in exciting uterine contractions are not equiactive in their effects on blood pressure. Blood pressure is affected only by extremely large doses of oxytocin, 2 units intravenously usually being required to produce a pressure fall lasting about a minute and occurring two to three minutes from the time of injection. Half a unit of valyl-oxytocin does not produce this effect, but 2 units will do so. In this respect the *B.P.* assay of the two substances on chicken blood pressure or isolated rat uterus is parallel to the comparison in the human subject so far as the limited tests we have made are able to show.

Summary

Following their synthesis of oxytocin, Boissonnas *et al.* (1956) prepared analogues of oxytocin having actions which were similar qualitatively but which differed quantitatively.

A comparison has been made of the actions of one of these analogues, valyl-oxytocin, with those of synthetic oxytocin in animals and in man.

The results are discussed, with special reference to the present methods of assay.

The oxytocin and valyl-oxytocin used in this work were generously supplied by Messrs. Sandoz, Basle, Switzerland. Dr. H. Holgate, of Sandoz, London, has kindly supplied us with the published information on the analogues of oxytocin. The preparations of oxytocin and valyl-oxytocin have been standardized by the Sandoz Laboratories, Basle, against the International Standard Pituitary Powder. Our thanks are due to the editor and publishers of the *British Journal of Pharmacology and Chemotherapy* for permission to reproduce the Table, and to the editor of the *Lancet* and of the *Journal of Obstetrics and Gynaecology of the British Empire* for permission to reproduce Figs. 4a and 4d.

In the post-partum assays I was grateful for the assistance of Miss M. N. Bainbridge and also of Miss J. Farrow, who assisted with the intravenous infusion assays. The staff of the Obstetric Unit, and in particular the Director, Professor W. C. W. Nixon, encouraged and assisted the work in many respects. Dr. H. O. Schild, reader in pharmacology, University College, London, has given generous assistance in planning the work.

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"Recent work on the hormonal prevention of conception in man by Pincus and his colleagues has depended on the suppression of ovulation and has been made practicable by the preparation of orally-active substances with progesterone-like activity. One of these seems to be promising in Pincus's clinical experiments. Presumably it overwhelms the follicular phase of the cycle partly by local inhibition and partly by interference with pituitary activity. It seems, however, that treatment is necessary over some 20 days in each cycle, probably in order to ensure that ovulation is prevented and not merely postponed, and for this and other reasons this work cannot yet be said to have put oral contraception on a practical basis. But it is most promising and exciting." This is from an article by Dr. A. S. PARKES, F.R.S., "Towards Oral Contraception," which describes the origin and work of the Oliver Bird Trust and the Council for the Investigation of Fertility Control (*Family Planning*, 1958, 7, 9). *Family Planning* is published quarterly and is obtainable by non-members from the Family Planning Association, 64, Sloane Street, London, S.W.1, price 2s. 6d. (post free) annually.

PROLONGED REMISSION IN CHRONIC LYMPHATIC LEUKAEMIA

BY

L. H. WALTER, M.B., D.M.R.E.

L. SZUR, M.B., F.F.R., D.M.R.

Department of Radiotherapy, Hammersmith Hospital, London

AND

S. M. LEWIS, M.B., B.Sc., D.C.P.

Department of Pathology (Haematology), Postgraduate Medical School of London

The duration of life of patients with chronic lymphatic leukaemia has been variously quoted, but Tivey (1954), in an analysis of 46 series of cases reported in the literature between 1925 and 1951, estimated the median survival to be about 1.6 years after commencement of therapy and 2.6 years after the onset of the first clinical symptoms. He found, however, that the survival curves were "badly skewed," and it is generally agreed that individual patients can live for a very much longer time. Amongst the longest survivors with chronic lymphatic leukaemia recorded is one of 29 years (Marlow and Bartlett, 1953) and one of 25 years (McGavran, 1938).

A number of cures of leukaemia have been reported in the literature. According to Forkner (1938) and Wintrobe (1956), in only a few can the possibility of a cure be considered. Schott (1955) describes the case of a patient with chronic lymphatic leukaemia who was symptom-free and had a normal peripheral blood count 10 years after radiation treatment.

The following case is presented as a further example of long-term remission in a patient suffering from chronic lymphatic leukaemia who is clinically well and has a normal peripheral blood count eight years after the last treatment. Marrow punctures have been carried out at various intervals during the time of observation, and are discussed below. An interesting additional feature is the development in this patient of carcinoma of the cervix, treated apparently successfully three years ago.

Case History

A married woman, then aged 49, was admitted to another hospital on February 23, 1946, with 2 weeks' history of weakness and giddiness, and 1 week's continuous vaginal bleeding following six months' amenorrhoea. There was no previous significant illness. She had had nine normal confinements. On examination at that time pallor was marked, there was a moderate generalized lymphadenopathy, and the liver and spleen were palpable. Pelvic examination did not reveal any local cause for her vaginal bleeding.

Investigations.—R.B.C., 770,000/c.mm.; haemoglobin, 2.5 g./100 ml.; W.B.C., 27,000/c.mm. (polymorphs 4%, eosinophils 1%, lymphocytes 93%, monocytes 2%). There were no nucleated red cells. Platelets, 31,000/c.mm. Bleeding-time, 10 minutes. Clotting-time, 8 minutes.

Puncture of the sternal marrow confirmed the diagnosis of lymphatic leukaemia. She was given repeated transfusions, and from March 4 to 28 was treated with urethane. This was followed by a profound fall in the W.B.C. and a tendency to spontaneous bleeding from the gums, with infection of the mouth and throat. Further transfusions, penicillin, "anahaemin" injections, and ferrous sulphate were given, with slow recovery (Fig. 1). She was discharged from hospital on August 3. Her attendance thereafter for follow-up was erratic.

On May 7, 1948, she was readmitted with a history of hot sweats, headaches, and cough. The blood count on admission was R.B.C. 1,600,000/c.mm.; haemoglobin, 5.3 g./100 ml.; W.B.C., 5,200/c.mm. (polymorphs 18%, lymphocytes 82%). Generalized enlargement of lymph nodes was again present. The liver and spleen were enlarged three fingerbreadths. Following transfusion she was transferred to Hammersmith Hospital on June 24. On admission she was very pale, and had spontaneous bruises and petechiae on both legs. Numerous large lymph nodes were found in the neck, axillae, and groins, and the liver and spleen were enlarged 6 cm. beneath the costal margin. An x-ray examination of the chest was normal. On June 25

a blood count showed: haemoglobin, 4.4 g./100 ml.; W.B.C., 5,500/c.mm. with 92% lymphocytes. A further sternal marrow aspiration showed the presence of numerous lymphocytes with very few cells of the myeloid and erythroid series. Approximately 90% of the lymphocytes were mature, intermediate in size, and of uniform pattern. There was a small percentage of prolymphocytes, and only 3% blasts. In the light of these findings aleukaemic lymphatic leukaemia was diagnosed. X-ray treatment through an anterior trunk bath was given from July 2 to 14, when it was discontinued owing to a severe fall in the leucocyte count. This finally reached 330/c.mm. In spite of the blood picture the patient's general condition remained fair.

After further transfusion she was discharged on August 16 (Fig. 2A).

In January, 1949, as her lymph nodes again enlarged and she complained of lassitude, a further course of irradiation was given. Again leucopenia developed, the leucocytes falling to 800 and lymphocytes to 120/c.mm., but the general condition remained good. A transfusion was given, and she was discharged on March 18, 1949 (Fig. 2B).

By May 25 the haemoglobin had risen to 15 g./100 ml., W.B.C. 3,600/c.mm. (polymorphs 50%, lymphocytes 40%, monocytes 9%). Since that time there has been no clinical sign of relapse of the leukaemia.

In 1954 the patient developed vaginal bleeding and was readmitted on May 9. Her general condition was good. No enlarged glands were found and the liver and spleen were not palpable. Vaginal examination revealed a papilliferous tumour of the cervix spreading to the vaginal vault. The clinical diagnosis was carcinoma of cervix stage II. The blood count on admission showed: haemoglobin, 12.3 g./100 ml.; W.B.C., 6,000/c.mm. (polymorphs 80%, lymphocytes 14%, eosinophils 3%, mononuclears 3%). A sternal marrow puncture showed little evidence of the earlier lymphocyte infiltration, for the lymphocytes, mature and small, constituted 25% of the nucleated cells. The myeloid: erythroid ratio was 4:1, and both these series showed normal maturation. The picture was considered to be consistent with chronic lymphatic leukaemia in a state of remission.

Treatment was given by three intrauterine applications of radium. X-ray therapy to the parametria was begun, but was abandoned as the leucocytes fell to 2,000/c.mm.

FIG. 1.—Effect of urethane on peripheral blood counts.

FIG. 2.—Effect of whole-trunk irradiation on peripheral blood count. (A) 1948; (B) 1949.

She was discharged on June 19. She has remained free from clinical evidence of recurrence of either disease. Blood counts have been performed regularly, and are shown in Fig. 3. These show a normal haemoglobin, with a slight leucopenia but a normal differential count. A further bone-marrow aspiration on November 23, 1956, showed a deterioration when compared with the previous marrow of 1954. Approximately 70% of the nucleated cells were lymphocytes. These were mature, but large in size, and there was an increase in the numbers of earlier cells—12% prolymphocytes and 8% blasts. The blasts showed coarse nuclear chromatin, and basophilic agranular cytoplasm; some of these cells resembled reticulum cells, and the earlier uniformity has been lost. The peripheral blood of this same period, and subsequently, showed a normal cell distribution, with normal morphology, the lymphocytes being small mature cells.

Discussion

This case presents a number of interesting features. There can be no reasonable doubt about the correctness of the diagnosis. Clinically and haematologically the patient presented features characteristic of chronic lymphatic leukaemia. As recently as November, 1956, a marrow puncture showed findings consistent with those found in this disease, but, since the patient's second course of radiotherapy by an anterior trunk bath in early 1949, her peripheral blood picture has shown a normal haemoglobin and differential white-cell count. With regard to the latter finding, this case differs from the two longest survivors described by McGavran (1938) and Marlow and Bartlett (1953), as mentioned above, in both of whom the differential count remained abnormal throughout life. It is, however, similar to the case described by Schott (1955). Our patient is now well, with a normal peripheral count, and has had no clinical signs of the disease for more than eight years. She might therefore have been regarded as having been clinically cured.

It may be argued that this freedom from disease has been prolonged by the irradiation treatment to the pelvis given for carcinoma of the cervix in 1952. There is, however, nothing to indicate that this is in fact so. Just before this

treatment the patient's total leucocyte count was 6,000/c.mm. with a normal differential count, and, following a transitory fall towards the end of the x-ray treatment, the leucocyte total returned to the pretreatment level. There were no symptoms or signs indicating any evidence of recrudescence or activity of the disease.

It is interesting to speculate whether the severe falls in the white-cell count which occurred during both treatments (330/c.mm. in 1948 and 800/c.mm. in 1949) were not an important factor in producing the prolonged remission. It is known from the treatment of acute leukaemia by chemotherapy—for example, 6-mercaptopurine and the folic acid antagonists—that satisfactory remissions are occasionally achieved when the marrow is almost completely destroyed by the drug and the peripheral white-cell count falls to a marked and often alarming extent. By analogy, therefore, it is possible that the x-ray treatment in this patient caused considerable aplasia of marrow, and that the regeneration, when it took place, was more pronounced in the erythropoietic and myeloid elements.

When considering the prognosis in chronic lymphatic leukaemia certain findings are thought to be of grave significance. Among these are marked weight loss, anaemia, marked splenomegaly, and thrombocytopenia. This patient had at least two of these—namely, a severe anaemia on presentation at the hospital and during the following three years, and a pronounced thrombocytopenia (31,000/c.mm. in February, 1946). The progress of the disease, however, in this case shows once again how difficult it is to give a definite prognosis in an individual case of chronic leukaemia.

The association of chronic lymphatic leukaemia with other forms of malignant disease has been noted by many authors—for example, Bichel (1949) and Beresford (1952). There appears, however, to be no clear causal relationship. There is also no evidence to suggest that there is any definite mutual influence on the progress of either condition, though some have suggested that there may be an inhibitory effect of the malignant disease on the leukaemia. Our patient does not throw any further light on this latter problem, and the occurrence of carcinoma of the cervix appeared to be unrelated to the presence of the leukaemia.

The most interesting feature in this case is undoubtedly the lack of correlation between the bone-marrow aspiration and the peripheral blood count findings. Although the patient appears to have been "cured" for eight years, the bone-marrow findings show a picture of chronic lymphatic leukaemia. It is obvious that the disease has been arrested and not eradicated. In the absence of normal marrow reports it is probable that a similar state of affairs may have existed in most of the reported cases of cure. It also confirms the known fact that lymphatic leukaemia can at times be a very "benign" disease.

Summary

The history and clinical findings of a patient with chronic lymphatic leukaemia first diagnosed in 1946 are described. In 1954 she developed carcinoma of the cervix, and the asso-

FIG. 3.—Peripheral blood counts from time of diagnosis to present time.

ciation of leukaemia with other forms of malignant disease is briefly discussed. She has remained free of symptoms and signs of her leukaemia for eight and a half years. In spite of a normal peripheral blood count, marrow aspiration reveals findings consistent with chronic lymphatic leukaemia. This lack of correlation as well as certain features affecting the prognosis in this disease is discussed.

We thank Professor J. V. Dacie for advice; and Dr. C. D. Coyle, medical superintendent, Whittington Hospital, for his help in making available to us the early case notes on this patient.

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CURRENT SMOKING HABITS IN 1957 BASED ON MASS RADIOGRAPHY SURVEYS IN THE MIDLANDS

BY

K. W. CROSS, Ph.D.

Senior Statistical Officer, Birmingham Regional Hospital
Board

L. A. McDOWELL, M.D., D.P.H.

Adviser in Mass Radiography, Birmingham Regional
Hospital Board

AND

E. POSNER, M.D.

Medical Director, Stoke-on-Trent Mass Radiography Unit

With the co-operation of G. P. Bardsley, M.B., and
R. J. Posner, M.R.C.S.

In conjunction with our colleagues of the mass radiography service in the Birmingham region, we are engaged in carrying out an investigation of certain aspects of cases of bronchial carcinoma discovered by mass radiography. Naturally we must examine the smoking habits of the patients concerned in relation to those of a control group. In considering this aspect of the inquiry we encountered the absence of reliable data relating to the smoking habits of the population in this region. The only exceptions are the data given by Lowe (1956) for tuberculous patients and for a control group chosen from in-patients and out-patients of "acute" hospitals in Birmingham. The "catchment area" of these hospitals and clinics is, however, considerably smaller than the area being examined by our units, and we therefore decided to use some of our routine mass radiography surveys to obtain data about current and past smoking habits of the population in the Midlands. In this way we hoped to obtain standards against which to compare our findings in the investigation of bronchial carcinoma.

The main purpose of this paper is a comparison of our groups *inter se*, and for this an analysis of "current smoking habits" in contradistinction to "total smoking habits" seemed to be sufficient. An analysis of "total smoking habits" has been reserved for a future study,

in which we shall attempt to compare our findings with the data by other authors, who mostly use this definition.

We consider it important to stress that the investigation took place during the first five months of 1957, and that the collection of data was completed before the issue of the Medical Research Council's report (1957) and before the subsequent statement about smoking risks by the Parliamentary Secretary to the Minister of Health on June 27, 1957. Furthermore, during the period of collecting data there was no marked change in the price of cigarettes or tobacco. We hope to re-investigate the same groups in the future, with a view to possible changes in smoking habits brought about by the changing economic or psychological climate of the country.

Definition of Smoking Habits.—In this paper a "current smoker" is defined as a person *who at the time of the interview smoked as much as one cigarette a day or ½ oz. (14 g.) of pipe tobacco a week*. Mixed smokers have been classified according to prevalent habit. The very small number of cigar smokers has been disregarded.

Methods of Investigation

It was decided to carry out the investigation during mass radiography surveys held in two industrial areas (Birmingham and Stoke-on-Trent), in a small town in Herefordshire (Leominster), in Shropshire, and in the urban district of Stourbridge (Worcestershire). These areas are typical of the places where mass radiography surveys are held in the Midlands. The surveys were not planned primarily with a view to obtaining a record of smoking habits, but were part of the normal mass radiography programme of each unit in accordance with the policy and procedure in this region. In fact, it was decided to record this information only shortly before the surveys began.

The groups examined were: (1) 7,680 employees of a large electrical engineering company in Birmingham; (2) 2,774 underground and surface workers in three North Staffordshire coal-mines; (3) 2,452 workers in ten pottery factories in Stoke-on-Trent, manufacturing general earthenware, glazed tiles, and sanitary earthenware; (4) 6,571 persons attending open public sessions in Herefordshire, in Stourbridge (Worcestershire), and in Shropshire. This last group included housewives, office workers, shop people, young persons, and other volunteers from the general public. The large majority of these persons were not employed in industry.

The proportion of employees examined was about usual for mass radiography industrial surveys in this region: 70% of the employees of the Birmingham factory responded, 69% of the pottery workers, and 73% of the colliery workers in the Stoke area. In the Herefordshire survey 63% of the available population attended (Posner, 1958).

The clerks of the units carrying out the surveys were thoroughly briefed to ask a standard set of questions relating to current and past smoking habits, and to enter the answer by simple coding on the registration cards. The volunteers co-operated fully in giving the requisite facts, and the number of persons who refused to give information or whose data were so vague as to be useless was extremely small: in the industrial surveys, for instance, only 48 out of 12,906 (0.4%).

Results

The well-known fact that proportionately more men smoke than do women is supported by the figures given in Table I. Proportions for men were roughly twice the corresponding values for women. The maximum proportion of smokers among men was that for miners at Stoke, and the result for the pottery workers at Stoke was only slightly less than this maximum. Almost 70% of men in the Shropshire and