytes and plasma cells; a few P.A.S.-positive inclusions were present in the nuclei and cytoplasm. Appearances were those of lymphosarcoma with cytology indistinguishable from that seen in Waldenström's essential macroglobulinaemia. The hyperplastic bone marrow extended to the middle of the femur. It contained large numbers of cells similar to those present in the nodes. The spleen (179 g.) showed tumour cells in trabecular lymphatics. The liver (1,965 g.) showed tumour infiltration of portal tracts.

The pericardium showed microscopic tumour infiltration. The heart (565 g.) had a left ventricle measuring 20 mm. and a right 5 mm. (see below). The lungs showed consolidation of upper lobes with a pale glistening appearance due to infection with *Pneumocystis carinii*.

Massive amyloid deposits were present in the neoplastic nodes (Fig. 4), especially striking where sarcoma-

tous nodes invaded muscle. Amyloid was deposited in the myocardium and in adipose tissue (Fig. 6). Otherwise there was only minimal amyloid in glomeruli and the adrenal capsule.

It could be argued that the suppuration 39 years before the symptomatic onset was the cause of the amyloid, since amyloid can occasionally run a course of a couple of decades or more (McMichael, 1966). However, significant myocardial infiltration by amyloid remaining clinically silent for over 30 years is highly improbable. The amyloid distribution seen here is relatively uncommon in amyloidosis due to sepsis, and, more cogently, the topographical association of tumour and amyloid supports the view that they are aetiologically related.

CASE 8 A man aged 83 complained of weight loss and abdominal swelling and was admitted to hospital in 1961. Marked sacral and leg oedema was present. Pulse was 80/minute, the blood pressure 160/75 mm. Hg. The jugular venous pressure was raised 7 cm. The apex beat was in the sixth intercostal space in the anterior axillary line. An ejection murmur, loudest at the apex and conducted into the neck, was accompanied by a thrill. A hard, nodular liver was palpated. Prostatectomy for hyperplasia had been performed in 1956, and an intravenous pyelogram had shown a large right kidney with calyceal elongation and inadequate filling, appearances considered then to be due to a cyst rather than to a tumour.

Haemoglobin was 9.7 g. %; W.B.C.s numbered 4,000/c.mm., E.S.R. was 90 mm./hr., blood urea 93 mg. %, serum protein 5.1 g. % (albumin 1.6 g. %, globulin 3.5 g. %); there was gross proteinuria with a loss of 7.5 g. in 24 hours. Chest radiographs showed left ventricular enlargement and pulmonary oedema. Cardiac failure was treated with digoxin, chlorothiazide and potassium supplements, despite which the patient died three months after the onset of symptoms.

Necropsy The right kidney (720 g.) was virtually replaced by a yellow and brown-red tumour, microscopy showing a clear-cell renal carcinoma with necrosis. The left kidney weighed 220 g. In retrospect the pyelographic appearances in 1956 were almost certainly due to renal tumour. The liver (1,865 g.) contained numerous metastases. There was a solitary metastasis in the pancreatic tail and one in the thyroid (58 g.). The spleen (145 g.) showed translucent lymphoid follicles. Tumour had replaced the nodes in the para-aortic, tracheobronchial, and hilar groups. The heart (538 g.) had a hypertrophied left ventricle. The aortic valve showed severe calcific sclerosis leading to a rigid orifice. Both lungs (1,200 g.) were oedematous.

The liver, kidneys, and spleen were affected by amyloidosis. Amyloid was also present in the hypernephroma and in the pancreatic and some nodal metastases (Figs. 7, 8, and 9).

DISCUSSION

Myelomatosis is a well-established cause of amyloidosis but the incidence of amyloid in myelomatosis

TABLE II

Case No.	Sex and Age (yr.)	Diagnosis	Duration of Illness (yr.)	Main Clinical Features	MAIN CLINICOPATHOLOGICAL DATA					Other Data and Comment
					Presence of Amyloid in Biopsy	Cause of Death	Tumour Distribution	Amyloid Distribution		
1	M 35	Benign Hodgkin's disease	13	Node swelling (L) neck; nephrotic syndrome 12 yr. later	Negative in 1946 and 1955. Positive in 1959 node biopsy	Uraemia due to amyloid with renal vein thrombosis	L. deep cervical nodes	Kidneys, spleen, liver, adrenals, nodes, small intestine		
2	M 24	Benign Hodgkin's disease	13	Node swelling (R) neck	Negative in node biopsy	Uraemia due to amyloid with renal vein thrombosis	No residual tumour at necropsy	Kidneys, liver, spleen, adrenals, some nodes	Miliary tuberculosis of lungs regarded as terminal; interpretation supported by kidney weight of 90 g. each, implying amyloid of some standing	
3	M 40	Myelomatosis	1	Macroglossia, bilateral carpal tunnel syndrome	Positive in tongue and in lumbar muscle	Broncho-pneumonia	Bone marrow	Tongue, skeletal muscles, smooth muscle of gut, minimal in bone marrow	No radiological signs of myelomatosis	
4	F 56	Myelomatosis	1½	Bence-Jones proteinuria Anginal pain, bleeding tendency, pain in arms and legs No Bence-Jones proteinuria on one specimen	No biopsy	Cardiac failure due to amyloid	Bone marrow	Liver, spleen, lungs, heart, kidneys, thyroid, adrenals, tongue, adipose tissue	No radiological signs of myelomatosis; in addition to myocardial amyloid, cor pulmonale due to amyloidosis of pulmonary capillaries	
5	F 42	Myelomatosis	8	Backache, pain in chest, bilateral carpal tunnel syndrome, cutaneous nodules eyelids and around anus, Bence-Jones proteinuria	Positive in skin, flexor retinaculum, and omental fat	Cerebral vascular accident	Bone marrow	Adipose tissue of peritoneum and pericardium, skin, flexor retinaculum	Radiological signs of myelomatosis	
6	M 63	Myelomatosis	7	Pain hips, back, pathological fracture femur, difficulty micturition, Bence-Jones proteinuria	No biopsy	Broncho-pneumonia	Bone marrow and possibly axillary nodes	Bone marrow and axillary nodes	Radiological signs of myelomatosis	
7	M 65	Lymphosarcoma with macroglobulinaemia	6	Dyspnoea, ankle oedema, cardiomegaly	Negative in node which was negative for lymphosarcoma	Congestive heart failure due to amyloid	Lymph nodes, liver, less in spleen, kidneys, pericardium	Lymph nodes, myocardium	See case report	
8	M 83	Hyper-nephroma	3/12	Anorexia, weight loss, abdominal swelling	No biopsy	Congestive heart failure	Kidney, liver, nodes, pancreas thyroid	Liver, spleen, kidneys, renal carcinoma and metastases	See case report	
9	F 76	Hyper-nephroma	4	Nodes destroyed	Positive in hypernephroma removed by nephrectomy	Uraemia due to atheromatous occlusion renal artery	No residual tumour	Kidneys and renal carcinoma, trace in pancreas, liver, and mediastinal nodes	Carcinoma cervix treated by radiotherapy 18 yr. before death	
10	M 75	Transitional cell carcinoma renal pelvis	11/12	Fatigue, weight loss, persistent pyrexia	Positive in rectal biopsy	Carcinomatosis and broncho-pneumonia	Kidney, abdominal and mediastinal nodes, (L) lung	Spleen, kidneys and pelvic carcinoma, abdominal nodes, rectum, tongue	Mild diverticulitis considered not related to amyloid but not completely ruled out	
11	M 76	Squamous carcinoma oesophagus	4/12	Dysphagia	Positive in resected oesophageal tumour	Post-operative death	Mediastinal nodes	Liver, spleen, adrenals, kidneys, primary oesophageal tumour and some nodal secondaries		
12	M 82	Adeno-carcinoma ampulla of Vater	7/12	Obstructive jaundice, bilateral carpal tunnel syndrome	No biopsy	Obstructive jaundice and broncho-pneumonia	Pancreatic head	Myocardium and scanty in alveolar walls, lungs		
13	M 78	Transitional cell carcinoma of bladder	2/12	Haematuria (cystectomy 2 weeks after onset)	Positive in biopsied and resected bladder tumour	Uraemia due to renal amyloidosis and papillary necrosis	No residual tumour	Spleen, kidneys, bladder carcinoma	Pyelitis and papillary necrosis. Since urine sterile before biopsy and amyloid present in biopsy and cystectomy specimens, infection considered terminal and unrelated to amyloidosis	
14	F 52	Adeno-carcinoma cervix uteri	1½	Vaginal bleeding and discharge	Positive in post-radiotherapy biopsy	Uraemia due to renal amyloidosis and hydronephrosis	Cervix, parametria nodes	Liver, adrenals, kidneys, cervical carcinoma		

TABLE III
INCIDENCE OF AMYLOIDOSIS IN MALIGNANT DISEASE

	Personal	Other Reports
Myelomatosis	14% (4/28)	4—19.5%
Hodgkin's disease	4% (2/51)	2.1—18%
Lymphosarcoma	1% (1/96)	0 (Razis <i>et al.</i>); 1% (Kimball)
Renal carcinoma	3.2% (2/62)	2.9% (Berger and Sinkoff)
Carcinoma excluding renal carcinoma	0.195% (5/2560)	No figures but 0.14% calculated from Kimball's series
'Control' series	0.066% (1/1500)	No figures available

varies in different series (under 4% Carson, Ackerman, and Maltby, 1955; 6% Kimball, 1961; 15% Kyle and Bayrd, 1961; 19.5% Snapper, Turner, and Moscovitz, 1953). Ten per cent. represents a conservative estimate (Table III). Because amyloid in myelomatosis is often deposited in unusual sites, its presence can escape notice unless it produces obvious clinical signs due to, say, myocardial involvement. Occasionally there is difficulty in distinguishing between myelomatosis with amyloidosis and so-called primary amyloidosis with non-neoplastic plasmacytosis, a difficulty that cannot always be resolved because there is no known clear-cut dividing line between the two conditions (Kyle and Bayrd, 1961). Four of our 28 cases of myelomatosis had amyloid disease (Figs. 1 and 2). A fifth case of plasma-cell leukaemia, reported elsewhere (Azzopardi, 1962), had amyloid deposits only in some of the laminated tubular casts of a 'myeloma kidney' (Fig. 3). Amyloid was also present in the casts of the 'myeloma kidney' in case 5 and in two other 'myeloma kidneys' not in the series. The presence of amyloid in the casts of 'myeloma kidney' has been denied in the past (*e.g.*, Snapper *et al.*, 1953) but our finding not only raises the figure for the incidence of amyloidosis in myeloma but also indicates that myelomatosis is the only disease in which renal casts have been shown to contain amyloid.

In the lymphoma group, Hodgkin's disease is associated with amyloidosis (Wallace, Feldman, Berlin, Harris, and Glass, 1950; Dawson, 1960). The incidence varies in different series (2.1% Razis, Diamond, and Craver, 1959; 3.4% Kimball; 8.3% Castleman, 1949; 18% Cardell, 1961). Two of our 51 patients with Hodgkin's disease had amyloidosis, an incidence of 4% (Table III). To explain these differences one must consider the effect of special interest in a particular disease in certain centres and the difficulty of distinguishing hyalinized collagen from amyloid if one relies solely on methyl violet and does not verify the results with thioflavine-T or Van Gieson. The effect of treatment is discussed later.

Both our cases are examples of benign Hodgkin's disease (paragranuloma). In part this reflects special interest in this variant; it may also reflect the more indolent course. Castleman reported Hodgkin

paragranuloma associated with amyloidosis, as did Jackson and Parker (1944, case 2). Cardell's cases, on the other hand, were all of the classical variety.

Treatment with nitrogen mustard increases the incidence of amyloidosis in Hodgkin's disease, but it is not the only factor involved since one of the five patients of Razis *et al.* (1959) had no mustard therapy nor did any of their patients with lymphosarcoma develop amyloid despite mustard treatment. By contrast, the striking effect of therapy in Hodgkin's disease is indicated by Cardell: of eight patients treated with nitrogen mustard or tretamine, four developed amyloid; of 14 not so treated, none developed amyloid. Treatment does not produce this effect merely by prolonging life for, in two of the four patients, albuminuria due to renal amyloid appeared within a few weeks of the therapy. Cardell, borrowing the terminology of experimental cancer workers, regards Hodgkin's as the initiating factor and therapy as the promoter of amyloid deposition. Since radiotherapy can accelerate the development of amyloidosis (Christensen and Hjort, 1959), this factor must also be considered. The extensive use of irradiation in Hodgkin's disease does not suggest that its role can be as important as that of the chemotherapeutic agents; large series of untreated controls for comparison are not available.

In Hodgkin's disease amyloid is deposited in the sites usually affected in secondary amyloidosis. Lymph node involvement by amyloid is prominent in some cases, *e.g.*, those of Jackson and Parker. In Castleman's remarkable case amyloid affected mainly the lymph nodes and kidneys; enlarged nodes measuring up to 9 cm. were regarded grossly as being replaced by Hodgkin tissue but microscopy of about 20 nodes showed diffuse replacement by amyloid in all, with minimal residual tumour tissue. In one of our cases there is extensive amyloid in the lymphomatous nodes but little in non-neoplastic nodes. At necropsy there is sometimes little evidence of Hodgkin tissue and death is due to amyloidosis (Jackson and Parker, 1944; Dahlin, 1949; both our cases).

In lymphosarcoma and leukaemia amyloidosis is less common. Razis *et al.* found no instance in 1,269 patients with lymphosarcoma and 220 with leukaemia

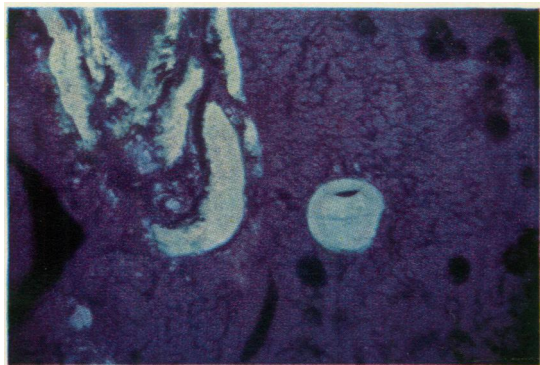


FIG. 1. Bone marrow showing partly laminated amyloid in myeloma tissue. Thioflavine-T (photographed in ultraviolet light) $\times 40$.

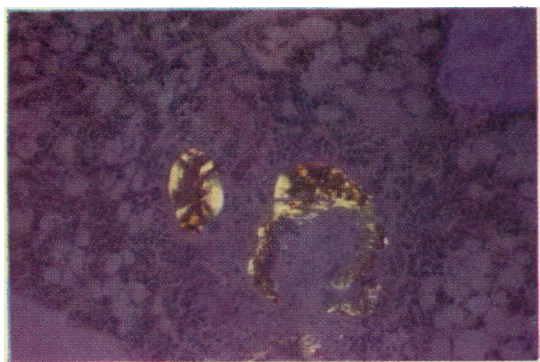


FIG. 2. Same case as Fig. 1 showing birefringence and dichroism. Congo red and crossed polaroids $\times 30$.



FIG. 3. Tubular casts in 'myeloma kidney' showing amyloid deposited mainly in outer laminae. Thioflavine-T $\times 240$.

in spite of the frequent use of nitrogen mustard in the former group. Kimball found only one instance of amyloidosis among 127 cases of lymphosarcoma. Only one case of amyloidosis was found among our 96 necropsies on patients with lymphosarcoma or reticulosarcoma (Figs. 4, 5, and 6) and this was associated with macroglobulinaemia (Table III). The incidence of amyloidosis in lymphosarcoma is probably of the order of a small fraction of 1%, if cases with macroglobulinaemia are excluded. It is probably higher in patients with macroglobulinaemia whether essential or associated with lymphosarcoma. Wunderly and Wuhrmann (1954) recorded a patient with macroglobulinaemia and amyloidosis; of the three patients of Braunsteiner, Oswald, Pakesch, and Reimer (1956) with macroglobulinaemia, one developed amyloid disease. Michon and Streiff (1959) quote Waldenström's finding of hepatic and renal

amyloid in a patient with Waldenström's macroglobulinaemia, and a similar case is reported by Gassner, Bittar, and Parrish (1961). There was no amyloid in the four patients of Kok, Whitmore, and Ainsworth (1963). The two patients of Hobbs and Morgan (1963) had cervical lymphadenopathy and macroglobulinaemia, and node biopsy showed a malignant lymphoma and amyloid deposits.

The role played by carcinoma, as distinct from myelomatosis or malignant lymphoma, in the induction of amyloidosis is contentious. A patient may have suffered from a disease many years previously which, though rendered inactive, was accompanied by clinically latent amyloidosis: this may lead to amyloidosis being associated at necropsy with a coincidental carcinoma. Carcinoma may be complicated by chronic sepsis which could be the cause of amyloidosis rather than the carcinoma *per*

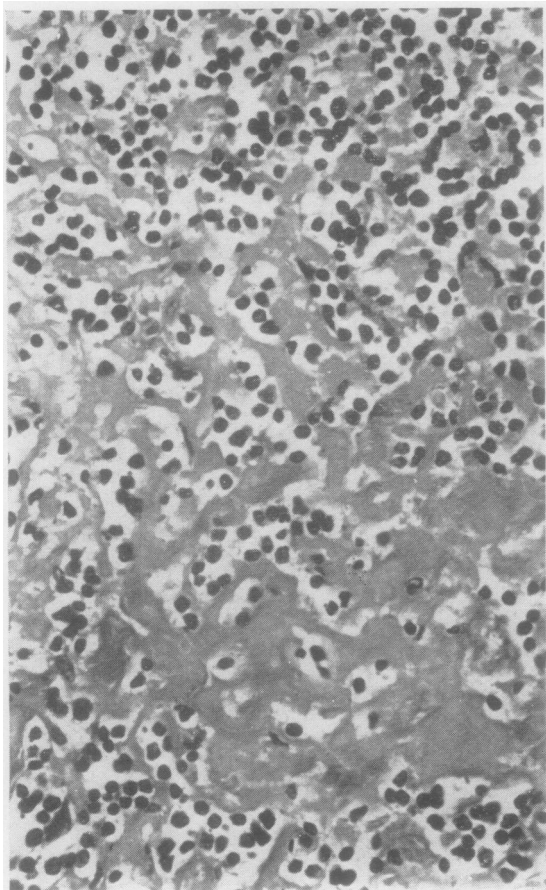


FIG. 4

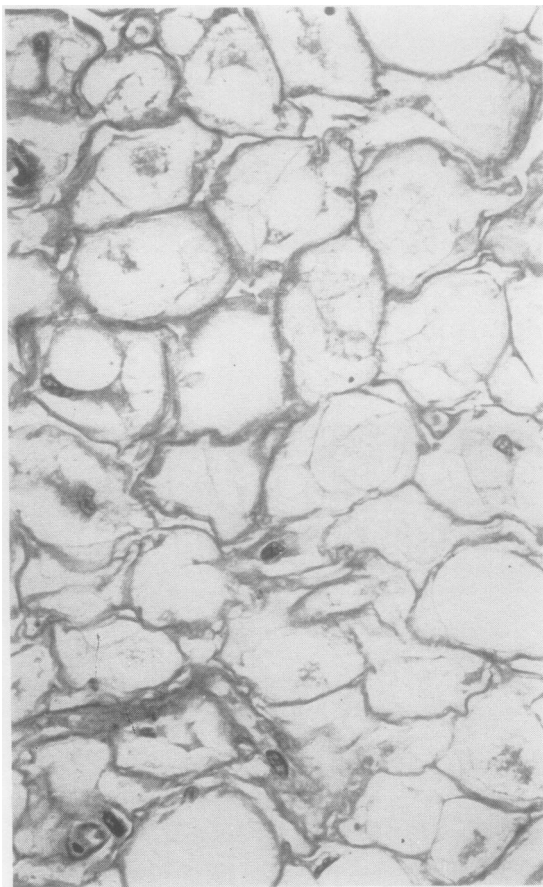


FIG. 6

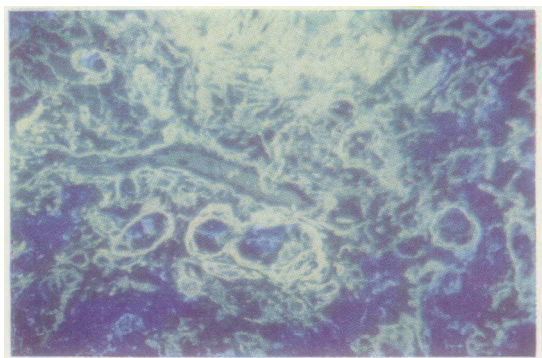


FIG. 5

FIG. 4. *Lymphosarcoma and amyloid deposits. Haemalum and eosin $\times 370$.*

FIG. 5. *Lymphosarcoma and amyloid deposits. Thioflavine-T $\times 40$.*

FIG. 6. *Amyloid 'rings' on adipose tissue cells, Haemalum and eosin $\times 370$.*

se. In an attempt to overcome some of these obstacles, we searched our records and found 2,622 cases of carcinoma and sarcoma, excluding the groups already considered and excluding cases accompanied by a recognized potential cause of amyloidosis. Seven of these 2,622 cases, or one in 375, were accompanied by amyloidosis. One thousand five hundred 'control' cases¹ were collected. Among these there was a solitary case of amyloidosis (Table III). This series of 1,500 needs supplementing by several thousand control cases from other centres.

In six of the seven cases of carcinoma the amyloid distribution is that usually seen in so-called secondary amyloidosis, while in one (case 12) the distribution is that usually seen in so-called primary amyloidosis. Symmers (1956) cautioned against relating a disease, or otherwise, to amyloidosis in a particular patient merely on the distribution of the amyloid deposits, since chronic sepsis can sometimes be associated with amyloid having a 'primary distribution' and, conversely, amyloid with a 'secondary distribution' can occur in the absence of a detectable cause. Bearing these exceptions in mind, the reverse is usually true (Lehner). The argument for a causal relationship between carcinoma and amyloidosis is strengthened if the amyloid has a consistent (and preferably a 'secondary') distribution. For one thing, this would exclude the senile, predominantly cardiac, form of amyloidosis occurring coincidentally with carcinoma.

Ask-Upmark (1940) noted the predominantly secondary type of distribution in amyloidosis with renal malignancy. In our cases of amyloid with renal carcinoma (Table II) and in those reported since Ask-Upmark's review (Table IV), the distribution is again of secondary type, with one exception. In a

¹See Appendix.

critical analysis, Le Coulant, Texier, Maleville, and Fauret (1961) found that 27 of 58 cases of carcinoma associated with amyloid were instances of hypernephroma. (This figure should be corrected to 25 of 56 as these authors refer to 20 cases collected by Ask-Upmark instead of 18.) In an exhaustive review Pigeaud (quoted by Bogaert, Loecker, and Tverdy, 1960), found 106 cases of amyloid associated with cancer: 26 of the tumours were renal carcinomas. The fact that between one-quarter and one-third of all cancers associated with amyloidosis are renal carcinomas is highly significant since renal carcinoma constitutes only 2 to 3% of all carcinomas (Willis, 1960). The occasional association of hypernephroma with unexplained pyrexia may be related to the fact that hypernephroma is more frequently associated with systemic amyloid than any other carcinoma. Of our 62 cases of hypernephroma, two (3.2%) have systemic amyloidosis (Figs. 7, 8, and 9). Berger and Sinkoff (1957) found an incidence of 2.9% in 273 patients. Renal carcinoma can induce amyloidosis even in the absence of metastases (*e.g.* Ellenberg, 1943; case 3 of Hyman and Leiter, 1946; case 3 of Bogaert *et al.*, 1960; our case 9).

Contrasting with the definite relationship between renal carcinoma and amyloidosis are the isolated reports of carcinomas of uterus, bronchus, stomach, bladder, ovary, biliary tract, etc. associated with amyloid disease (Le Coulant *et al.*, 1961; Dahlin, 1949; Kimball, 1961). Some of these cases may well be attributable to coincidental primary amyloid, *e.g.*, our case 12 and some of those collected by Le Coulant *et al.* (1961). In other instances the secondary type of distribution of the amyloid is suggestive of a causal relationship, though for reasons given before it is impossible to establish or refute a causal relationship merely on the distribution of amyloid.

TABLE IV
RENAL CARCINOMA AND AMYLOIDOSIS

Author	Metastases	Distribution of Amyloid
Ask-Upmark (1940)	18 cases (2 personal ones) tabulated. Amyloid had secondary distribution.	
Ellenberg (1943)	None	Kidneys, spleen, adrenals, liver
Hyman and Leiter (1946)	1 Vaginal. Died, no necropsy 2 Died, no necropsy 3 None 4 Other kidney, lungs, liver, heart	Resected kidney Resected kidney Liver, kidneys, spleen Kidneys, spleen
Potvliege and Carpent (1959)	Lumbar spine	Myocardium, adipose tissue
Bogaert <i>et al.</i> (1960)	1 Other kidney 2 Died, no necropsy 3 Alive 2½ yr. post-operatively	Adrenals, kidneys, spleen, liver, gastrointestinal tract Liver, kidney (biopsy only) Resected kidney
Picard <i>et al.</i> (1960)	Other kidney, adrenals, lungs	Liver, spleen
Kimball (1961)	Other kidney	Spleen, kidney, liver, heart, adrenals, pancreas

The cases of Berger and Sinkoff (1957) had amyloidosis with a '2° distribution' or had amyloid in the resected kidney; those of Dahlin (1949) and Briggs (1961) 'of secondary type' but distribution was not specifically stated.

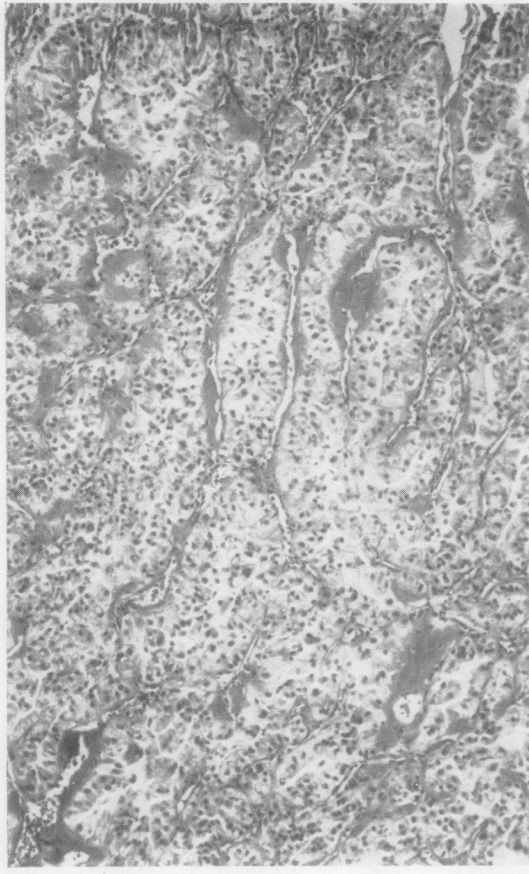


FIG. 7

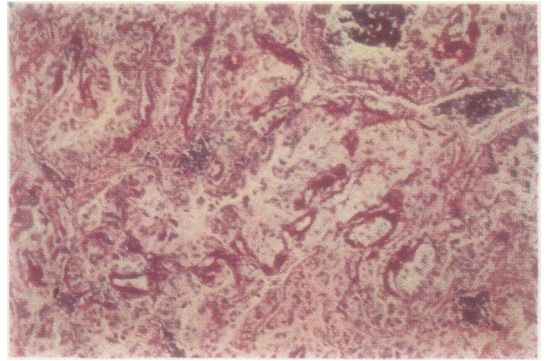


FIG. 8

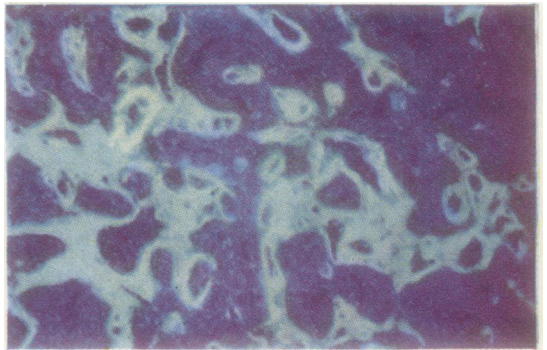


FIG. 9

FIG. 7. *Renal carcinoma showing amyloid deposits beneath the vascular endothelium. Haemalum and eosin $\times 100$.*

FIG. 8. *Renal carcinoma with amyloid along vascular framework. Methyl violet $\times 40$.*

FIG. 9. *Renal carcinoma with amyloid along vascular framework. Thioflavine-T $\times 40$.*

FIG. 10. *Amyloid in a carcinoma of the renal pelvis. Thioflavine-T $\times 40$.*

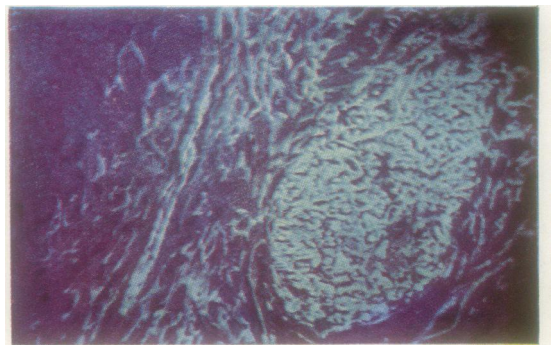


FIG. 10

LOCALIZATION OF AMYLOID IN TUMOURS Attention was focused on whether there were any features of amyloidosis in patients with carcinoma which might establish the latter as the aetiological agent. In amyloidosis due to chronic sepsis in lung or bone, tuberculosis etc., there is no particular tendency to deposition of amyloid in and around the infective focus. In myelomatosis, regional association of tumour and amyloid is not usually described, though, in one of our four patients (case 6), amyloid is intimately associated with tumour in the bone marrow and is present in axillary lymph nodes but in no other site (Figs. 1 and 2). Some cases of Hodgkin's disease show local admixture of tumour and amyloid, but since amyloid may be found in nodes in any type of amyloidosis, admixture of the two may occur simply by chance. However, Castleman's extraordinary case indicates that in Hodgkin's disease there may be greater deposition of amyloid in the neoplastic tissue than hitherto realized. In our case 1, Hodgkin paraganuloma affected only the left cervical lymph nodes; at necropsy, five out of six of these nodes were extensively replaced by amyloid and one had small amounts; by contrast, the right axillary nodes showed minimal amyloidosis, another striking instance of topographical association of amyloid with Hodgkin tissue. In the patient with macroglobulinaemia and lymphosarcoma, there is again a topographical association between tumour deposits and amyloid (Figs. 4 and 5). In our cases of carcinoma associated with amyloidosis, six out of seven show admixture of neoplastic cells and amyloid. This is the more significant as the carcinomas are mixed with amyloid in sites like the uterine cervix, bladder mucosa, and oesophagus where amyloid is relatively infrequent. The transitional-cell carcinoma of the renal pelvis shows this relationship in the renal medulla and in lymph nodes (Fig. 10). Case 8 shows striking amyloidosis of the sinusoidal vessels in the hypernephroma and case 9 is similar (Figs. 7, 8, and 9). Even more revealing is the pancreatic metastasis in case 8: the pancreas shows only slight amyloidosis of occasional vessels but in the renal carcinoma metastatic to the pancreas there is heavy deposition of amyloid along the vascular framework of the tumour.

If interference with antibody production plays a role in the pathogenesis of amyloid, one could postulate either that the abnormal protein produced in the reticuloendothelial system is deposited in the carcinoma or else that part of the abnormal protein is formed around the tumour itself as a local response of reticuloendothelial cells. Though we were unable to find evidence of a marked local reticuloendothelial response in our material, this does not exclude its presence at an earlier stage. The pathogenesis of

amyloidosis is disputed, but, on either of the two main theories (Teilum, 1964), deposits of amyloid within carcinomas provide support for the view that the tumour is the aetiological agent responsible.

On the basis of our findings, a diagnosis of amyloidosis can sometimes be made on examining a biopsied or resected carcinoma, an observation only made in retrospect in four patients. In another patient, Hodgkin's disease and amyloid were diagnosed on a node biopsy after the association between these diseases had become apparent. Early diagnosis of amyloid by this means is not simply of academic interest since it can help to clarify diagnostic problems arising postoperatively.

APPENDIX

Because the incidence of amyloidosis in the population is unknown and, in an attempt to establish a baseline for comparison with other diseases, we examined the records of patients with diseases in which there were no grounds for believing that an association with amyloidosis existed and in whom no malignant tumour was present at necropsy or had been previously excised. (Rodent ulcers, solar keratoses, etc., were ignored.) We included patients with myocardial infarction, large myocardial scars believed to represent old infarcts, hypertensive heart disease without a background of glomerulonephritis, pyelonephritis, etc., congenital heart disease, essential malignant hypertension and ischaemic renal hypertension, cerebral vascular accidents including subarachnoid haemorrhage, non-syphilitic aortic aneurysms, severe atheromatous disease leading for instance to mesenteric vascular occlusion or peripheral gangrene, haemorrhage from peptic ulcer, patients with perforated peptic ulcer, strangulated hernia, or non-neoplastic intestinal obstruction dying within four weeks of the acute episode, patients with peptic ulcer dying within four weeks of operation, and cases of violent death only where a thorough necropsy had been carried out. Children under 15 years were excluded to rule out major age differences between the test and the control series. Patients with diabetes mellitus, cirrhosis, glomerulonephritis, collagen disorders, and cor pulmonale were excluded.

One thousand five hundred cases were collected in the period 1935 to June 1961 inclusive; among these 'controls' there was a solitary patient with amyloidosis; this had a 'secondary distribution'. The patient was a 56-year-old man who died of cardiac failure due to hypertensive heart disease. Since he had renal amyloid and this may itself lead to hypertension, this case may represent a 'false positive'. Ideally, hypertensive patients should be excluded from the controls

but this would substantially reduce the number of controls.

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