any stress or strain which he is undergoing, informing him of the importance of the annual vacation, of leaving his work and worries in the office, of hobbies and outside interests, and, finally, of relaxation.

Conclusion

The employee is one of the most valuable assets in any company, and of the employees the management group or executives are particularly valuable because of their training, motivation, and high degree of technical and administrative skill. A health maintenance scheme for the executive is an essential part of any industrial medical programme. Its main object is the detection of disease in its incipiency in order that corrective action may be taken so as to maintain him in good health and increase his longevity and efficiency.

REFERENCES

Franco, S. C. (1950). *Industr. Med. Surg.*, **19**, 213.
Hartman, H. R. (1952). "The Executive and Health." Panel discussion at the Sixteenth Annual Meeting of the Industrial Hygiene Foundation, Pittsburg. Abstracted in *Industr. Med. Surg.*, 1952, **21**, 140.
Irvin, E. A. (1952). "The Executive and Health." Panel discussion at Sixteenth Annual Meeting of the Industrial Hygiene Foundation, Pittsburg. Abstracted in *Industr. Med. Surg.*, 1952, **21**, 141.
Proudfit, A. T. (1957). "Health is Good Business." Industry and Tropical Health, III. Proceedings of the Third Conference—Industrial Council for Tropical Health—Harvard School of Public Health, pp. 5-9.
Roberts, C. G. (1951). "The Health of Executives: Mental Stress and Breakdown." I.W.S. Inc., London.
Roberts, N. J. (1958). *Industr. Med. Surg.*, 27, 153.
Ruffin, W. H. (1957). "Industry's Responsibility for the Health and Safety of Its Employees.' Address at the Annual Meeting of the Industrial Health Council, Birmingham, Alabama, March 12, 1957.
Thompson, C. E., and Staack, H. F. (1956). *Industr. Med. Surg.*, **25**, 175.
Trickett, J. M. (1952). Ibid., **21**, 5.

EFFECT OF PREDNISOLONE ON ANAEMIA ASSOCIATED WITH MACROGLOBULINAEMIA

BY

W. R. PITNEY, M.D., M.R.A.C.P.
Department of Haematology, Royal Perth Hospital

W. J. O'SULLIVAN, B.Sc.
Department of Biochemistry, Royal Perth Hospital

AND

J. A. OWEN, Ph.D., M.B., B.Sc.
Department of Biochemistry, University of Melbourne

In spite of numerous case reports, the pathogenesis of macroglobulinaemia remains obscure. The diversity of clinical features in patients with this abnormality (Waldenström, 1952; Wilde and Hitzelberger, 1954; Long *et al.*, 1955; Ferriman and Anderson, 1956; Mackay *et al.*, 1956, 1957; Jim and Steinkamp, 1956; Martin and Close, 1957; Wanner and Siebenmann, 1957; Kappeler *et al.*, 1957) suggests that it does not itself constitute a disease entity, though it appears in many cases to be associated with neoplastic disease of reticulo-endothelial tissue. In most cases therapeutic measures have not affected the macroglobulinaemia and have failed to shed light on the nature of the anomaly. In view of this, we record the findings in an elderly woman with unexplained anaemia and macroglobulinaemia who has shown marked improvement, in respect both of her anaemia and of her macroglobulinaemia, while being treated with prednisolone.

Case Report

The patient, now aged 73, has attended the Royal Perth Hospital periodically for the past 15 years. Hospital records show that in 1943 and again in 1945 the haemoglobin value of her blood varied between 8 and 9 g./100 ml. No further haematological investigations had been undertaken at those times.

In 1955 she was investigated for anaemia. The clinical history was not informative. She did not suffer from a bleeding tendency. Apart from pallor, clinical examination revealed no abnormality. The liver and spleen were not palpable and the lymph nodes were not enlarged. Anaemia

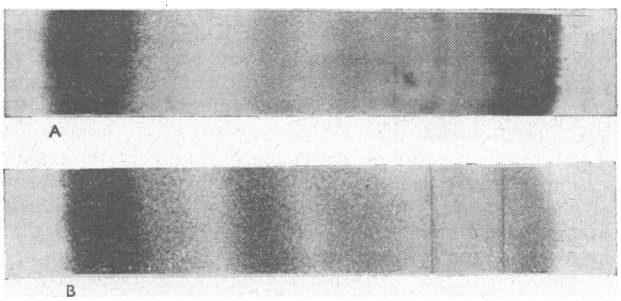

FIG. 1.—Paper electrophoresis of serum. A, Before prednisolone therapy (October, 1956). B, On cessation of prednisolone (June, 1957). The strips have been aligned with the albumin bands to the left.

was of normochromic normocytic type with a haemoglobin value varying between 7.1 and 8.6 g./100 ml. The erythrocyte sedimentation rate was elevated, lying in the range 74 to 155 mm. fall in one hour (Westergren). The total serum proteins as determined by the alkaline biuret reagent of Weichselbaum (1946) were 9.2 g./100 ml. Salt fractionation with 26.9% sodium sulphate solution gave values of 2 g./100 ml. for albumin and 7.2 g./100 ml. for globulin. Paper electrophoresis of serum (Flynn and de Mayo, 1951), using azocarmine B as a protein stain, showed a discrete band of abnormal protein in the γ-globulin region similar to that shown at A in Fig. 1. Bence Jones proteinuria was not present. Examination of sternal marrow and radiological examination of the skeleton failed to reveal any further abnormality, so that a provisional diagnosis of myelomatosis was not sustained. After unsuccessful therapy with a variety of haematinics the patient was treated with blood transfusions.

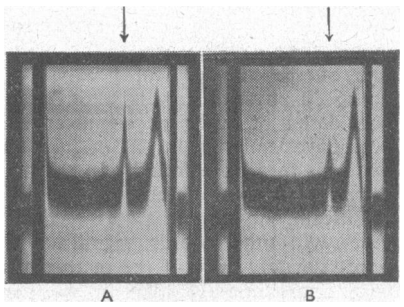

FIG. 2.—Ultracentrifuge pattern of serum. A, Before prednisolone therapy (October, 1956). B, On cessation of prednisolone (June, 1957). Arrows indicate the major macroglobulin component.

In 1956 an enlarged lymph node was noted in the left axilla. Further investigations showed that the abnormal serum protein was macroglobulin. It did not migrate from the point of insertion when electrophoresis was carried out in starch gel (Silberman, 1957). On examination in the ultracentrifuge* the serum was found to contain an abnormal component constituting 23% of the total protein (total protein 7.3 g./100 ml.), with a sedimentation constant of 15.3 S. There was also a small amount of a faster sedimenting protein (Fig. 2, A). In addition the serum gave a positive result with the Sia test, although this is not exclusive to macroglobulinaemia.

At this time the haemoglobin value of the blood was 9.1 g./100 ml. and the haematocrit 29%. The reticulocyte

*Spinco model-E ultracentrifuge; rotor An-A; centrifugal force, number × gravity = 182,000; serum dilution of 1+4 in 0.2 M NaCl solution; *p*H = 7.0; temperature of rotor, 20° C.

count was 2.4% and the Coombs reaction on the patient's red cells negative. Survival of the patient's ^{51}Cr-labelled red cells in her own circulation was normal. The total leucocyte count was 6,600/c.mm., with 53% polymorphs, 37% lymphocytes, 8% monocytes, and 2% eosinophils. The sternal bone marrow was of normal cellularity and showed a moderate increase in lymphocytes, which numbered 29% of all nucleated cells present. There were 2% plasma cells and 16% normoblasts. Further skeletal *x*-ray films showed no abnormality.

Progress is illustrated in Fig. 3. The patient was transfused in October and December, 1956. Prednisolone therapy was then begun at an initial dosage of 40 mg. a day, which was soon reduced to 20 mg. After an initial fall in the haemoglobin value there was a steady improvement, first noticed one month after starting prednisolone. By April, 1957, the haemoglobin value was 14.2 g./100 ml. and the haematocrit 43%. The patient was in good health except for recurrent furunculosis.

In June she developed an acute sinusitis, which progressed to an orbital cellulitis requiring surgical drainage. During her stay in hospital prednisolone therapy was discontinued. The haemoglobin value of the blood fell to 10 g./100 ml. over a period of a week. With the control of infection it spontaneously rose to 12 g./100 ml. and maintained itself at about this level for six months without further therapy.

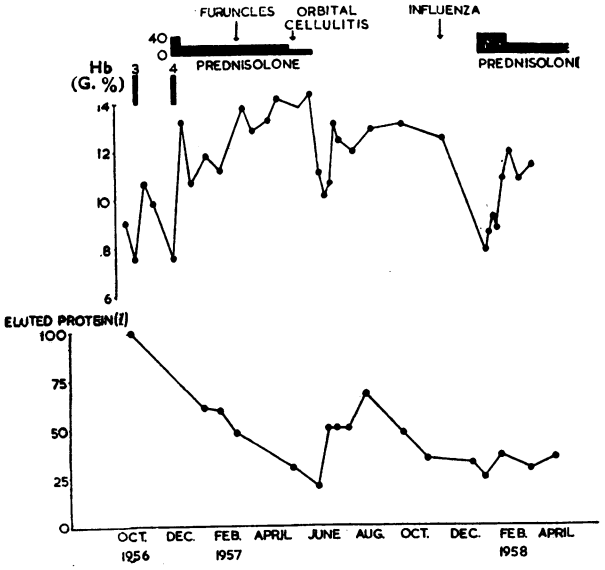

FIG. 3.—Effect of therapy on blood haemoglobin value and concentration of protein migrating electrophoretically as γ-globulin. The figures 3 and 4 refer to pints of blood transfused. Concentrations of dye eluted from the γ-globulin region are expressed as a percentage of the concentration found in October, 1956.

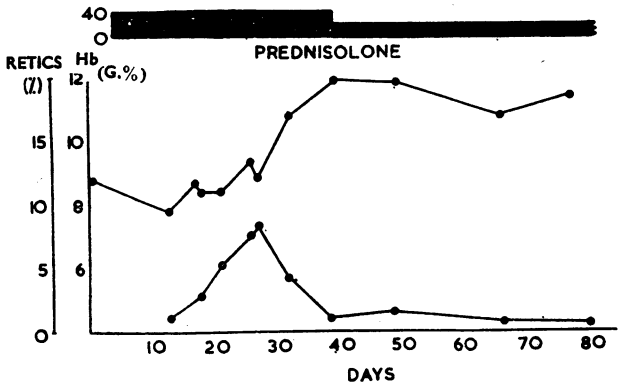

FIG. 4.—Reticulocyte percentages (lower curve) and haemoglobin values (upper curve) during the second course of prednisolone therapy (January, 1958).

In December she suffered from influenza. When she was seen one month later, her haemoglobin value was 8.6 g./100 ml. and therapy with prednisolone was recommenced. Subsequent haematological findings are shown in Fig. 4. After 23 days the reticulocytes rose to 8.3%. The haemoglobin value improved shortly after this, and has been maintained since between 12 and 13 g./100 ml. At the time of writing the patient was being treated with a maintenance dose of 10 mg. of prednisolone daily.

Since the beginning of treatment in December, 1956, total serum proteins have been estimated and serum paper electrophoresis performed at frequent intervals. By May, 1957, the dense band of abnormal protein in the γ-globulin position on the electrophoretic strip was distinctly less, and by June, 1957—that is, six months after beginning prednisolone therapy—it had disappeared (Fig. 1, B). Paper electrophoresis at this time showed a slight increase in the α_1- and α_2-globulins. Macroglobulins could still be detected on ultracentrifuge analysis, however, but in less amount than previously (12% of total protein; total protein, 6.4 g./100 ml.) (Fig. 2, B). The Sia test was still positive.

Fluctuations in the amounts of serum protein migrating as γ-globulin were followed by eluting the dye from the relevant area of the electrophoretic strips with 2.5 M sodium hydroxide and measuring the amount of dye photometrically. The results, expressed as a percentage of the initial value, are shown in Fig. 3. Between October, 1956, and June, 1957, there was a steady decrease in protein concentration in the γ-globulin position to 21% of the initial value.

On cessation of prednisolone therapy, concurrent with the onset of orbital cellulitis, the γ-globulin fraction rose sharply, then fell again and has since maintained a fairly steady value. The abnormal band reappeared in the γ-globulin position on the electrophoretic strip one month after prednisolone therapy was stopped and has persisted since then. The second course of treatment had produced no obvious change in the electrophoretic pattern at the time of writing.

Discussion

The mechanism of the anaemia is obscure and its duration uncertain. In the absence of other demonstrable causes of anaemia, it seems reasonable to suggest that the low haemoglobin values recorded in 1943 had the same aetiology as the present anaemia. Although the bone marrow contained an excess of lymphocytes, it is unlikely that the anaemia was due to marrow infiltration, as erythropoiesis appeared adequate. The anaemia was not haemolytic in nature. The degree of marrow erythropoiesis was normal, reticulocyte counts have not been increased apart from therapy, and the patient's red cells gave a negative Coombs reaction. Furthermore, the patient's red cells survived normally in her own circulation. On the other hand, an autoimmune mechanism is suggested by the response to prednisolone therapy. The delayed reticulocyte response noted during the second course of prednisolone therapy suggests that the drug corrected the anaemia through some intermediary mechanism, as specific haemopoietic factors usually show demonstrable effects in a shorter time than this.

A patient of Wilde and Hitzelberger (1954) suffered from autoimmune haemolytic anaemia associated with macroglobulinaemia. As might be expected, this responded to cortisone therapy. Other reports in the literature of cortisone therapy in patients with macroglobulinaemia refer to cases in which the clinical findings resembled lymphosarcoma (Di Guglielmo and Antoninix, 1955; Mackay, 1956; Jim and Steinkamp, 1956). In these patients the therapy had little effect.

The duration of macroglobulinaemia in our patients is uncertain. Almost certainly macroglobulins were responsible for the abnormal serum protein results first noted in 1955.

No cause for macroglobulinaemia has been demonstrated. Although the patient has a marrow lymphocytosis and one enlarged axillary lymph node, the liver and spleen are not enlarged, and the findings differ from many of the cases of macroglobulinaemia so far described—for example, Mackay *et al.* (1956), who suffered from a disease resembling lymphosarcoma. However, it is possible that she may eventually develop this syndrome. It is purely speculative to suggest that lymphocytes might be the source of the abnormal protein.

The alteration in the serum electrophoretic pattern after prolonged prednisolone therapy is of great interest. It should be stressed that the values for γ-globulin shown in Fig. 3 represent both "normal" γ-globulin and macroglobulin. Therefore there are difficulties in interpreting fluctuations in their values, as a diminution in either would result in a decrease of total γ-globulin. However, the decrease in values between October, 1956, and June, 1957, was so marked that it is reasonable to conclude that it represents diminution in macroglobulin concentration. This is also confirmed by ultracentrifuge data, which estimated the macroglobulin to have diminished during this time. Furthermore, the discrete component on the paper electrophoretic strip which was presumably due to macroglobulin (Fig. 1, A) could not be seen on the later strip (Fig. 1, B).

The patient probably shows an increased susceptibility to infection, having suffered from recurrent furunculosis, orbital cellulitis, and a respiratory infection over a period of 18 months. It is possible that she suffers from hypogammaglobulinaemia, demonstration of which would be made difficult by the appearance of macroglobulin in the γ-globulin region on serum paper electrophoresis. Evidence to suggest hypogammaglobulinaemia is furnished by the electrophoretic strip performed in June, 1957 (Fig. 1, B). This shows an intensity of staining in the γ-globulin region within normal limits. As the serum still contained a considerable amount of macroglobulin demonstrable by ultracentrifuge analysis, the normal γ-globulin component was probably reduced.

Summary

The clinical findings are described in the case of an elderly woman who suffered from an unusual form of anaemia and macroglobulinaemia for at least three years. Treatment with prednisolone corrected the anaemia, and this was associated with a diminution in the amount of abnormal protein in the blood.

Dr. John O'Dea, Commonwealth Serum Laboratories, Victoria, carried out the ultracentrifuge analyses. One of us (J. A. O.) has received a grant from the National Health and Medical Research Council.

REFERENCES

Di Guglielmo, R., and Antoninix, F. M. (1955). *Sang*, **26**, 249.
Ferriman, D. G., and Anderson, A. B. (1956). *Brit. med. J.*, **2**, 402.
Flynn, F. V., and de Mayo, P. (1951). *Lancet*, **2**, 235.
Jim, R. T. S., and Steinkamp, R. C. (1956). *J. Lab. clin. Med.*, **47**, 540.
Kappeler, R., Krebs, A., and Riva, G. (1957). *Schweiz. med. Wschr.*, **87**, 1246.
Long, L. A., Riopelle, J. L., Francoeur, M., Pare, A., Poirier, P., Georgesco, M., and Colpron, G. (1955). *Canad. med. Ass. J.*, **73**, 726.
Mackay, I. R. (1956). *Aust. Ann. Med.*, 5, 244.
—— Eriksen, N., Motulsky, A. G., and Volwiler, W. (1956). *Amer. J. Med.*, **20**, 564.
—— Taft, L. I., and Woods, E. F. (1957). *Brit. med. J.*, **1**, 561.
Martin, N. H., and Close, H. G. (1957). *Lancet*, **2**, 8.
Silberman, H. J. (1957). Ibid., **2**, 26.
Waldenström, J. (1952). In *Advances in Internal Medicine*, edited by W. Dock and I. Snapper, **5**, 398. Year Book Publishers.
Wanner, J., and Siebenmann, R. (1957). *Schweiz. med. Wschr.*, **87**, 1243.
Weichselbaum, T. E. (1946). *Amer. J. clin. Path.*, **16**, *Tech. Bull.*, **7**, 40.
Wilde, H., and Hitzelberger, A. L. (1954). *Blood*, **9**, 875.

DEATH CERTIFICATION OF CHILDREN

BY

JOHN L. EMERY, M.D., D.C.H.

AND

K. A. IRVINE, M.B., B.Ch., D.C.H.

Department of Pathology, the Children's Hospital, Sheffield

The certification of the cause of death is, to the lay person and the administrator, a simple statement of fact. To the pathologist, on the other hand, the "cause of death" is the summation of a number of factors each of which in isolation may be of little importance. At best one knows in part what a person dies with, but not necessarily what he dies from.

The practice of clinical medicine necessitates a concentration on the treatable aspects of disease and a simplification of pathology requisite for a practical approach to the patient. The present form of death certification is designed by necessity for use by clinicians. It has a twofold approach: first, steps in the progress of a major disease, and, secondly, associated disease. Its form is probably as good as can be devised.

The present small survey of 150 deaths was made to assess the efficiency of death certification as carried out in a children's teaching hospital. The resulting figures are statistically significant and show a degree of inaccuracy not generally appreciated.

Material and Method of Survey

Permission is requested to carry out a post-mortem examination on every child dying in the Sheffield Children's Hospital and is granted in over 90% of cases. At the same time the house officers are asked to indicate on the death certificate that additional information may be available later as a result of the necropsy. The cause of death is revised by the pathologist when the final necropsy diagnosis is made.

Other than this being a consecutive series, no particular selection of the 150 cases was made. The children's ages at death varied from several hours to 12½ years: 78 (52%) died at or before 3 months; 12 (8%) between 4 and 6 months; 24 (16%) between 7 months and 1 year; 23 (16%) between 2 and 3 years; and 13 (8%) between 4 and 12½ years. Thus 137 (92%) of the deaths occurred at or before 3 years of age. The cause of death entered on the death certificate was compared with the final pathological diagnosis made after consideration of the clinical findings, naked-eye pathology, and histology of the case. A record was also made of the duration the child had been in hospital, or, in cases where there had been more than one admission for the same condition, the duration under medical supervision was estimated. Each case was then placed in one of five groups, according to the following criteria.

Group 1.—Cause of death recorded on the death certificate accurate and complete as compared with the pathological findings.

Group 2.—Cause of death accurate in major respects but incomplete in minor points, which did not alter the final diagnosis.

Group 3.—Cause of death inaccurate as compared with the major pathological findings, but minor points accurate.

Group 4.—Pathological findings necessitated a complete revision of the cause of death.

Group 5.—Cause of death as recorded not substantiated by post-mortem examination and no adequate pathological cause of death found.