for education and intelligent propaganda among the public on the lines indicated by the N.A.P.T., with especial emphasis on the education of females in the middle-age group of the population. How far the possibilities of propaganda have been neglected is seen in the tardiness with which patients with haemoptysis or pleurisy consult their own practitioners.

So far as the general practitioner is concerned there is room for more rapid diagnosis. According to Varrier-Jones (1933) the reason is because "in the first place the vast majority of students qualify and enter practice without seeing possibly a single early case of infiltration. They are thus unable to detect tuberculosis at its onset." This view is held also by Gregory Kayne *et al.* (1939). There seems to be a strong case for better education in tuberculosis in both the undergraduate and the postgraduate stages of medicine. A student residency in a sanatorium is advocated by Nelson (1939), but it would appear preferable that such a period of time should be spent examining the early cases of phthisis which are to be seen at the dispensary.

In patients with a history of haemoptysis there should be no further delay by the practitioner before the case is notified or is referred for specialist examination. In a number of instances "streaks" of blood in the sputum were not regarded as "suggestive" of phthisis.

Again, after an attack of pleurisy, there should not be a further delay before the case is satisfactorily diagnosed. This delay is needless, because, as Burrell (1937), Wynn (1940), Maxwell (1941), and others have suggested, in all cases in which acute pleurisy appears to be "primary" it is well to assume that the cause is tuberculosis unless definite proof of some other cause is forthcoming. There is much to be said for the opinion which urges that "primary" or idiopathic pleurisy should be made a non-specific notifiable disease which could be referred to a chest or tuberculosis dispensary for observation and final diagnosis. This would avoid the danger of branding some non-tuberculous pleurisies as phthisis and would close the avenues whereby such cases escape consultant opinion. At the same time the general practitioner would have the satisfaction of having been instrumental in finding a potential case of pulmonary tuberculosis.

Sputum.—As already observed, sputum was sent for examination by the patients' doctor in only 22% of the 250 cases in which it was present. This suggests that practitioners fail to make use of the existing free public health facilities for the examination of sputa—a failure that may in some measure be responsible for the delay in diagnosis.

Sanatorium.—The time-lag which elapsed between a patient's being notified or referred to the tuberculosis dispensary and his admission to sanatorium is to some extent a reflection on wartime conditions. In part these deficiencies appear to be due to the inadequacy of both nursing and domestic personnel in fulfilling the needs of the sanatoria (Heaf and Rusby, 1942; Snell, 1942). The corollary is that serviceable wards in satisfactory condition are out of use because of staff difficulties while patients clamour for admission. Another factor is the lack of sanatorium beds in certain areas of the country owing to "blocks" being reserved exclusively for the boarding of troops. Moreover, the existing problems have been accentuated by the wartime rise in the incidence of phthisis.

History of Contact associated with Debility.—Of the investigated cases 99 (33%) were noted to have a history of phthisis associated with debility. Thus the field of contact examination appears to provide an early and very fruitful means of finding cases.

General.—It should here be stressed that such measures as are suggested for the limitation of delay in the diagnosis of pulmonary tuberculosis and the initiation of sanatorium therapy are on no account an alternative to mass radiography. They merely re-emphasize certain well-established principles in case-finding, with a plea for their application to the public and all branches of the medical services.

Summary

Three hundred cases of phthisis were investigated with special reference to the time-lag occurring before treatment at sanatorium was started and after symptoms "suggestive" of phthisis had been established. The delays were classified according to age and sex. Particular note was taken of the delay in diagnosis following pleurisy and haemoptysis. The number of

sputa sent for examination by practitioners was the subject of analysis. The following reforms are advocated.

1. A more generous plan of public education on tuberculosis on the lines pursued by the National Association for the Prevention of Tuberculosis.
2. A revision of existing undergraduate and postgraduate medical teaching, with greater emphasis on the "early" case.
3. The notification of pleurisy (primary or idiopathic) as a non-specific disease, with facilities for the reference of such cases to the tuberculosis or chest dispensaries for a more adequate and final diagnosis.
4. The more extensive employment of existing public health facilities for sputum examination.

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LYMPHADENOMA AND LEUKAEMIA

BY

A. WILSON GILL, M.D.Ed., M.R.C.P.

Honorary Physician, North Staffordshire Royal Infirmary

AND

A. J. McCALL, M.D.Liverp., M.R.C.P.

Pathologist to the Infirmary

There are many evident clinical similarities between lymphadenoma and the leukaemias, and the suggestion has been made that a close relationship exists between these diseases. This suggestion is supported by the observation that occasionally both may occur in the same patient. The case now described appears to have been such an example.

Case History

A girl aged 18, unmarried, was first seen in April, 1940, complaining of general weakness, enlarged glands on both sides of the neck, in the right axilla and the left groin, with attacks of suffocation and dyspnoea at night suggesting mediastinal involvement. The spleen was not palpable. A blood count showed: Hb, 82%; R.B.C.s, 4,450,000; C.I., 0.92; W.B.C.s, 9,375—polymorphs 58%, lymphocytes 38%, monocytes 1%, eosinophils 3%. The family history disclosed that the patient's two sisters had died in infancy from unknown causes, and the mother suffered from anaemia of undetermined type.

Radiographs of the patient's chest revealed a mass surrounding the aorta in the upper mediastinum. A supraclavicular gland was removed. This showed the histological features of lymphadenoma. There was reticulum-cell hyperplasia with the formation of numerous Sternberg-Reed giant cells. Eosinophil leucocytes were scattered throughout the gland, and occasional plasma cells were seen. Some areas of the gland were replaced by dense collagen, and in the more cellular areas there was a fine reticular fibrosis.

Treatment by deep x rays (Dr. C. Bellamy) resulted in rapid disappearance of the superficial glands, considerable diminution of the intrathoracic mass, and complete relief of all symptoms. Other blood counts revealed no significant alteration. Further irradiation was given at intervals during the next two years, during which period the general health remained excellent.

In March, 1942, a sudden and dramatic change was evident. Extreme anaemia developed. Blood counts were as follows:

April 18, 1942.—Hb, 34%; R.B.C.s, 1,650,000; C.I., 1.03; W.B.C.s, 49,800—polymorphs 2.5%, lymphocytes 94.5%, mono-

cytes 0.5%, lymphoblasts 1%, metamyelocytes 0.5%, neutrophil myelocytes 1%. Anisocytosis and slight polychromasia were present. No nucleated red cells were seen. In this and all subsequent counts platelets were very scanty.

May 24, 1942.—Hb, 40%; R.B.C.s, 1,950,000; C.I., 1.03; W.B.C.s, 29,800—polymorphs 0.5%, lymphocytes 98%, lymphoblasts 1.5%. Anisocytosis ++. No nucleated red cells were seen. The only granular cells seen were 1 myelocyte and 1 polymorph.

May 26, 1942.—Hb, 22%; R.B.C.s, 1,270,000; C.I., 0.8; W.B.C.s, 180,000—polymorphs 2%, lymphocytes 75%, myelocytes 1%, premyelocytes 1%, lymphoblasts 20%.

No enlarged superficial glands were found, the spleen was not palpable, no external haemorrhages occurred, and the mediastinal shadow was not increased. There was an irregular pyrexia, which, however, showed no tendency to periodicity of the Pel-Ebstein type. Blood transfusions were given on three occasions with slight improvement. Thereafter deterioration was rapid, with the onset of uterine haemorrhage, which persisted for two weeks despite ergot, progestin, vitamin K (kapon), and ascorbic acid.

The rapidly developing anaemia associated with scanty platelets and the increasing leucocyte count now seemed to us to establish a diagnosis of acute leukaemia. The high proportion of lymphocytes appearing in the later blood counts suggested that the leukaemia was lymphoid in type. The primitive cells observed were identified as lymphoblasts after supravital staining with janus green and neutral red. The mitochondria thus demonstrated in these cells were large and heavy and of the lymphoblastic type; these cells showed no peroxidase granules. In Romanovsky-stained films the nuclear membrane was well defined and the nucleoli distinct. Of the cells classified as lymphocytes a number showed immature characteristics in that the chromatin pattern was much finer than that of mature lymphocytes and a suggestion of nucleoli was sometimes present. Occasionally Rieder forms of lymphocytes were seen. Smear-cells were not so numerous as is usual in lymphoid leukaemia.

The above observations were regarded as confirming the diagnosis of acute lymphoid leukaemia.

Death occurred on May 29, but unfortunately no necropsy was allowed. Blood films were examined by Prof. L. J. Witts, who confirmed the diagnosis of lymphoid leukaemia. Dr. A. H. T. Robb-Smith examined a section from the lymph gland and confirmed the diagnosis of lymphadenoma.

Previously Recorded Cases

Watson (1938) has fully discussed the association of lymphadenoma with leukaemia. One of the earliest cases in which the diseases were thought to coexist was described by Fabian (1908), who observed myeloid leukaemia and chloroma, with histological changes suggesting lymphadenoma. Dietrich (1912) described his case as showing lymphadenoma and "mixed-cell" leukaemia. More recently Warthin (1931) described six cases of lymphadenoma which ultimately developed the blood picture of lymphoid leukaemia, and two further cases terminating in myeloid leukaemia. McCartney (1928) thought his case showed lymphoid leukaemia, lymphosarcoma, lymphadenoma, and endothelioma, but Ewing (1928) doubted the diagnosis of leukaemia. Hittmair (1928) maintained that transitional forms between lymphadenoma and leukaemia occurred; he described a case of lymphadenoma with "leukaemic reticulo-endothelial reaction."

A case in which the occurrence of lymphadenoma and acute myeloid leukaemia appears to have been quite clearly established was recorded by Skworzoff (1930). The leukaemia responded well to irradiation before the existence of lymphadenoma was discovered. Dubberstein (1931) recorded the simultaneous occurrence of lymphadenoma and subleukaemic lymphoid leukaemia, and a similar case was described by Craver (1936). In two cases cited by Watson (1938) lymphadenoma was observed with a subleukaemic blood picture of lymphoid type, and histological evidence of leukaemic infiltration was found.

Unless the blood is frankly leukaemic the coexistence of the two diseases must sometimes be doubtful in the absence of a necropsy, for it is recognized that a high leucocytosis may occasionally be found in lymphadenoma (Hirschfeld, 1925). A further point requiring notice is that lymphadenomatous lesions in the marrow, which were observed in 50% of lymphadenoma cases examined by Symmers (1924), may cause immature white cells to appear in the blood. In our case there was no necropsy, but we do not think that the blood changes could be regarded as a leuco-erythroblastic reaction.

In some of the published cases both conditions have been present when the patient was first seen, and in others leukaemia has appeared in a patient already suffering from lymphadenoma. It is more difficult to be certain that lymphadenoma has ever developed in a patient suffering from leukaemia. Dietrich (1912) thought this sequence occurred when lymphadenoma was found at necropsy on his patient, who had developed leukaemia 19 months previously. No biopsy was, however, done on this case, and it is possible that lymphadenoma may have existed before the development of leukaemia and escaped detection.

Irradiation Therapy

Forkner (1938) thought there was some evidence that irradiation might be one factor, perhaps in especially susceptible individuals, in the production of leukaemia. The question therefore arises whether the treatment of lymphadenoma by irradiation has any influence in inducing leukaemia in these cases. This possibility cannot be completely excluded, but it may be observed that although irradiation is almost universally used in the treatment of lymphadenoma, leukaemia occurs very infrequently in these cases. It is noteworthy that in six cases of lymphadenoma described by Warthin (1931) leukaemia developed in the absence of radiotherapy, and that Craver (1936) was unable to find any evidence that the development of leukaemia in cases of lymphosarcoma was attributable to irradiation therapy.

Lymphadenoma, Leukaemia, and the Reticuloses

Observations on the pathological processes that may affect the reticulum cell have resulted in the introduction of the term "reticulosis" to include "all conditions in which there is generalized enlargement of the spleen, lymph nodes, and liver, due to hyperplasia of differentiated or undifferentiated mesenchymal cells" (Hadfield and Garrod, 1938). It is clear that the leukaemias and lymphadenoma are both included within this definition, and the close generic relationship between these diseases has been repeatedly and strenuously argued by Warthin (1927, 1928, 1931), and was supported by Pullinger (1932).

In the classification of the reticuloses suggested by Robb-Smith (1938) the leukaemias and lymphadenoma are designated "haemic reticuloses" and "fibro-myeloid reticulosis" respectively. The name "fibro-myeloid reticulosis" had previously been suggested by Pullinger (1932), who pointed out that lymphadenoma began as a proliferation of reticulum cells, which were the root-cells of the haemopoietic tissues. She thought that differentiation of some of the reticulum cells to haemic cells occurred, as shown by the finding of myeloid cells in lymphadenomatous lesions. The leukaemias, on the other hand, were characterized by proliferation of cells which were the more-differentiated progeny of reticulum cells, and which were already determined to leucopoiesis before the proliferative process started. Pullinger's views are supported by the occasional association of lymphadenoma and leukaemia.

It appears reasonable to adopt the suggestion that lymphadenoma and leukaemia are members of a larger group of closely related diseases—the reticuloses. This serves to emphasize the close relationship between the cell-types which characterize the two diseases, though it does not imply that the stimuli which initiate lymphadenoma and leukaemia are necessarily identical.

Summary

A case of lymphadenoma confirmed by biopsy is described. There was a good response to x-ray therapy, and no abnormality was found in the blood.

After two years of good health, maintained by careful irradiation, the clinical picture and blood findings of acute lymphoid leukaemia developed.

Other examples are quoted in which established cases of lymphadenoma have terminated with leukaemia or in which lymphadenoma and leukaemia have been present simultaneously.

The generic relationship between the two diseases is emphasized, in conformity with the view that both should be regarded as members of the group of reticuloses.

The evidence available does not suggest that the treatment of lymphadenoma by irradiation is responsible for a leukaemic termination in this disease.

We wish to express our thanks to Prof. L. J. Witts and Dr. A. H. T. Robb-Smith, who were kind enough to examine material from this case.

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Medical Memoranda

Successful Treatment of Influenzal Meningitis with Sulphonamides

Pfeiffer bacillus meningitis is usually regarded as a fatal disease. The following report summarizes the case notes of a patient who recovered comparatively rapidly from influenzal meningitis with sulphonamide therapy.

CASE REPORT

A boy aged 5½ years fell ill suddenly on May 30, 1942, with headache and vomiting. Next day his doctor, suspecting meningococcal meningitis, requested immediate admission to hospital. There was no history of any febrile attack among his family or immediate contacts prior to his illness.

On admission the patient's temperature was 101°, pulse 160, and respiration rate 22. He was conscious and intelligent, and complained only of headache. Physical examination revealed no abnormal findings apart from slight neck rigidity and a positive Kernig's sign. Lumbar puncture yielded a turbid cerebrospinal fluid, pale yellow in colour and under slightly increased pressure. The laboratory report was: protein, 165 mg./100 c.cm.; chlorides, 670 mg./100 c.cm.; sugar, absent. Cells, 387: neutrophils 64%, lymphocytes 30%, arachnoidal cells 6%. R.B.C.s, occasional. Culture showed *Haemophilus influenzae*.

Sulphapyridine 1.5 g. was given by mouth immediately, and was repeated after four hours; thereafter 0.5 g. was given 4-hourly. Because of the troublesome vomiting before admission nicotinic acid 50 mg. was given with each dose of sulphapyridine. The patient's general condition improved, vomiting ceased, and, apart from slight cyanosis, no new sign or symptom appeared. Lumbar puncture was repeated on June 5, when pressure was normal, and the laboratory report was: protein, 50 mg./100 c.cm.; chlorides, 670 mg./100 c.cm.; sugar, diminished. Cells, 267: neutrophils 72%, lymphocytes 24%, arachnoidal cells 4%. Culture gave a slight growth of *H. influenzae*. On the same day the W.B.C. count was 10,000 per c.mm., 58% being neutrophils.

Unlike the typical course of meningococcal meningitis, the temperature took six days to settle to normal, but on June 9 it was judged safe to discontinue sulphapyridine when a total of 30 g. had been given. All signs of meningitis had gone, and the child's general condition was excellent. However, on June 11 it appeared that a recrudescence of infection had occurred. The temperature rose to 102°, and the pulse to 124; the child was irritable and photophobic, and had slight neck rigidity again. Lumbar puncture showed the C.S.F. to be under slightly increased pressure and just opalescent to the naked eye. Culture did not confirm our clinical diagnosis of a renewed meningeal infection. The laboratory report was: protein, 60 mg./100 c.cm.; chlorides, 670 mg./100 c.cm.; sugar, considerably diminished; culture, sterile. Cells 76: neutrophils 14%, lymphocytes 62%.

As soon as the recurrence of pyrexia was reported sulphathiazole was prescribed in large doses: 2 g. being given immediately and 1.5 g. 4-hourly thereafter, with nicotinic acid 50 mg. and mist. alk. 1/2 oz. The dose of sulphathiazole was reduced to 1 g. on the second day and 0.5 g. on the fourth day, and was discontinued on the seventh day at a total of 32 g. By this time the child was afebrile, bright, and normal in every way. Subsequent convalescence was rapid and without further setbacks. The patient was discharged home in excellent health on July 3.

There have been several reports published within the last twelve months of the sulphonamide treatment of Pfeiffer bacillus infections, with variable success. It would appear that a primary meningitis responds favourably to chemotherapy. Two important factors in the successful outcome of this particular case were undoubtedly the early institution of treatment and adequate dosage with the drug employed.

City Isolation Hospital, N. ARCHER, D.M., D.P.H.
 Oxford. E. SINGER, M.R.C.S., L.R.C.P., D.C.H.

Reviews

BIOCHEMISTRY AND MORPHOGENESIS

Biochemistry and Morphogenesis. By Joseph Needham, F.R.S. (Pp. 787; illustrated. 52s. 6d.) Cambridge: The University Press. 1942.

Dr. Needham seems to have read all that has ever been written about embryonic development, normal and abnormal growth, tumours and grafts, regeneration of tissues, etc., and the influence on all of these of the internal and external chemical environment. Moreover, he is blessed with an amazing memory and a laudable desire to give to every worker his meed of credit. The result is a volume which is a mine of well-documented (in fact, too well documented) information in which it is sometimes difficult to see the wood for the trees. Nevertheless, the determined reader who tackles the 677 pages with the aid of the table of contents, the glossary, and the series of well-planned indexes will find a mass of information on any aspect of the subject of cell growth and differentiation which happens to interest him.

One of the best sections of the book, and one which will appeal to medical readers, is that which summarizes the work on the chemical nature of the "organizer." When the fertilized egg of the amphibian reaches the stage at which the uppermost layer of the cells of the blastula start to invaginate to form the gastrula, certain elongated cells appear on the dorsal lip of the blastopore. At the location of these cells there now develop the neural folds, which give rise to the neural tube, the forerunner of the spinal cord, and below them the notochord, the forerunner of the backbone. The axis of symmetry of the embryo is thus laid down and the position of the other organs as they develop is fixed in relation to this axis. By means of highly skilful microsurgery it has been shown that in normal development the stimulus to the morphological differentiation of the neural tube and notochord comes from these special cells at the tip of the blastopore. By excising these cells and grafting them into another blastula, invagination and the laying down of the embryonic axis can be made to take place at any position on the surface, and by inserting two or sometimes three grafts into the same gastrula the same number of embryonic axes can be made to develop. The discovery was later made that the organizer cells can induce growth even if killed by boiling, though the development induced is chaotic, and that extracts of dead cells from adult organisms can induce the same effect. Moreover, extracts from the tissues of one species can induce differentiation in the embryo of another. The growth stimulant (the evocator) is therefore a chemical substance; it appears to be a sterol and closely related in chemical structure and properties to the male and female hormones and to the carcinogens. It is present not only in the embryo but throughout all the tissues of the adult body, though normally maintained by some means in an inactive form.

The idea that normal differentiation (as distinct from mere cell proliferation) is also based on the presence of certain definite chemical substances and that these are located in definite regions in the egg cell is borne out by Swedish work on the developing egg of the sea-urchin. In this work it is shown that definite localities in the egg pass to definite cells in the early cleavage stages and that, up to the 16-cell stage, the cells of one or more embryos can be separated and re-combined in a number of permutations and combinations. Provided that the different zones of the original egg are present in a certain ratio in the reconstituted embryo a normal development will follow in spite of the drastic microsurgical history of the embryo. If, however, an abnormal quantity of any one zone is present (or if the zone is missing) abnormal development follows. Dr. Needham develops the thesis that normal growth and differentiation depend on the action of a stimulus (a definite chemical substance) acting on a tissue which is in the correct condition to receive it. The stimulus acting on a tissue not in the correct condition will lead to disordered growth, resulting in the formation of pathological abnormalities, among which teratomata are listed. In considering growth and development, the important influence of the genes—which certainly has a chemical basis—is not overlooked, certain pathological conditions, such as the absence of the brain in the fully developed foetus, being due to the presence of a particular gene.