foetus to cause one case of leukaemia in 40,000 births, they do show that the tendency is not very much greater. The incidence of 8 leukaemic deaths per 16,948 live births, 1 in 2,118, is slightly higher for Queen Charlotte's Hospital than for the country as a whole; but this is due to the much higher incidence of leukaemic deaths in the non-irradiated (control) group, 1 in 1,808, compared with the irradiated group, 1 in 4,291, and cannot therefore have been caused by irradiation.

I thank Dr. Alice Stewart for providing the lists of deaths from leukaemia, Dr. Rohan Williams for the figures on irradiated cases, and the Board of Governors of Queen Charlotte's and Chelsea Hospitals for secretarial aid in searching.

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PHENYLBUTAZONE AND LEUKAEMIA

A POSSIBLE ASSOCIATION

BY

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This paper reports six instances of leukaemia developing in patients who had received phenylbutazone. In the first patient there appeared to be a sequential progression from the development of an early toxic reaction to the patient's death from myeloid leukaemia. In the other five patients a history of administration of the drug was obtained in retrospect.

Case 1

This patient, a man aged 69, had complained of low back pain since 1918. Radiological examination demonstrated marked degenerative spondylitic changes in his lumbar vertebral column. He had not received any *x*-ray therapy for this.

In February, 1957, he was treated with phenylbutazone. The initial dose was 600 mg. a day, after a few days reduced to 400 mg. a day. Shortly after the treatment was begun he developed a sore throat, and two weeks later a swelling and a rash upon his legs. He was admitted to hospital after three weeks' treatment. Examination showed him to be apprehensive and in poor nutritional state, with a dry, red, glazed tongue. He had a scattered toxic erythematous rash upon his legs and feet, enlarged lymph nodes in his neck and axillae, and a palpable spleen. Blood examination showed a haemoglobin of 13.4 g./100 ml. and total W.B.C. 17,000 c.mm. (polymorphs 75%, lymphocytes 11%, monocytes 9%, eosinophils 4%, and basophils 1%). The red cells showed anisocytosis and poikilocytosis. Platelets were abundant and the lymphocytes and monocytes slightly abnormal, with pale vacuolated cytoplasm. Serum albumin was 3.3 g. and globulin 3.6 g./100 ml.

A left axillary gland was removed, and the report upon the section was: "The architecture of the gland is largely replaced by a medullary disturbance of the reticulum cells together with alteration of age of the lymphoid elements. The picture is consistent with an early reticulosis." The patient was given supportive therapy, including a high-protein diet and parenteral vitamins, and steadily improved. Three months later he was much better, and, although examination still revealed enlarged glands and a palpable spleen, these features were less prominent. His weight had increased. His haemoglobin had risen, and the total W.B.C. had fallen, but his platelet count had increased to 507,000. There were still 400 eosinophils present.

After a further five weeks he was again admitted to hospital. On this occasion he was very sick, with a generalized bullous rash, conjunctivitis, urethritis, and recurrent glossitis with mouth ulceration. He was thought to be suffering from erythema multiforme and he was again treated symptomatically. His Hb had fallen to 11.25 g./100 ml. His reticulocytes were 3.3% and his platelets had risen to 980,000. A blood film showed a neutrophilia with a shift to the left and toxic granulation. The platelets were predominately large forms. A marrow biopsy showed a normal marrow. He rapidly improved and was discharged approximately four weeks later when his Hb had risen to 12.4 g. However, he had persistent neutrophilia and eosinophilia, and his platelets remained abnormal, being plentiful and showing clumping.

Three months later he had again improved, his spleen was palpable on inspiration and his glands smaller but very firm. His haemoglobin had risen to 14 g., W.B.C. 15,000/c.mm. with 11% eosinophils, and platelets 780,000. The blood film remained abnormal. He was again admitted in January, 1958 (one year after his original treatment), when the findings were much the same, his blood showing neutrophilia and eosinophilia. The zinc turbidity had risen a little higher and a further gland was removed. The biopsy report stated: "Macroscopy: a small hard gland throughout which there are irregular deposits of hard white tissue. Microscopy: areas of caseation accompanied by chronic inflammatory and giant-cell reaction. Probably tuberculous." On this occasion his liver was palpable with a firm edge. He was discharged shortly after this and felt much improved.

He was again reviewed 17 months after his original illness, when he appeared to be again improving. His appetite was good and his weight increasing. Examination revealed that his lymphadenopathy was less, although the glands palpated remained very hard. His liver had also receded and his spleen was not palpable. Examination of his blood gave the following results: Hb, 13.6 g./100 ml.; total W.B.C. 10,700 (polymorphs 71%, lymphocytes 25%, monocytes 1%, eosinophils 3%); platelets, 510,000; E.S.R., first hour 15, second hour 37. Both polymorphs and lymphocytes were atypical, with coarse granular nuclei, and about 30% of the polymorphs were younger forms. The blood film was consistent with early myeloid leukaemia. His serum albumin was 3.7 g. and serum globulin 3.2 g./100 ml., and zinc sulphate turbidity 10 units.

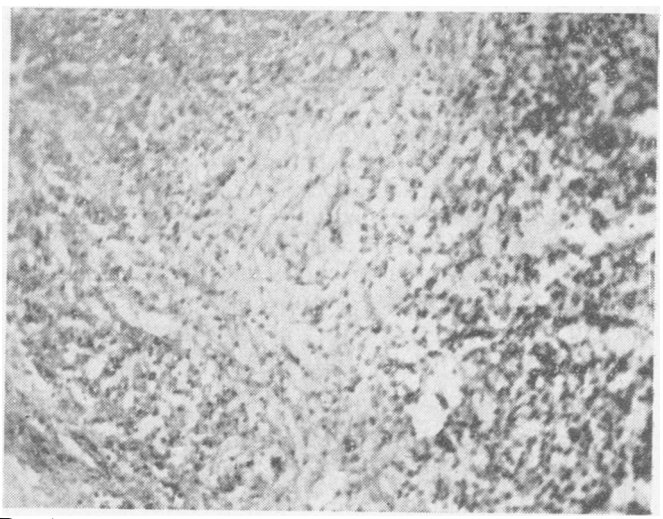

FIG. 1.—Case 1. Histological appearance of the involved glands.

He was seen three months later, in October, 1958. A marked deterioration had taken place. He complained of recurrent swelling of his glands, weakness, and loss of weight. Examination revealed that he had a generalized lymphadenopathy. The glands were more numerous and

larger than on any previous occasion. His liver edge did not appear to have changed since examination in July, but his spleen had greatly enlarged.

Examination of his blood revealed Hb 10.9 g. His W.B.C. had risen to 88,300, with the following distribution : mature polymorphs 39%, younger forms 52%, mature lymphocytes 5%, younger lymphocytes 2%, eosinophils 1%, and atypical plasma cells 1%. The appearance of the film was that of chronic myeloid leukaemia. An *x*-ray film of the chest was clear on admission, and he was given 50 mg. of busulphan (" myleran ") ; however, six days later he developed staphylococcal bronchopneumonia, from which he died. Fig. 1 shows the histological appearance of the involved glands.

Post-mortem examination revealed staphylococcal bronchopneumonia. There was generalized glandular enlargement, the glands having a yellow appearance, with caseous foci. The bone-marrow, spleen, kidneys, and liver were extensively infiltrated by leukaemic cells. Tubercle bacilli were cultured from the enlarged glands. There was no evidence of pulmonary tuberculosis on either gross or microscopical examination.

Case 2

This patient, a man aged 67, had suffered from pulmonary tuberculosis for many years, but his chest had remained stable since a lobectomy four years prior to this admission. During this period he had not been taking any chemotherapy for tuberculosis. He had suffered from lumbar spondylitis for many years and had taken phenylbutazone intermittently over the past four years. Since his lobectomy his health had been reasonably good, and he was able to carry out a full day's work on his farm. His recent illness had started four months before admission, when he complained of increasing tiredness and dyspnoea.

Examination revealed a pale elderly man with a palpable spleen and a tender sternum. His haemoglobin was 4.4 g./100 mg., and total W.B.C. 44,400 (neutrophils 4%, lymphocytes 90%, eosinophils 1%, and smear cells 5%). The platelet count was 50,000 and large forms were present. The reticulocytes were 0.54%. The lymphocytes were predominantly younger forms with lobulated indented nuclei and nucleoli in many cells. Aspiration biopsy of his bone-marrow revealed a uniform marrow picture dominated by atypical immature lymphocytes. Myelopoiesis was scanty and no red-cell precursors were seen.

The patient was treated with transfusion, thiotepa, A.C.T.H., and prednisolone. There appeared to be a temporary improvement with thiotepa, but frank haemolysis developed and he died suddenly approximately 10 weeks after admission.

Post-mortem examination revealed the cause of death to be pulmonary oedema. His bone-marrow was pale and fatty, with little or no erythropoietic tissue. His spleen was enlarged, pale, and firm, and there was slight enlargement of lymph nodes. Microscopy revealed widespread infiltration of marrow, kidneys, liver, and spleen with lymphoblasts. Fig. 2 shows the histological appearance of the bone-marrow.

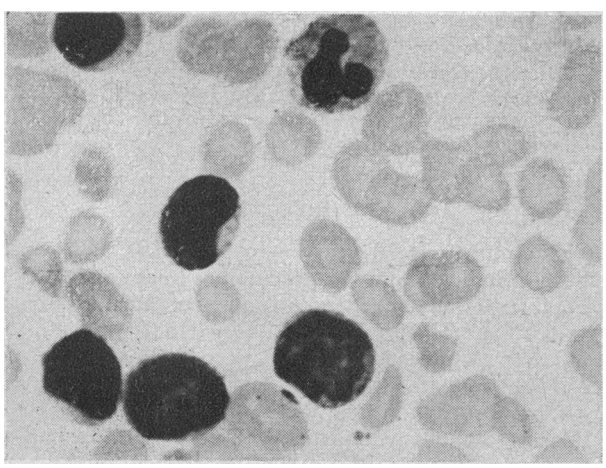

FIG. 2.—Case 2. Histological appearance of bone-marrow.

Case 3

This patient, a man aged 70, had received multiple gunshot wounds in the 1914–18 war. Since his injury he had suffered from left-sided sciatica, with wasting of his left leg. Over the last five years his sciatic pain and backache had become more severe. He stated that he had been treated with phenylbutazone tablets approximately five months before admission to hospital. In the initial period he took one to three 200-mg. tablets a day. Three months prior to admission he complained of epigastric discomfort, pains in his hips and shoulders, and anorexia. Acquaintances commented upon his pale appearance. The dosage of phenylbutazone was increased when he complained of recurrent pains, which appeared to be neuritic in type.

Examination revealed a sick-looking, pale, well-covered elderly man. He had palpable glands in his neck and axillae. His liver was enlarged and tender. His spleen was not palpable. There was evidence of degenerative cardiovascular disease.

Investigations.—Blood examination revealed Hb 6.2 g.; total W.B.C., 3,800 (polynuclears 1,520, band forms and metamyelocytes 380, lymphocytes 1,444, monocytes 380, eosinophils 38, basophils 38). Examination of the blood smear revealed 19 nucleated red cells per 100 white cells, some spherocytes, immature neutrophils, and lymphocytes. Platelets were scanty. His serum albumin was low and his gamma-globulin fraction as measured by zinc turbidity was very low. This was later confirmed by ultracentrifugation. Aspiration of bone-marrow was difficult, as there was virtually no haemopoietic tissue. Large masses of malignant cells were present, and the provisional diagnosis was malignant anaplastic tumour of unknown type. The largest axillary gland was removed and on section showed disorganization of the normal gland structure by a mass of cells. The appearance was thought to be consistent with reticulosarcoma. Kidney biopsy showed this organ to be heavily infiltrated with similar cells. A repeat blood smear revealed the presence of large lymphocyte-like cells with prominent nuclei and atypical cytoplasm.

He was thought to be suffering from leukaemia, probably subacute lymphatic in type, with marrow hypoplasia and haemolytic anaemia. He was treated with blood transfusion and " nitromin " (Yoshimoto Pharmaceutical Industries, Osaka, Japan). He showed temporary improvement and his total W.B.C. and neutrophils increased. However, his rate of red-cell destruction remained high, and a peripheral blood examination revealed an increasing content of large immature cells now considered to be either young lymphocytes or monocytes. The patient insisted upon returning to his home in the country, and failed to report for review. I later learned that he had died at home from anaemia approximately three weeks after discharge. During the last few weeks of his life he had suffered from recurrent acute bronchitis and acute otitis media.

Case 4

This patient, a man aged 80, had calcified lesions in both lungs, thought to be healed pulmonary tuberculosis. He had suffered from osteoarthritis and spondylitis for many years. In 1957 he was treated with phenylbutazone, and it was later stated that he did not tolerate the drug well. No further details are available. In December, 1958, he was noted to have an enlarged spleen at a routine examination. Examination of his blood revealed a haemoglobin of 9 g./100 ml., total W.B.C. 112,000 (polynuclears 69,440, myelocytes 29,680, monomyelocytes 1,120, myeloblasts 560, lymphocytes 3,360, monocytes 3,360, eosinophils 1,120,

basophils 3,360. He received 50 mg. of busulphan, but died suddenly 14 days later.

Post-mortem examination demonstrated chronic bronchitic changes and acute pulmonary oedema of both lungs. The tracheo-bronchial lymph nodes were enlarged. The spleen was greatly enlarged. The bone-marrow was pale and grey in appearance. Microscopy revealed infiltration of his spleen, bone-marrow, and kidneys with primitive myeloid cells. The tracheo-bronchial nodes showed myeloid infiltration and a caseous reaction consistent with tuberculous adenitis (see Fig. 3).

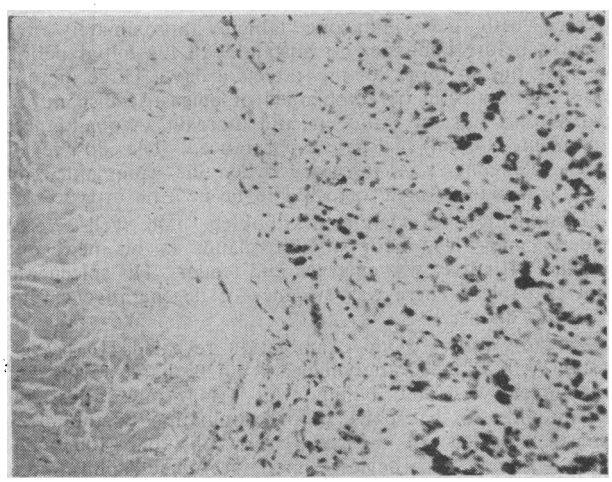

FIG. 3.—Case 4. Histological appearance of tracheo-bronchial nodes.

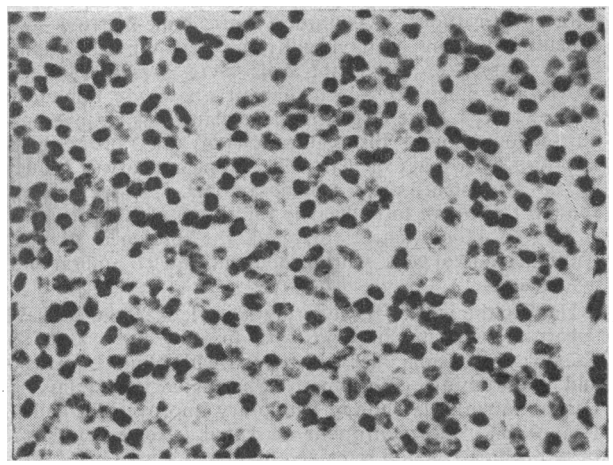

FIG. 4.—Case 5. Histological appearance of the gland.

Case 5

This patient, a man aged 66, had suffered gunshot wounds in the 1914–18 war. For nine years prior to admission he had complained of increasing pain and stiffness in his hips, and over the preceding four years he had received phenylbutazone. The initial dosage was 600 mg. a day, but this had been gradually decreased to 100 mg. a day. The patient stated that he had obtained considerable relief from the drug, and had not noticed any adverse effects. His most recent admission had been for recurrent diarrhoea, and at examination he was found to have an enlarged spleen and enlarged lymph nodes in his neck, axillae, and groins. A blood examination revealed a haemoglobin of 12.8 g./100 ml., total W.B.C. 3,450 (polynuclears 2,070, lymphocytes 1,035, monocytes 172, eosinophils 173, and platelets 190,000/c.mm. Examination of his bone-marrow did not reveal any abnormal features. An axillary lymph node was removed, microscopy revealing the tissue to be uniformly infiltrated with small round cells. These cells had invaded the gland capsule. The pattern was consistent with either lymphatic leukaemia or a lymphosarcoma. (Fig. 4 shows the histological appearance of the gland.) This patient has since been treated with small doses of tretamine with some improvement. A further gland biopsy six months after that illustrated showed an identical histological appearance.

Case 6

This patient, a man aged 63, had suffered from osteoarthritis of his left knee for many years and had received at least one course of phenylbutazone, consisting of 50 100-mg. tablets, approximately 18 months before his admission to hospital. He had also suffered from coronary heart disease with angina of effort for a number of years.

He was admitted to hospital complaining of a recent increase in the severity of his angina pectoris and severe gnawing epigastric pain. His haemoglobin was 7.9 g./100 ml., and total W.B.C. 4,200/c.mm. (neutrophils 16%, lymphocytes 76%, monocytes 7%, eosinophils 1%). The erythrocytes showed a wide variation in morphology; bizarre cells of all shapes and sizes were seen, with occasional normoblasts. The white cells appeared morphologically normal, but there were many giant forms in a normal total platelet count. This appearance was strongly suggestive of myelofibrosis. A barium-meal examination showed evidence of ulceration in the prepyloric region of the stomach, but this was not confirmed by gastroscopy. In spite of antibiotics, blood transfusion, and other supportive treatment the patient's condition continued to deteriorate and his total W.B.C. count fell further, with the gradual development of atypical myelocytes.

Examination of the bone-marrow showed a marked disturbance of both erythropoiesis and myelopoiesis. Erythropoiesis was very active, and many immature and abnormal forms, including megaloblasts, were present. Myelopoiesis was not very active, and consisted almost entirely of primitive cells. The bizarre bone-marrow picture was therefore suggestive of either an acute myeloproliferative disorder or erythroleukaemia. The patient's haemoglobin was maintained only by repeated blood transfusions. Two months after admission he developed bronchopneumonia, and was treated with antibiotics. Although his chest gradually cleared, his physical condition deteriorated rapidly. Three weeks later his peripheral blood showed a haemoglobin of 9.2 m./100 ml., and a sudden rise of white cells to 18,800 (90% neutrophils, the majority atypical younger forms). The morphology of the red blood cells had greatly improved, and there was only moderate anisocytosis and hypochromia. The blood picture at this stage was consistent with myeloid leukaemia. Six days later the patient died suddenly.

Post-mortem examination revealed evidence of a recent myocardial infarct, old coronary heart disease, and lobar pneumonia. The spleen was enlarged (260 g.) and congested. The liver and kidneys were enlarged, and the suprarenals showed wide and ill-defined cortices.

Microscopical examination showed widespread infiltration of lungs, heart, suprarenals, liver, kidneys, and spleen by immature white blood cells, with characteristics indistinguishable from myeloblasts.

Discussion

Over the past 30 years many chemical agents used both in industry and in medicine have been shown to be capable of inducing neoplasia in experimental animals and man (Haddow, 1958). In the present state of our knowledge, only circumstantial evidence can be presented to indicate whether an agent is a carcinogen or not. In these cases the association of the use of phenylbutazone and the development of leukaemia may be entirely due to chance, but the fact

that this group of cases has been observed in a relatively short period in a medical service whose clientele is largely limited to veterans of the 1914–18 and 1939–45 wars must be given some weight.

If in these patients phenylbutazone has acted as a carcinogen, then this is the result of a dose and a duration of treatment that have varied from 10 g. over a three-weeks period in Case 1 to some hundreds of grammes in four years in Case 2. In Case 1 there was a definite progression from the time of administration of the drug to the development of frank myeloid leukaemia 16 months later. It might be argued that this patient suffered from a leukaemoid reaction secondary to tuberculous lymphadenitis, but there are features which make the diagnosis of leukaemia inescapable—namely, the duration and progression of the illness, the presence of increased and abnormal platelets, and the post-mortem findings of diffuse myeloid infiltration of most body tissues. Case 6 shows similar features. The dosage of phenylbutazone was small, the period between the administration of the drug and the development of leukaemia was approximately 18 months, and the appearance of abnormal platelets antedated the development of leukaemia. If these findings were isolated no conclusion could be reached, but when the group is considered as a whole the argument develops greater weight.

Some features of this series deserve further consideration. Firstly, all patients are elderly and rather poorly nourished. (The population of this hospital is largely male.) Secondly, tuberculosis occurred in three of these patients. In this regard I have previously noted the occurrence of tuberculosis in patients suffering from other haematological reactions after the administration of phenylbutazone. There does not seem to be any consistent pattern in this association. Thus in Case 1 the tuberculous adenitis appears to have reached its maximum activity during the year after the initial reaction to the drug, and to be becoming quiescent when leukaemia supervened. Case 2 was a known sufferer from pulmonary tuberculosis, but there is no evidence that administration of the drug caused any alteration in his pulmonary disease. Case 4 had old pulmonary tuberculosis, and, at necropsy, foci strongly suggestive of active tuberculosis were found in the tracheo-bronchial lymph nodes.

There have been several cases in the literature in which caseous reaction has been reported to follow the administration of phenylbutazone (MacCarthy and Jackson, 1955). The histological appearance of the lesions described in these papers is strongly suggestive of tuberculosis, and technical difficulties may well explain failure to demonstrate the organisms. It may be of some significance that, recently, extracts of tubercle bacilli have been shown to have an adjuvant effect in the production of many reactions, many of these of the auto-immune type (*British Medical Journal*, 1959).

In Cases 3 and 5 there was an associated hypogammaglobulinaemia. In my experience this type of disturbance is not uncommon in reticuloses. Cases 3 and 6 had several severe acute pyogenic infections during the last weeks of their lives.

A third feature is the bizarre clinical and histological picture present in these cases. In the more acute cases the peripheral blood film and bone-marrow morphology were atypical and difficult to interpret. Bone-marrow aplasia and haemolysis were associated with the illness in at least three out of the six cases. In the first four cases and the last one the leukaemic phase was extremely short, and treatment apparently produced, at the best, transitory improvement.

Court Brown and Doll (1959) have demonstrated an apparent increase in the incidence of leukaemia. The information gathered by them may be interpreted in different ways, but it seems reasonable to conclude that there has been an increase in the acute leukaemias, particularly in elderly persons. They suggest that radiation has played an important part in this change. There had not been any exposure to *x*-ray therapy in the present series. Perhaps more attention might be paid to the role of chemical agents. In this regard a remark of Rupert Willis (1948) is worth noting: "All drugs or other substances known to be capable of causing agranulocytosis should also be suspected as a possible cause of leukaemia."

Summary

Six cases of leukaemia occurring in elderly males are reported.

In all of these patients there was a history of the recent administration of phenylbutazone.

In one of the cases there appears to have been a strong sequential relationship between the drug and the disease, starting from an early typical toxic reaction to the drug and terminating 18 months later in death from myeloid leukaemia.

I thank Dr. A. Bardsley, specialist medical officer of the Repatriation Department, for referring Case 5 to me and for his assistance in preparing this paper, and I am grateful to the chairman of the Repatriation Commission for permission to publish it.

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The International Brain Research Organization, founded to co-ordinate results and facilitate training and research in this branch of science, has been established recently as a result of a four-day meeting at Unesco House in Paris. The meeting brought together 18 scientists from 12 countries as members of a central committee representing the seven principal branches of neurology: neuroanatomy, neuroendocrinology, neurochemistry, neuropharmacology, neurophysiology, the behavioural sciences, and biophysics. The meeting was convened on behalf of Unesco by the Council for International Organizations of the Medical Sciences, and committee members came from Argentina, Australia, Canada, France, the German Federal Republic, Italy, Norway, Poland, Sweden, the United Kingdom, the U.S.S.R., and the United States. The meeting adopted the statutes of this new international non-governmental organization and elected its executive committee. Professor H. H. Jasper, of Montreal, neurophysiologist, was chosen as executive secretary of the committee, which included Dr. P. K. Anokhin (U.S.S.R.), Dr. A. Fessard (France), Professor G. W. Harris, F.R.S. (United Kingdom), Dr. H. W. Magoun (U.S.A.), Dr. Giuseppe Moruzzi (Italy), while Dr. Heinrich Waelsch (U.S.A.), Dr. D. Bovet (Italy), Dr. A. Brodal (Norway), and Dr. W. A. Rosenblith (U.S.A.) were chosen as alternative members of the committee.