Clinicopathological Conference

A Case of Malignant Lymphoma with Cold Agglutinins

PRESENTED AT THE ROYAL POSTGRADUATE MEDICAL SCHOOL, LONDON

Clinical History

Dr. M. C. BRAIN (1): The patient (Case No. 317011; P.M. No. 12477) was 61 years old at the time of his death in 1968. His early medical history was of rheumatic fever during the 1939–45 war, for which he was invalided out of the services with a 30% disability pension, and a myocardial infarction in 1960. In November 1964 he had an influenza-like illness and then became increasingly pale. In December 1964 he was admitted to Milford Chest Hospital, where he was found to have an autoimmune haemolytic anaemia (haemoglobin 5·6 g./100 ml., direct antiglobulin test positive, and a raised level of cold agglutinins in the serum). He was treated with blood transfusions, and with prednisone 60 mg. per day. His anaemia responded, the haemoglobin rising to more than 12·0 g./100 ml., and the dose of prednisone was reduced to 15 mg. per day.

He remained well until early in 1966. He then became short of breath on exertion and had heavy night sweats. He was readmitted to Milford Chest Hospital in March 1966. He was not anaemic, but the chest *x*-ray film showed widespread mottling of both lung fields. In July 1966 he developed a deep vein thrombosis of the left leg and was transferred to Hammersmith Hospital for further investigation. On admission the patient was found to be obese, with Cushingoid features, and he was depressed mentally. He was afebrile, and had no abnormal signs in his chest apart from a soft apical systolic murmur. The blood pressure was 125/80 mm. Hg. Bilateral ankle oedema and pitting oedema of the left calf were present. No lymph nodes were enlarged, and the liver and spleen were not palpable. No proteinuria was found. Investigations confirmed that he had a compensated autoimmune haemolytic anaemia: the haemoglobin was 12·2 g./100 ml., the M.C.H.C. 30%, the reticulocytes 9·0%, and the white blood count 8,000/cu. mm. (neutrophils 92%, lymphocytes 4%, monocytes 4%), platelets 157,000/cu. mm., sedimentation rate 20 mm./hour. The blood film showed polychromasia of red cells but was otherwise normal; the bone marrow showed increased erythropoiesis with slight megaloblastic features. The serum vitamin B_{12} was 330 μg./ml., the folate 4·4 ng./ml.

The direct antiglobulin test was strongly positive, owing to complement on the red cells, and the serum contained a cold agglutinin with titres against normal cells of 512 at 4° C., 16 at 20° C., 2 at 25° C., 1 at 28° C., and 0 at 37° C. This antibody had the usual specificity of a cold agglutinin. It was an anti-I—that is, it agglutinated the majority of adult red cells very strongly while reacting only weakly with the red cells from neonates. The serum protein levels were albumin 2·4, globulin 3·8 g./100 ml.; immunoglobulins: IgG 1,250 (normal range 600–1,600), IgA 200 (150–450), IgM 280 (50–160) mg./100 ml. The blood urea, serum uric acid, plasma electrolytes, and tests of liver function were normal.

Lung Shadows

Investigation of the shadowing of the lung fields seen in the chest radiograph yielded largely negative results. The film (Fig. 1) showed widespread linear shadows throughout both lung fields with numerous discrete rounded opacities. Mediastinal emphysema was also present. Sputum and gastric aspirates were negative for acid-fast bacilli on staining and culture. No malignant cells were seen in the sputum. The Mantoux test was negative at 1:1,000, and skin tests for aspergillus and mixed moulds were negative. Serum complement fixation tests against influenza A, B, and C, Sendai virus, mycoplasma, adenovirus group, Q fever, psittacosis, and L.G.V. group viruses were negative. The W.R. was anticomplementary and the V.D.R.L. slide test was negative.

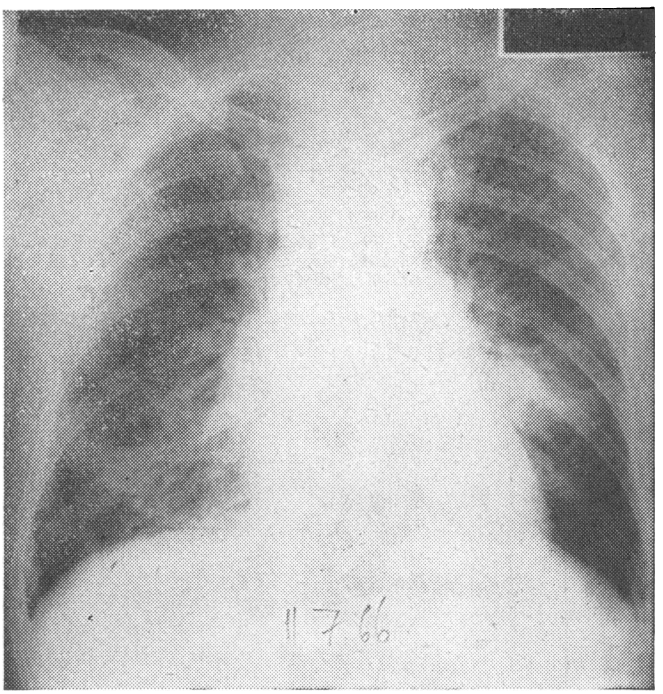

FIG. 1.—Chest radiograph on 11 July 1966.

As these efforts to establish the nature of the pulmonary shadowing were negative, biopsies were obtained from a scalene node, from the liver, and finally from the lung by open biopsy. The scalene node biopsy was normal, the liver biopsy showed only mild fatty change, and the lung biopsy revealed granuloma, the exact nature of which will be discussed by Professor Harrison later. No acid-fast bacilli were seen or cultured, and no other organism was grown from it.

A localized staphylococcal infection occurred at the site of the scalene node biopsy, and the lung biopsy was followed by a staphylococcal septicaemia, which responded rapidly to treatment with methicillin. As the lung granuloma did not appear to be due to an infection, it was decided that there was no contraindication to the use of immunosuppressive therapy, a treatment which has been found to be more effective than prednisone in the treatment of some patients with cold agglutinin syndrome.[1] The dose of prednisone was progressively reduced from 45 mg. to 15 mg. daily, and chlorambucil 4 mg. per day was started.

The patient proved remarkably sensitive to this treatment, so much so that at first we had difficulty in believing that his response was to the treatment rather than a spontaneous remis-

sion. The effect of the various immunosuppressive drugs used on the level of haemoglobin, reticulocytes, IgM globulin, and agglutination and haemolysin titres is shown in Fig. 2. His general condition improved, the night sweating ceased, the breathlessness became less, the shadowing in the chest radiograph cleared (Fig. 3). This symptomatic improvement was

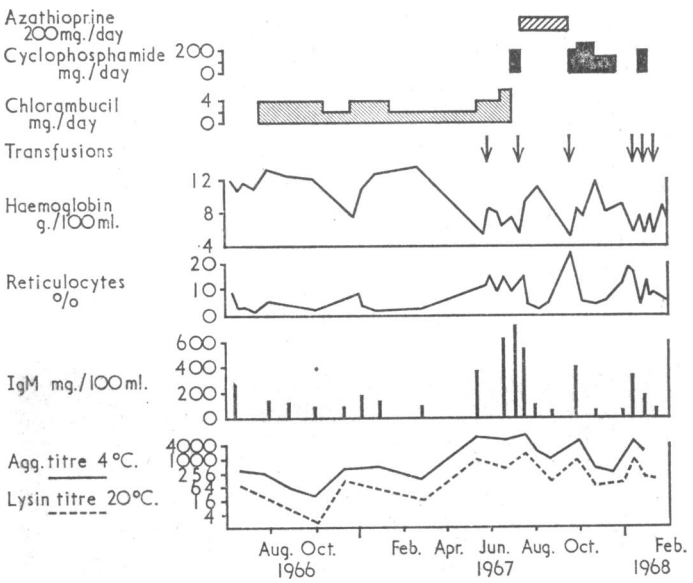

FIG. 2.—Haematology chart. The IgM levels in the serum and the cold agglutinin and lysin times against normal and enzyme-treated red cells, respectively, are also shown.

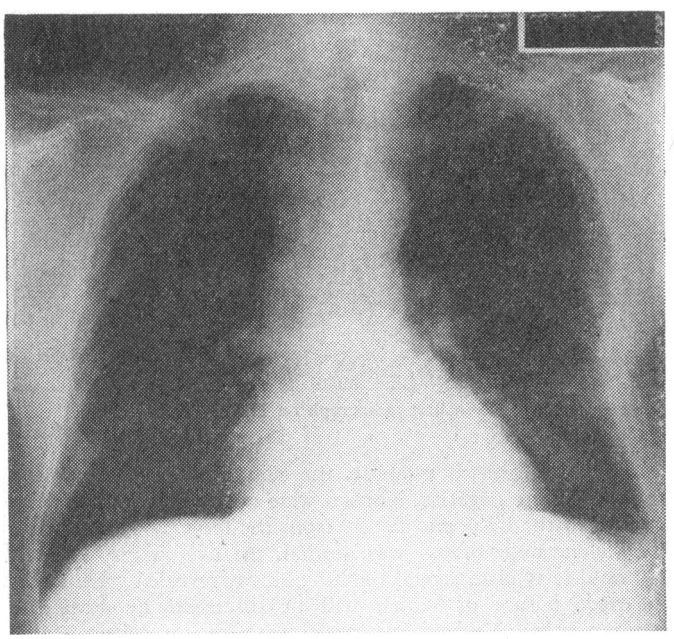

FIG. 3.—Chest radiograph 20 December 1966.

accompanied by a fall in the level of IgM globulin and of the agglutinin and lysin titres, while the haemoglobin was maintained. In view of this improvement the dose of chlorambucil was reduced to 2·0 mg. per day on 11 November, but by 19 December his condition had relapsed, with a recurrence of the anaemia and a rise in the levels of the IgM globulin and in the antibody titres. The dose of chlorambucil was again increased to 4·0 mg. per day, the level of haemoglobin rose, and the IgM level again fell, and in February 1967 it was again felt reasonable to reduce the dose of chlorambucil to 2·0 mg. daily. He was well in April, but anaemic again in June, and he had to be readmitted to hospital and was given a blood transfusion. The dose of chlorambucil was increased to 4·0 mg. and then to 6·0 mg. per day without apparent benefit. The treatment was changed to cyclophosphamide and he was given 200 mg. intravenously daily for seven days. This treatment led to neutropenia, so he was maintained on oral azathioprine, 150 mg. daily. These measures were followed by an improvement in the anaemia and a fall in the IgM level (see Fig. 2), but while on the azathioprine his anaemia recurred and the IgM level rose again, suggesting that the response had been due to the intensive course of cyclophosphamide. He was readmitted and given a blood transfusion and a further seven-day course of cyclophosphamide, which was followed by oral treatment with cyclophosphamide. He again improved, but he developed neutropenia and the treatment had to be stopped.

He was readmitted to hospital in January 1968 because of recurrence of anaemia, but on this occasion no improvement followed a further seven days of intravenous cyclophosphamide. His general condition had deteriorated and he was febrile (38·8° C., 102° F.). Repeated specimens of blood and urine were sterile on culture. Lymph nodes in the left axilla began to enlarge, and a clinical diagnosis of a lymphosarcoma or reticulum-cell sarcoma was confirmed by a finding of abnormal reticulum-like cells in aspiration biopsies of the bone marrow and of the enlarged lymph nodes. Despite further blood transfusions his condition deteriorated and he died on 29 February 1968.

Clinical Diagnosis

(1) Autoimmune haemolytic anaemia due to a high-titre cold agglutinin.

(2) Pulmonary granuloma of uncertain aetiology.

(3) Terminal reticulum-cell sarcoma.

Post-mortem Findings

Professor C. V. HARRISON (2): Three biopsies were received during August 1967. A lung biopsy (Fig. 4) contained about six granulomatous nodules of 1–3 mm. diameter. These had a centre of necrotic exudate and a surrounding infiltration of lymphocytes, plasma cells, and histiocytes. We failed to demonstrate any micro-organisms and the origin of these nodules remains unknown: they did not resemble a lymphoma. A liver biopsy and a scalene node biopsy were not helpful; neither showed any evidence of a lymphoma.

Necropsy Findings

The body was that of a moderately jaundiced man of average nutrition (170 cm., 68·5 kg.) with the healed scar of a lung biopsy incision along the left 7th rib. There were palpable lymph nodes in the left supraclavicular fossa.

Haemopoietic System.—The left supraclavicular and anterior mediastinal lymph nodes were moderately enlarged, and so were the peribronchial nodes. The left axillary nodes were enlarged to a maximum of 30 mm. and were matted. The right axillary nodes were slightly enlarged; the coeliac, para-aortic, and inguinal nodes were of normal size. Microscopically, nodes from all these sites showed total replacement by a malignant lymphoma (Fig. 5). The normal lymphocyte population was replaced by anaplastic reticulum cells, among which were numerous giant cells. The latter were often bizarre, but there were sufficient recognizable Sternberg–Reed giant cells to justify a diagnosis of Hodgkin's disease of anaplastic type—the Hodgkin's sarcoma of Gall and Mallory or the reticular Hodgkin's of Lukes.

The *spleen* was enlarged from 150 g. to 420 g. Its cut surface was speckled with pale deposits of lymphoma averaging a few mm. diameter. Microscopically these were similar to the lymph nodes, and from their relation to the arteries appeared to have originated in the Malpighian bodies. In addition there was fairly severe siderosis of the pulp histiocytes.

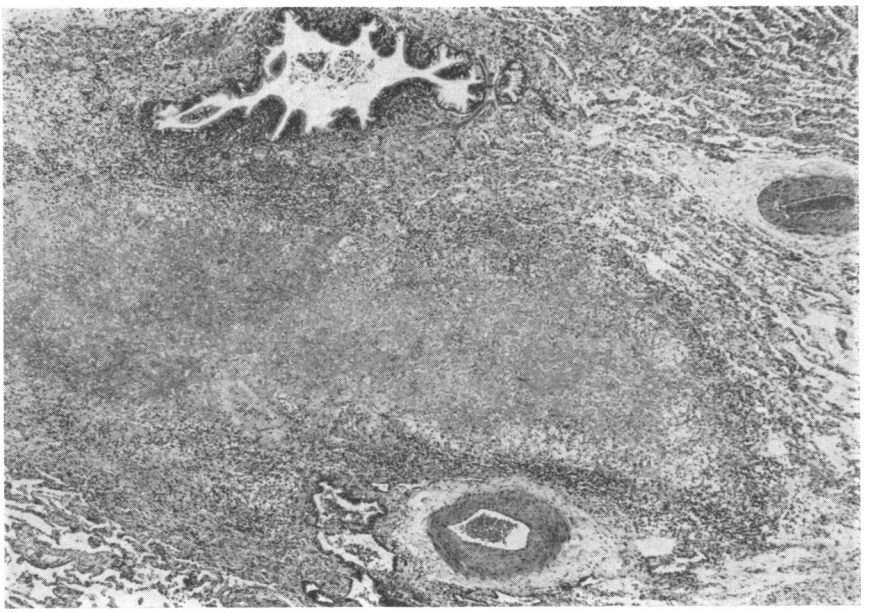

FIG. 4.—Granuloma in lung biopsy. (H. and E. ×43.)

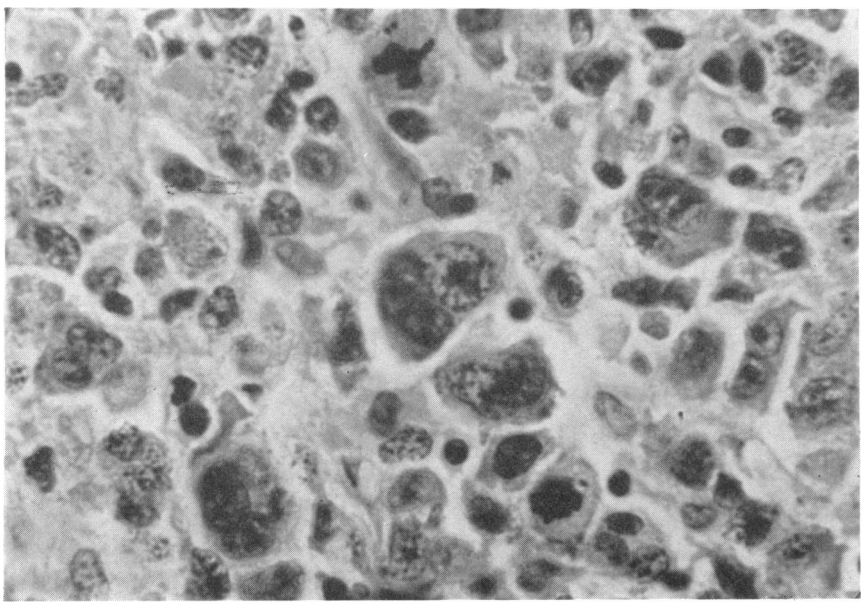

FIG. 5. — Malignant lymphoma showing anaplastic and multinucleate reticulum cells. Note the two mitoses present. (H. and E. ×702.)

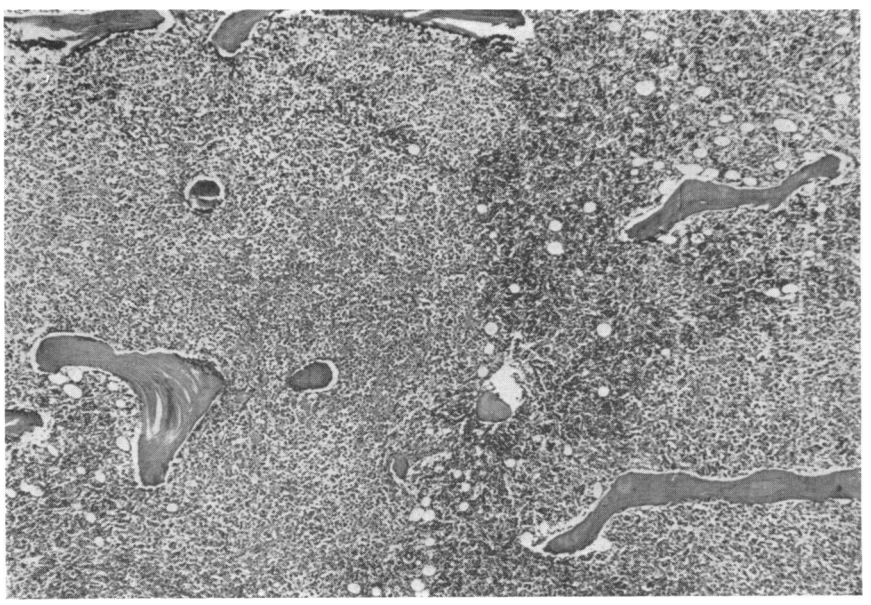

FIG. 6.—Vertebral bone marrow showing nodular infiltration with tumour. Parts of two nodules are shown; the surviving normal marrow can be identified by the fat cell present. (H. and E. ×43.)

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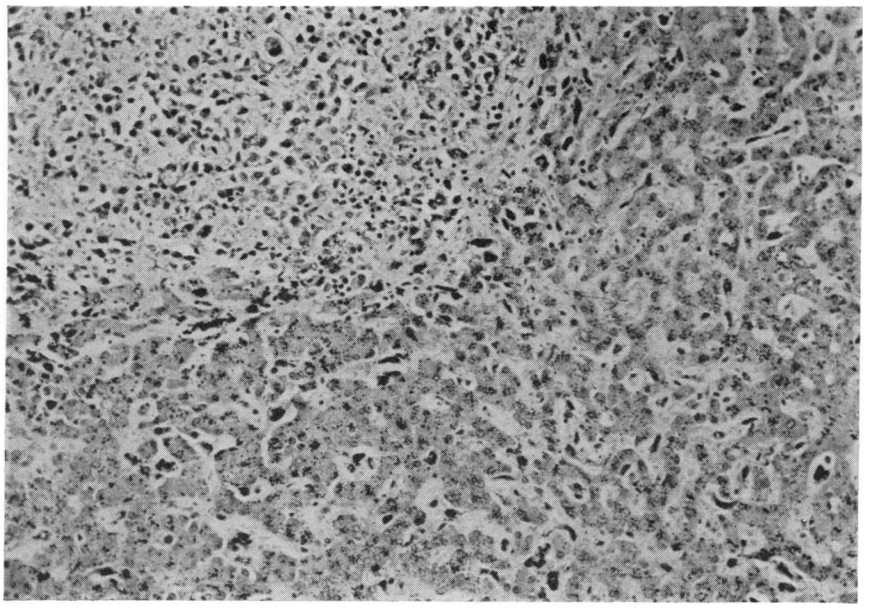

FIG. 7.—Liver showing part of a portal tract (top left) infiltrated by tumour. The dark pigment in the liver is iron. (Perls's reaction. ×129.)

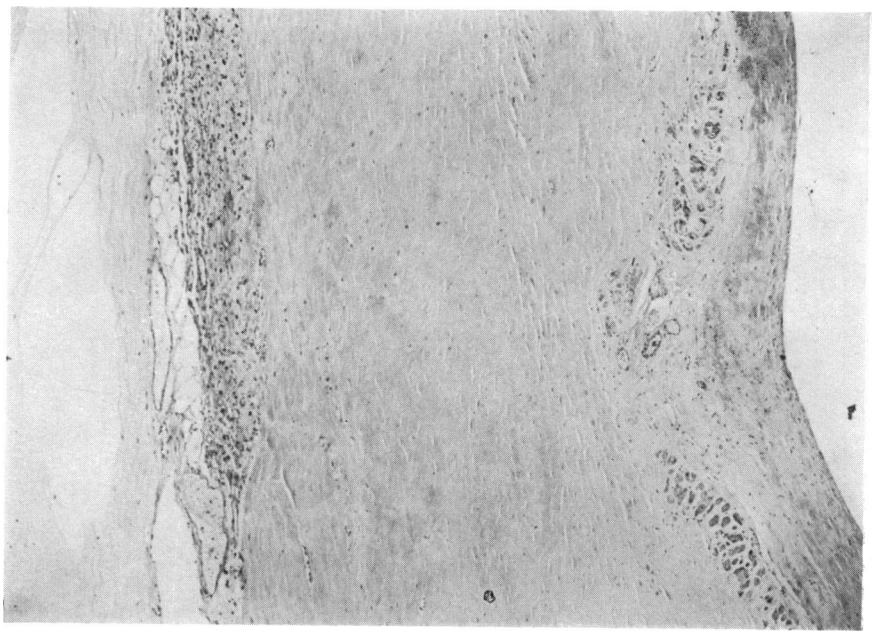

FIG. 8.—Old infarct in left ventricle. Thin bands of surviving muscle are present on the endocardial and pericardial surfaces, but nearly all the thickness of the ventricular wall is composed of collagen. (H. and E. ×43.)

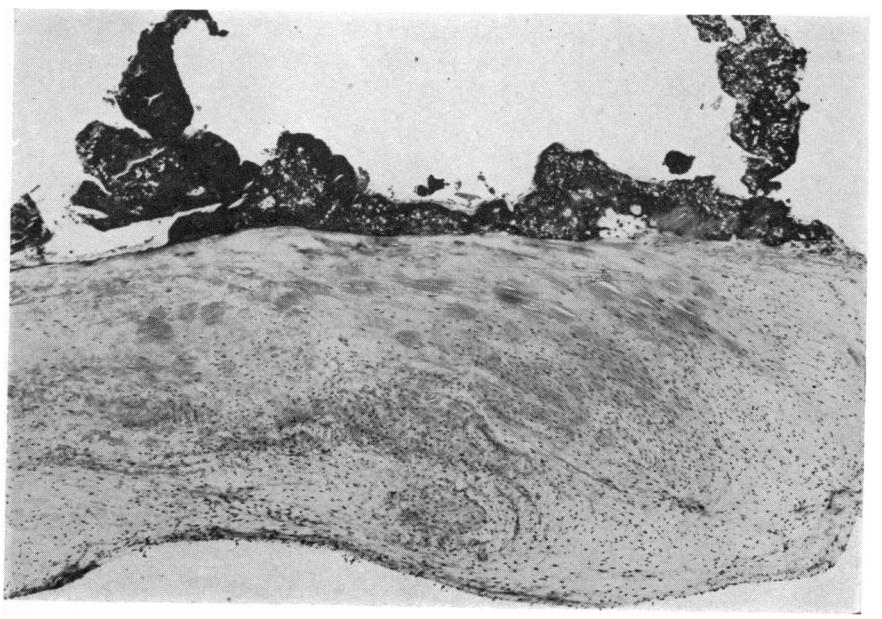

FIG. 9.—Mitral valve leaflet with thrombotic endocarditis. Note the absence of inflammatory infiltration. (H. and E. ×43.)

The *bone marrow* was hypertrophied, and there was red marrow to the lower end of the femur. In all sites—spine, sternum, rib, iliac crest, and femur—the red marrow was speckled with closely packed white deposits of lymphoma averaging about 1 mm. diameter (Fig. 6). Microscopically these resembled the lymph node deposits.

The *liver* was enlarged from 1,500 g. to 1,830 g. Sparse deposits of about 1–2 mm. were scattered under the capsule and throughout the parenchyma (Fig. 7). Microscopically they were like the other deposits, and in addition there was moderate fatty change. There was moderate siderosis of Kupffer cells and liver cells.

The *heart* (510 g.) was about 190 g. overweight and showed dilatation and hypertrophy of both ventricles. In the posterolateral part of the left ventricle there was a full thickness infarct scar 6 × 5 cm. (Fig. 8). The descending left coronary artery was totally occluded. There were partly occlusive plaques in the other coronary arteries. Both mitral and aortic valves showed slight fibrosis without significant deformity, and there were small thrombotic vegetations on both cusps of the mitral (Fig. 9) and the non-coronary cusp of the aortic. The *aorta* showed relatively less atheroma, there being only fatty streaks and plaques. Microscopically these lesions were confirmed.

The *lungs* showed a little terminal congestion and oedema (left 440 g., right 465 g.). There was a plaque of pleural fibrosis at the site of the biopsy (apex of left lower lobe). In the apical part of the right lower lobe there was a necrotic focus 2 × 3 × 8 mm., but apart from this we failed to find any scar or other sign of the earlier lung granulomata. Microscopically this focus had a necrotic centre and a fibrous wall, but it had hardly any inflammatory cells. It presumably represented the end stage of one of the granulomatous foci.

The *alimentary tract* was normal, but the gall bladder contained eight mulberry-shaped pigment stones and showed slight cholesteatosis. The *adrenals* (9 g., Normal = 12) were rather small and the cortices thin. Other endocrines were normal.

The *kidneys* showed an occasional small cortical scar, probably pyelonephritic. The prostate contained a small abscess in the left lobe.

The *nervous system* was macroscopically normal, but at a few sites platelet aggregates were found in arteries. These might have come from the platelet vegetations on the heart valves.

Pathologist's Diagnosis

(1) Hodgkin's disease affecting lymph nodes, spleen, bone marrow, and liver.

(2) Old thrombosis of descending left coronary artery with healed infarction of left ventricle.

(3) Slight old fibrous scarring of mitral and aortic valves with terminal thrombotic vegetations on both.

(4) Adrenal cortical atrophy following steroid therapy.

(5) Pigment gall stones.

(6) Siderosis of spleen and liver.

(7) Abscess in prostate.

(8) Residual pulmonary granuloma.

Discussion

Dr. BRAIN: I do not think that any of us had suspected that he had such a widespread distribution of this lymphoma. We did note the enlargement of the left axillary lymph nodes a few weeks before he died, and it is reassuring to hear that Professor Harrison considered these to be barely increased in size. The bone marrow aspirate contained a few abnormal cells, but clearly we did not enter any of the masses of lymphoma which were demonstrated at necropsy, and indeed we might not have aspirated anything if we had.

The course of this patient's illness was particularly interesting for a number of reasons. Firstly, we have the nature of the antibody which was the cause of this patient's haemolytic anaemia. Dr. Cooper has recently been studying these antibodies, and his work has thrown considerable light on the structure and function of these abnormal proteins.

Then we come to the point that Professor Harrison raised on the relationship between the malignant lymphoma and the ability of these cells to synthesize the abnormal protein, and the malignant termination.

I wonder whether the rapid improvement in this man which followed treatment with cytotoxic drugs, and which initially we ascribed to chance, might not reflect the inherent malignancy of the underlying lymphoma. Patients who have more malignant diseases not infrequently initially respond briskly to treatment with various cytotoxic drugs, only to relapse with equal rapidity when the treatment is withdrawn or the underlying disease escapes. I should be interested to hear from Dr. Worlledge whether other patients have shown such a rapid rate of response and relapse, and whether this might have some bearing on the malignancy of the underlying disease. Perhaps the patients who don't respond, or respond less rapidly, may have less malignant disorders.

Finally we have the problem of the pulmonary infiltration—anybody's guess, I suppose. It is certainly dissatisfying not to be able to tie it up, but if anyone who has had similar patients has any comments I should be most interested to hear them.

Monoclonal Proteins

Dr. A. G. COOPER (3): I should like to discuss briefly the concept of monoclonal proteins and to show how cold agglutinins fit into this category.

If antibodies formed during the course of an infection are isolated by their specificity, they will be found to be present in very small amounts (only up to a few milligrams per 100 ml.); and most of these preparations will contain at least two, often three, classes of immunoglobulins. If the light chains of these immunoglobulins are examined both kappa and lambda types will be found. Further, these light chains give a number of bands (up to 10 for each antibody preparation) on starch-gel electrophoresis, and detailed amino-acid analysis shows considerable variation at the same positions along the light chain. Thus the antibodies produced in response to a normal antigenic stimulus are composed of a heterogeneous population of molecules with different light and heavy chains, even though they appear homogeneous in respect of their antibody activity. Since it is generally agreed that one clone of antibody-producing cells forms antibodies of only one heavy chain and one light type, it can be assumed that these normal antibodies are made by several clones and they are called polyclonal proteins.

The polyclonal nature of naturally produced antibodies is in sharp contrast to the abnormal proteins of myeloma and macroglobulinaemia, which are produced without any known antigenic stimulus and usually have no antibody activity. They are present in the serum in very large amounts (up to 6 g./100 ml.) and on electrophoresis form a definite spike in the gamma- or beta-globulin region. Purified preparations of these protein molecules usually have only one type of light chain and one type of heavy chain. Moreover, starch-gel electrophoresis of the light chains reveals only one or two bands. These proteins are thought to be homogeneous and to be produced by a single clone of cells, and they are called monoclonal proteins.

The cold agglutinins of chronic cold haemagglutinin disease resemble the monoclonal proteins of myeloma and macroglobulinaemia, but in addition they have a well-defined antibody activity. They are present in the serum in moderately large amounts, usually in the range of several hundred milligrams per 100 ml., and on electrophoresis they often show a

small sharp peak in the beta-gamma region of the serum. They are invariably IgM and have a single type of light chain, almost always kappa.

The property of these antibodies to absorb on to red cells in the cold and be released on warming has enabled me to separate them from other serum proteins and purify them in relatively large quantities. The purified antibodies can then be broken down into their constituent heavy and light chains, and these can be separated by chromatography on Sephadex. The isolated light chains, when examined by starch-gel electrophoresis, show a restricted number of bands very similar to the light chains from myeloma proteins and in striking contrast to the multiple bands of light chains from normal antibodies isolated by their antigenic specificity. This is strong evidence in favour of the homogeneity of these cold agglutinin molecules and hence of a monoclonal origin. Furthermore, when we examined the N-terminal amino-acid in cold agglutinins isolated from five different patients we found the same amino-acid in all. If this is also true for amino-acids at other positions every molecule would be exactly alike.

The most interesting aspect of this work, however, still remains to be done. One of the basic problems of immunology is to correlate the structure of the immunoglobulin with the specificity of the antibody. Unfortunately, detailed amino-acid analysis has been done, as yet, only on light chains derived from myeloma proteins without any known antibody activity. From these studies it can be shown that each light chain has two regions, one which is very similar in all light chains of the same class whatever the source, and the other which shows considerable variation, especially at certain positions, in light chains from different sources even though of the same general class.

The same general pattern of a variable region and a constant region is thought to occur in light chains derived from normal antibodies, and some of the variation is believed to be the basis of antibody specificity. But since myeloma proteins have been used we still do not know how many of these amino-acids are in the antigen-combining site or what part of the molecules is concerned. The details of the amino-acid sequence of cold agglutinins from different patients will be particularly interesting; perhaps it will show that certain variable areas are relatively constant and thus pin-point the antigen-binding site.

Professor T. RUSSELL FRASER (4): May I ask how you pick up the cold agglutinins? Do you start from the population of haemolytic anaemias?

Dr. COOPER: They are picked up in the laboratory by the registrar or technician noticing agglutination of the red cells when spreading or examining slides of peripheral blood made at room temperature.

Professor FRASER: Having picked them up that way, do the patients have any pattern of disease?

Dr. COOPER: Yes, most of them have a chronic haemolytic process of varying degrees with haemoglobin levels of from 7–12 g./100 ml. and a raised reticulocyte count. There is also a very definite pattern of intravascular haemolysis, with constant haemosiderinuria and occasional haemoglobinuria.

Relation to Virus Illnesses

Professor FRASER: Don't some of these illnesses occur after viral infections?

Dr. COOPER: Yes, but the group has many different features. The antibodies in the cases associated with viral infection are thought to be polyclonal and have both kappa and lambda light chains and other characteristics of heterogeneity.

Professor FRASER: We have had a lot of data presented to us about cold agglutinins and antibodies. Do we think, looking back to November 1964, that the patient's influenzal illness was in any way precipitating?

Dr. BRAIN: It was probably irrelevant. I should have thought from the data that Dr. Cooper has presented that this patient had a monoclonal antibody, which is strongly against it being evoked by an infection.

Dr. COOPER: The monoclonal antibody in this patient appears to be different from the polyclonal antibody temporarily produced by a patient with, say, atypical pneumonia. I know of no case where the continuous production of these antibodies has been shown to follow this type of influenzal disease.

Site of Antibody Production

Dr. BRAIN: Might I ask which cells these antibodies originate from? Was it possible in this patient to demonstrate antibody in the lymphoma cells in the post mortem specimens? Does Dr. Cooper think that the cells that we saw are antibody producing or not?

Dr. COOPER: In those cases in which fluorescent techniques have been used, including one case with an underlying lymphoma, IgM antibody production seemed to occur in normal lymphocytes and plasma cells and not in the obviously abnormal tumour cells. I doubt that the obviously lymphomatous cells were producing antibody.

Dr. J. R. HOBBS (5): There is some other evidence here. This patient died with something like 2 kg. of tumour, Professor Harrison?

Professor HARRISON: Oh no. Only a tiny fraction of that. The liver weighed 1,900 g. and I have shown you that the tumour was restricted to barely visible points of pin head size; the spleen weighed 1,600 g., in which tumour forms only a minority of the tissue. The lymph nodes: I doubt if we could have got 100 g. from the patient if we put them all together. No, the amount of this tissue was very small.

Dr. HOBBS: But the vertebrae you showed us were heavily involved.

Professor HARRISON: The bone you actually saw was the femoral bone marrow, and I suppose that half of the volume was composed of this tumour. However, let me be quite clear—I think it unlikely that the tumour which I had demonstrated could have produced anything.

Dr. HOBBS: Exactly. If there was a great deal of tumour in the bone marrow—50% of the bone marrow would be 1·5 kg. —and very little IgM at death then you can say that most of the cells of that tumour could not have been producing IgM.

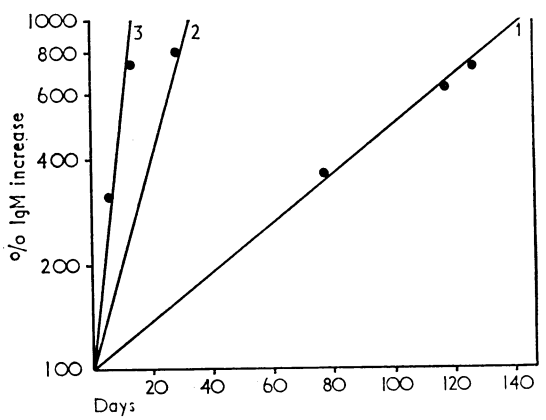

FIG. 10.—Rate of increase of IgM level in the serum during three relapses.

Fluorescent antibody study might show that only 10% of cells were differentiating to produce IgM. This is the finding in lymphomas associated with monoclonal immunoglobulins.[2] Most of the cells that are left by the time the treatment had been given to this patient were not producing protein.

Now there is some beautiful evidence, which Dr. Cooper hasn't brought out, and that is that this patient relapsed at least four times before he died. With each relapse, the rate of increase of serum level of IgM got faster and faster. Even if only 10% of the cells were producing immunoglobulin, the IgM was marking the rate of growth of the tumour. The tumour was therefore growing faster and faster at each relapse. I think this is one of the first cases in which there is concrete evidence for this—the changing doubling time for the serum level of IgM. At each relapse there seems to have been a selection of cells which are more and more primitive, so that the ones which eventually killed this patient were the least efficient at producing IgM and the fastest growing.

Dr. COOPER: Fig. 10 shows the rate of increase of IgM production each time this patient relapsed. During the first relapse the amount of IgM doubled in 43 days. During the second the same increase took nine days, in the third it took five days. This increase in rate of production suggests that the cells producing these cold agglutinins were increasing in number.

Treatment

Dr. HOBBS: The only other point I would make is that McCallister's group[3] did stress that the treatment of macroglobulinaemia each time the patients relapsed it was more difficult to get them under control. They were very much in favour of continuous treatment of some kind. It might be only two days each week, but it was given continuously. Any longer break, as in this patient, seems to be inviting trouble.

Dr. SHEILA WORLLEDGE (6): These patients are, indeed, rather difficult to treat. Since the antibody will not react with the red cells at 37° C., they can be treated by giving them warm clothing and in that way reducing the amount of red cell destruction. However, the clothing is very clumsy, and most people find it very uncomfortable. They can also be treated by advising them to emigrate to a tropical country, but most people would find this impracticable. It is not much use treating them with corticosteroids or with splenectomy—both of which are useful in the treatment of autoimmune haemolytic anaemia of warm antibody type. It is interesting, however, that this particular patient did seem to respond partially to corticosteroids. So what is left is treatment with cytotoxic drugs with the aim of reducing the amount of antibody.

Professor FRASER: How do you think the corticosteroids worked ?

Dr. WORLLEDGE: I don't know. In warm autoimmune haemolytic anaemia the haemolysis appears to be mainly extravascular and to be due to phagocytosis and destruction by the cells of the reticuloendothelial system. Corticosteroids perhaps work by their action on stabilizing cell membranes or their action on macrophage activity. But in cold haemagglutinin disease, in which the haemolysis is mainly intervascular, corticosteroids are not usually useful. I cannot explain the response in this man.

To return to the treatment with cytotoxic drugs. We rather naively thought, in analogy with Waldenström's macroglobulinaemia, that it was lymphocyte-like cells that were proliferating in cold haemagglutinin disease and perhaps producing the abnormal antibody. So, taking examples from treatment of chronic lymphatic leukaemia, we selected chlorambucil as the appropriate drug. We have used this drug in the treatment of nine patients. We have had a successful result—that is, a rise in the haemoglobin level and a lowering of the IgM level—in three patients ; temporary success in one patient—that is, the patient who has been described today ; and improvement, with lowering of the IgM level, in two patients. No response at all has occurred in three patients in spite of treatment for 4, 8, and 12 months respectively.

The case we have been talking about today does raise an additional point. We know that these cytotoxic drugs are mutagenic, and there is the possibility that the drug induced the change in his disease that appeared clinically. However, a story like this—a patient presenting with what appears to be uncomplicated cold haemagglutinin disease and continuing that course for many years, but finally showing all the symptoms and signs of a malignant lymphoma—can occur without these drugs. In our series of patients with cold haemagglutinin disease, clinical lymphoma was present either from the start of the illness or as a terminal event in about 10–15% of cases.

Dr. L. R. I. BAKER (7): There seems to be a great variability in the severity of symptoms due to the cold antibody in these patients. Some present with severe Raynaud's phenomenon with very little haemolysis ; others, like this man, have very little in the way of cold sensitivity but a severe haemolytic anaemia. Is there any explanation for this ?

Professor J. V. DACIE (8): I think the commonly put forward explanation is roughly this. The patients that develop Raynaud's phenomenon have an antibody which causes powerful agglutination at a temperature which corresponds to the temperature in the skin capillaries—namely, 28 or 30° C. The patients who develop haemolysis are those who have antibodies which actively fix complement.

Professor FRASER: Thank you very much—I think we must stop there.

APPOINTMENTS OF SPEAKERS AT THE ROYAL POSTGRADUATE MEDICAL SCHOOL

(1) Dr. M. C. Brain, Lecturer, Department of Haematology.
(2) Professor C. V. Harrison, Professor of Morbid Anatomy.
(3) Dr. A. G. Cooper, Research Fellow, Department of Haematology.
(4) Professor T. Russell Fraser, Professor of Clinical Endocrinology.
(5) Dr. J. R. Hobbs, Senior Lecturer in Chemical Pathology.
(6) Dr. Sheila M. Worlledge, Senior Lecturer in Haematology.
(7) Dr. L. R. I. Baker, Registrar, Department of Medicine.
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