months and required paracentesis only twice. Three effusions due to metastases from gastro-intestinal carcinoma showed no response.

These results are comparable with those reported by other authors. In a series of 43 patients treated by Weisberger *et al.* (1955) there was improvement in 28 (65%) and no reaccumulation of fluid in 20, the most favourable response being in patients with mammary or ovarian carcinoma. Bonte *et al.* (1956) treated 40 patients, with improvement in 25 (62%). A further 88 patients reported by Weisberger (1958) showed approximately the same percentage—64—to be improved, and again the most favourable response was obtained in patients with breast and ovarian tumours. In a series of 25 patients with bronchial carcinoma described by Bass (1960) five with malignant effusions were treated by the direct intrapleural injection of HN2, there being no reaccumulation of fluid up to the time of death in four.

Many authors agree (King *et al.*, 1952; Storaasli *et al.*, 1953; Kent *et al.*, 1954; Wheeler *et al.*, 1955) that Au-198 can produce slowing down or cessation of malignant effusions in about 50–60% of patients, and that the best response is obtained where the primary tumour arises in the breast or ovary. Hilton *et al.* (1957) reported the results of treatment with Au-198 of 94 patients at University College Hospital. 40 of these showed a good response with no further fluid formation, and eight a moderate response, the fluid forming less rapidly. 21 patients with bronchial carcinoma showed a good response, with an average duration of 6.6 months, one patient living 16 months without significant reaccumulation of fluid. The average duration of improvement in seven patients with ovarian carcinoma showing a good response was 7.2 months, one patient being alive after two years, at the time of writing, with no ascites. The average duration of improvement in 10 patients with carcinoma of the breast was 8.4 months, eight being alive at the time of writing. The results of 235 patients with malignant effusions who were treated at the Royal Marsden Hospital with Au-198 are reviewed by MacKay (1957). In his series 59 patients showed good inhibition and 16 showed some inhibition of fluid formation. 26 survived over one year, two with effusions due to breast carcinoma living six years.

Müller (1956) found that the general body dose was less than 10 milliroentgens (mr.) and the hand dose 20 to 50 mr. for the giving of a dose of 150 millicuries (mc.) of Au-198. These figures can be kept within such limits only if the operator is quick and skilled, and would certainly be exceeded if it were given by a slow and inexperienced person. Thus Au-198 for routine use involves little radiation exposure in experienced hands provided adequate facilities for protection and monitoring are available.

It would seem that the results of treating malignant effusions with Au-198 or with HN2 are virtually the same. The latter would appear to have definite advantages in that no radiation hazard is involved, no protective measures are required, and administration is consequently simple and can be done in a general hospital without a radiotherapy department. It is perhaps also pertinent to point out that 20 mg. of HN2 costs 5s. and the average dose of Au-198 (100 mc.) costs £6 15s.

The series of patients reported here is small, but there is no clear pattern of response to the HN2, and, subject

to the patient being in reasonable general condition, treatment should be attempted in all cases of increasing malignant effusions causing symptoms and requiring tapping. It is not possible, from the histology, to forecast which patients will respond satisfactorily.

Summary

Nineteen patients with malignant effusions were treated with the direct intracavitary injection of nitrogen mustard. Eleven showed improvement, and in six no further paracentesis was required up to the time of death.

The literature on the treatment of malignant effusions with radioactive colloidal gold and with nitrogen mustard is briefly reviewed, and about 60% of patients can be expected to respond satisfactorily to either method. The latter has the advantage that no radiation hazard is involved.

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ROLE OF CYTOTOXIC AGENTS IN PRODUCTION OF AMYLOIDOSIS IN HODGKIN'S DISEASE

BY

B. S. CARDELL, M.D.

Reader in Morbid Anatomy, King's College Hospital Medical School, London

That amyloidosis may occur in Hodgkin's disease is fairly well recognized, though it is mentioned in only 6 out of 20 standard textbooks of pathology or monographs on Hodgkin's disease that have been consulted. The frequency of this association has been described by these authorities as "rare" or "occasional."

It was rather a surprise, therefore, to find that of 20 cases of amyloidosis occurring in a series of 3,192 consecutive necropsies performed in a general hospital between 1947 and 1959 Hodgkin's disease was the commonest concomitant of secondary amyloidosis. Of these 20 cases, six had primary amyloidosis; and the associated diseases with secondary cases were Hodgkin's disease four, multiple myelomatosis three, pulmonary tuberculosis three, rheumatoid arthritis two, osteomyelitis one, and empyema one. Furthermore, all four cases of Hodgkin's disease with amyloidosis had been treated with either nitrogen mustard or tretamine (triethylene melamine).

The purpose of this paper is to report these four cases and to review the literature on amyloidosis and Hodgkin's disease, with special reference to the effects of cytotoxic drugs.

Case 1

A woman aged 25 had noticed enlarged glands in her right axilla and neck for two years. A fortnight before admission in February, 1947, the skin overlying the axillary swelling had ulcerated and she also developed an unproductive cough. Examination confirmed the presence of enlarged firm lymph nodes, and a biopsy showed the fibrotic stage of Hodgkin's disease. Chest x-ray examination revealed a mass of enlarged lymph nodes. While in hospital she had an irregular fever varying from 99 to 102° F. (37.2 to 38.9° C.). She was given a course of x-ray therapy and five injections of nitrogen mustard (total dose 18.1 mg.). She was discharged afebrile and with some decrease in size of the lymph-node masses.

By June she had become very weak and was readmitted. The lymph-node masses had reappeared and she was again febrile. There was no proteinuria. A further course of six injections of nitrogen mustard was given (total dose 21.6 mg.). Over the next six months she had further febrile episodes, but remained relatively well, and in December there was no proteinuria.

She was not seen again until her final admission in April, 1948. Examination showed gross wasting, together with oedema of the right arm, both legs, and lumbar region. The urine now showed protein ++++. Death occurred 10 days after admission.

Necropsy.—There was moderate oedema of the right arm and of both legs. The axillary and cervical lymph nodes were much enlarged, particularly on the right side, where the axillary nodes were adherent to the skin, which was ulcerated in places. The thoracic lymph nodes were also moderately enlarged. Both lungs contained scattered nodules of Hodgkin's tissue 1–2 cm. in diameter, and small white mucosal plaques were present in the lower trachea and main bronchi. The heart (160 g.) was atrophic, and the liver (1,500 g.) showed only moderate congestion. The spleen (300 g.) had a typical "sago" appearance on its cut surface, and both kidneys (combined weight 435 g.) were firm and waxy, with minute semi-translucent dots just visible throughout the cortex. No significant changes were present in other organs and tissues.

Histology.—Microscopically, typical Hodgkin's tissue was found in the axillary, cervical, and thoracic lymph nodes, spleen, trachea, and lungs. Amyloid deposits were present in the spleen, where it was massive, and in both kidneys. Sections of the liver, bone-marrow, and intestine showed no evidence of Hodgkin's disease or amyloidosis.

Comment.—This is a typical case of Hodgkin's disease, treated with x rays and two courses of nitrogen mustard. Death occurred 10 months after the end of the second course of nitrogen mustard. Amyloid disease was not suspected in life and was diagnosed only at necropsy. In retrospect, there were no symptoms or signs referable to amyloidosis until the last admission when she had massive proteinuria.

Case 2

A man aged 22 attended hospital at the end of March, 1955, having noticed a painful tender lump in his lower abdomen for six weeks. Examination showed a large mass in the left iliac fossa deep to the abdominal wall. He was febrile, and a few small cervical lymph nodes were also noted. Laparotomy revealed a large mass of lymph nodes in the abdomen. Histological examination of an excised lymph node showed destruction of the normal architecture of the node and replacement by masses of tightly packed non-caseating tubercle follicles: no acid-fast bacilli were demonstrated. Investigations: Hb, 13.0 g./100 ml.; W.B.C.,

5,900/c.mm., normal differential count; blood urea, 30 mg./100 ml.; serum proteins, 6.52 g./100 ml. (albumin 4.06 g., globulin 2.46 g.); urine, no protein present; Mantoux reaction, negative at 1/100 dilution. A diagnosis of sarcoidosis was made, and over the next few months he was treated with streptomycin, isoniazid, P.A.S., and cortisone.

There was no response at all to this therapy and his condition slowly deteriorated, with increasing anaemia and a progressive loss of weight. Repeated bacteriological examination of sputum, urine, and faeces yielded no tubercle bacilli, and the temperature chart revealed a typical Pel-Ebstein pattern. Throughout this illness there had never been any proteinuria. The cervical lymph nodes had meanwhile slowly enlarged, and eventually, in September, one of these nodes was excised. Histological examination showed typical Hodgkin's disease, and culture and animal inoculation of material from the node yielded no tubercle bacilli. The sections of the previous abdominal lymph-node biopsy were re-examined, and between the non-caseating tubercle follicles typical Hodgkin's tissue could be seen.

For four days, starting on October 8, he received an intravenous injection of tretamine (total dose 10 mg.). His general condition steadily deteriorated, however, and by the end of October his haemoglobin was 5 g./100 ml., slight ankle oedema was present, and examination of the urine showed protein +. The oedema became more marked, he developed increasing jaundice, and died a fortnight later, in the middle of November, 1955.

Necropsy.—The whole body was moderately jaundiced. Both legs showed gross pitting oedema; about half a litre of clear yellow fluid was present in each pleural cavity and about 2 litres in the peritoneal cavity. The cervical, axillary, inguinal, thoracic, and abdominal lymph nodes were all much enlarged. The liver (2,750 g.), spleen (560 g.), and kidneys (combined weight 430 g.) all showed changes of severe diffuse amyloidosis; the spleen also showed nodules of Hodgkin's tissues, and so did the lumbar vertebrae. The only other abnormal finding was a small chronic duodenal ulcer. There was no macroscopic evidence of tuberculosis, and cultures and animal inoculation with material from many organs and tissues yielded negative results.

Histology.—Typical Hodgkin's tissue was found in all the enlarged lymph nodes, liver, spleen, and bone-marrow. Extensive amyloid deposits were present in the liver, spleen, and kidneys. Sections of lungs, heart, tongue, intestine, parotid, pituitary, adrenal, thyroid, testis, and conjunctiva showed no abnormality. In none of the tissues examined was there any evidence of sarcoidosis or tuberculosis.

Comment.—Apart from the initial misadventured diagnosis of sarcoidosis this is a very ordinary case of Hodgkin's disease. The histological finding of non-caseating tubercle follicles ("sarcoid" reaction) in Hodgkin's disease is not so very uncommon (Smetana and Cohen, 1956), but such extensive replacement of a node as in the first biopsy in this case must be rare and is certainly a diagnostic pitfall. No other disease was found that might account for these follicular lesions.

Case 3

A woman aged 39 first attended hospital in March, 1955, with a history of enlarged glands in the neck for 14 months and lassitude, cough, and night sweats for seven months. Enlarged lymph nodes were present on both sides of the neck and in both axillae, and the spleen was just palpable. She had an evening pyrexia ranging from 100 to 103° F. (37.8 to 39.4° C.). Chest x-ray examination showed considerable enlargement of the paratracheal lymph nodes. Investigations: Hb, 5.3 g./100 ml.; serum protein, 6.8 g./100 ml.; no proteinuria. She improved after blood transfusions and x-ray therapy.

Over the next month she remained anaemic despite repeated blood transfusions. In January, 1956, she had a

further course of x-ray therapy: there was still no proteinuria. In February she had a course of tretamine (total dose 10 mg.). In April oedema of the ankles was noticed and investigations showed: urine, protein +; serum proteins, 3.62 g./100 ml. (albumin 1.98 g., globulin 1.64 g.); blood urea, 30 mg./100 ml. The oedema and proteinuria increased, and death occurred at the end of May, 1956. During the last fortnight of her life there was a slight purulent discharge from the left ear, and culture yielded a growth of *Staphylococcus aureus*.

Necropsy.—The body was emaciated, both legs showed gross oedema, and the peritoneal cavity contained a litre of clear fluid. Enlarged lymph nodes, up to 3 cm. in diameter, were present in the neck, axillae, inguinal regions, thorax, and abdomen. The liver (2,925 g.), spleen (325 g.), and kidneys (combined weight 350 g.) all showed changes of severe diffuse amyloidosis. Small nodules of Hodgkin's tissue were visible in the spleen and both lungs. The left middle ear contained several beads of pus. The heart was atrophic (178 g.). No other noteworthy changes were present in the body.

Histology.—The spleen, both lungs, and all the enlarged lymph nodes showed typical lesions of Hodgkin's disease. The liver showed massive replacement by amyloid deposits and no Hodgkin's tissue could be identified. The spleen and kidneys also contained extensive amyloid deposits. The heart and bone-marrow showed no Hodgkin's tissue and no amyloid deposits.

Comment.—This is another typical case of Hodgkin's disease. After treatment with tretamine, however, a nephrotic syndrome developed and gross amyloidosis was present at necropsy. The terminal suppurative otitis media can have played no part in the production of amyloidosis.

Case 4

A man aged 65 first attended hospital in October, 1957, having had a slowly enlarging swelling in the neck for eight months. A large mass of enlarged lymph nodes was found in the left posterior triangle, and histological examination of an excised node showed the classical cellular stage of Hodgkin's disease. There was no proteinuria. A course of nitrogen mustard was given (total dose 18.9 mg.).

He remained well until May, 1958, when the cervical lymph nodes enlarged again and other enlarged nodes were noticed in both axillae and inguinal regions. There was no proteinuria and a further course of nitrogen mustard was given (total dose 15 mg.).

When next seen in October he had moderate oedema of the ankles. In November he was admitted to hospital extremely ill with gross cachexia and marked oedema of the legs. He also had persistent diarrhoea. Investigations: urine, protein ++; Hb, 11.6 g./100 ml.; W.B.C., 8,700/c.mm., normal differential count. A further course of nitrogen mustard was given (total dose 15 mg.), but death occurred one week after admission.

Necropsy.—There was considerable oedema of both legs, but no effusions were present in the body cavities. The cervical, thoracic, and abdominal lymph nodes were moderately enlarged. The liver (1,600 g.), spleen (280 g.), and kidneys (combined weight 490 g.) all showed changes of diffuse amyloidosis but no obvious deposits of Hodgkin's tissue. The thyroid was firmer than normal and a little enlarged. The only other significant macroscopic finding was an early bilateral bronchopneumonia.

Histology.—The enlarged lymph nodes consisted of rather fibrotic Hodgkin's tissue, and scanty similar deposits were found in the liver and spleen. Abundant amyloid deposits were present in the liver, spleen, kidneys, and adrenals. A little amyloid material was also present in the thyroid. The lungs showed bronchopneumonic changes only.

Comment.—A typical case of Hodgkin's disease, treated with several courses of nitrogen mustard, in which oedema and proteinuria subsequently developed.

A clinical diagnosis of amyloidosis was made in the patient's last admission, but he was considered to be too ill for any diagnostic biopsy or Congo-red test. Extensive amyloidosis was found at necropsy.

Discussion

The four fatal cases of Hodgkin's disease reported here all showed extensive secondary amyloidosis at necropsy. All were typical clinical cases of Hodgkin's disease with the usual histological features of the ordinary type of Hodgkin's disease ("Hodgkin's granuloma"). In each case the amyloid material stained well with iodine in the gross specimens and with Congo red and methyl violet in tissue sections. None of these cases showed any other disease process that might account for the amyloid deposition. In only one case was amyloid suspected during life, but on referring to the case notes of these patients it was found that they all showed the appearance of oedema and proteinuria late in the course of their Hodgkin's disease; and some cases progressed to a fully fledged nephrotic syndrome with generalized dropsy, massive proteinuria, and depletion of the serum albumin. All four cases had been treated with nitrogen mustard or tretamine prior to the onset of any clinical features attributable to amyloidosis.

As mentioned in the introduction, these four cases made Hodgkin's disease the commonest disease associated with secondary amyloidosis in a series of 20 cases of amyloidosis occurring in 3,192 consecutive post-mortem examinations. Among these necropsies there were altogether 22 examples of Hodgkin's disease: of eight patients treated with nitrogen mustard or tretamine, four had amyloidosis, while in the 14 patients not so treated no case of amyloidosis was found. It would appear from this series of cases, small though it is, that these cytotoxic drugs may facilitate the formation of amyloid material in patients suffering from Hodgkin's disease. Perusal of the extensive literature on both Hodgkin's disease and amyloidosis lends some support to this view.

It is difficult to obtain reliable figures relating to the incidence of amyloidosis in Hodgkin's disease—or, more precisely, in cases of Hodgkin's disease not complicated by other diseases, such as tuberculosis, that may produce amyloidosis. The words "rare" and "occasional" of the textbooks and monographs are of little help. In the older literature (reviewed by Fabian, 1911) there are no reliable figures at all, for two reasons: firstly, the diagnostic criteria for differentiating Hodgkin's disease from tuberculosis were not adequate; and, secondly, many cases of Hodgkin's disease in those days were undoubtedly complicated by tuberculosis. Turnbull (1915) reported 25 cases of Hodgkin's disease, found in a series of 7,924 consecutive necropsies, with amyloidosis in three of them. However, three of these patients also had tuberculosis and they included two of the amyloid cases, so that the corrected incidence figure for "pure" Hodgkin's disease is only 1 out of 22 cases. Castleman (Case Records of the Massachusetts General Hospital, 1949) found amyloidosis in 5 out of 60 cases of Hodgkin's disease coming to necropsy. Wallace, Feldman, Berlin, Harris, and Glass (1950), in an incomplete review of the literature, collected 29 cases of amyloidosis in Hodgkin's disease and quoted a personal communication from Rottino, who found only one case of amyloidosis in 40 necropsies on patients with Hodgkin's disease. Wildhack (1956) reported three cases

of amyloidosis coming to necropsy (and two of these had had triethylene melamine therapy) in a series of 71 cases of Hodgkin's disease. All these recorded series, then, give a very much lower incidence of amyloidosis in Hodgkin's disease than occurred in the present series.

There are now several reports in the literature of amyloidosis occurring in cases of Hodgkin's disease after treatment with nitrogen mustard (Case Records of the Massachusetts General Hospital, 1949; Wallace *et al.*, 1950; Teilum, 1954; Croizat, Creyssel, Morel, and Mornex, 1955; Spain, 1956; Leonard, 1957; Kilburn, 1958; Case Records of the Massachusetts General Hospital, 1960) or with tretamine (two cases, Wildhack, 1956)—together with the cases here reported they make a total of 14. All these cases showed typical secondary amyloidosis: they presented clinically with a nephrotic syndrome, and amyloid material that stained well with all the appropriate stains was deposited in the classical sites. The interval between treatment and the onset of features of amyloidosis ranged from a few weeks up to several years: in two cases where the interval was only about a month (Spain, 1956; Case 2 of present series) abundant amyloid deposits were found at necropsy, and it would appear that these cytotoxic drugs only accelerate a process that is already taking place—in the language of cancer research they act as “promoting” agents rather than as “initiating” agents.

These cases must be carefully scrutinized to see if there is any other possible explanation for the occurrence of amyloidosis. In the case reported by Spain (1956) the patient had had, during her last month of life, an abscess in the buttock which was draining pus from which *Staph. aureus* was cultured: this does not seem to be an adequate cause for the development of amyloidosis. The case reported in the Case Records of Massachusetts General Hospital (1960), however, had a major and long-standing suppurative lesion which may well have produced amyloidosis; after pneumonectomy for a Hodgkin's lesion in the lung she developed an abscess at the thoracotomy site and had an empyema draining for the last two years of her life.

There is some clinical and experimental evidence to suggest that the development of amyloidosis may be encouraged by steroid therapy and by hypothyroidism (Teilum, 1954; Symmers, 1956). Of the cases under discussion, three had treatment with cortisone or prednisone (Wildhack, 1956; Case Records of the Massachusetts General Hospital, 1960; Case 2 of present series) and one was treated for thyrotoxicosis with radioactive iodine (Croizat *et al.*, 1955). Radiotherapy has occasionally been mentioned as accelerating the development of amyloidosis (Christensen and Hjort, 1959), but it can hardly be incriminated in the present instances, as irradiation is so commonly used in Hodgkin's disease without ill effect and in 5 of the 14 cases considered here radiotherapy was never used.

Few of these patients therefore had any disease process or form of therapy (apart from Hodgkin's disease and the cytotoxic drugs) to account for their amyloidosis. It seems reasonable to suggest, therefore, that the cytotoxic drugs may have had a “promoting” effect following an “initiating” effect of the Hodgkin's disease. Some experimental support for this view has been forthcoming from the work of Teilum (1954), who found that nitrogen mustard accelerated the development of amyloidosis in mice previously treated with injections of sodium caseinate.

Clearly, further case reports and experimental work will be needed to confirm the association noted in this paper between treatment of Hodgkin's disease with cytotoxic drugs and the development of amyloidosis. In patients so treated, however, watch must be kept for the onset of oedema or proteinuria, and the occurrence of these should be a sign to cease this particular form of therapy.

Summary

Four cases of Hodgkin's disease are reported in which amyloidosis developed after treatment with nitrogen mustard or tretamine. These cases occurred in a series of 3,192 consecutive necropsies performed in a general hospital. Among these necropsies there were 22 patients with Hodgkin's disease; of eight patients treated with cytotoxic drugs, four developed amyloidosis, while in 14 patients not so treated amyloidosis did not occur.

Although it is well recognized that amyloidosis may sometimes occur in patients with Hodgkin's disease, the high incidence in the present series suggests that cytotoxic drugs may promote the formation of amyloidosis in Hodgkin's disease.

I am indebted to my clinical colleagues for allowing me to use case notes of patients under their care, and to Professor H. A. Magnus for helpful advice and criticism.

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A group of workers in the fields of deaf education, welfare, and research met in 1958, under the chairmanship of Mr. A. W. Kettlewell, headmaster of the Royal School for the Deaf, Exeter, for the purpose of clarifying the problem which deaf children have to face. At an early stage it was decided to set up a committee, selected from members of the group, to identify those aspects of educating the deaf which were most in need of further investigation, and the following list of matters requiring attention was drawn up: (a) To examine the problems of definitions of children with defective hearing and the bases of placement of those children requiring special educational treatment. (b) To investigate the conditions in which deaf children are able to gain effective capacity to understand and to use spoken language. (c) To investigate what educational provisions should be made for those children who have not gained effective capacity to understand and to use spoken language, and to promote appropriate experimental studies. (d) To investigate the place of manual communication in the education of the deaf. (e) To consider and make recommendations regarding the curriculum of deaf children of secondary-school age, taking into account the range of employment open to them. (f) To investigate the need for, and the provision of, further education for deaf children after leaving school, especially in relation to employment. The group is now reviewing current research bearing on these problems.