SOME OBSERVATIONS ON LEUKAEMIA: A PRELIMINARY NOTE*

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The nature of the leukaemias or leukoses has been a subject of much discussion ever since the disease was first described by Craigie, and by Bennet, and by Virchow, just a century ago and the problem is far from solved even yet. That this is still true is very apparent from the account of the proceedings of the Ciba Symposium on Leukaemia Research held in November 1953 when, it seems, a common basis for discussion by the various authorities there gathered was difficult to find (*vide loc. cit.* p. 32 *et seq.*)

Various theories have been put forward concerning the nature of these diseases, for example, the infective, nutritional deficiency, and neoplastic theories. The infective theory was in the background so far as mammalian leukaemia was concerned for many years, but has recently been brought to the fore again as a result of the experimental work, in mice, of Gross, who claims to have demonstrated a filter-passing causative agent (Gross, 1954).

So far as the nutritional or maturing-factor deficiency theories are concerned, there is very little evidence in their favour, however attractive they may be as ideas in that they hold out more hope of cure than a neoplastic theory does. The only advocate of this theory who need be taken seriously is Sir Lionel Whitby (1951), but there are many loopholes in his arguments and his views have been criticized by Furth (1951).

The observations submitted here are, of course, tentative and are only put forward as a basis for discussion.

Of the neoplastic nature of human leukaemia I feel there is no doubt. The hypothesis I wish to submit here, which I do not claim as original although I have been unable to find any reference to a similar suggestion elsewhere, is that the chronic leukaemias may be regarded as benign neoplasms and the acute leukaemias as malignant neoplasms. No attempt can be made here to define

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these two terms, benign and malignant, except to give the simplest of examples to show what is meant. A circumscribed, non-metastasizing tumour of, for example, fibrocytes, is a benign fibroma; a metastasizing invasive tumour of fibrous tissue, on the other hand is malignant—a sarcoma. It is also known that the first may change into the second and, further, that these terms are not entirely (although they are usually) synonymous with clinical ideas of benign and malignant. As Ewing many years ago pointed out, 'If malignancy were a purely clinical conception, it would be impossible to draw any rigid distinction between benign and malignant tumors, since nearly all tumors may prove fatal' (Ewing, 1940).

BLOOD AS A TISSUE

Now in considering these concepts certain points must be emphasized. Firstly a stumbling block to acceptance of the neoplastic nature of these diseases that is apparent in the literature is the absence of tumorous deposits. But a fundamental fact which must be borne in mind is the concept probably universally accepted, but not emphasized sufficiently, that the blood constitutes a fluid tissue not separate from but co-terminous with the blood-forming organs, whether bone marrow, lymph-nodes or spleen. Boycott introduced this idea with his term the 'erythron' (Boycott, 1929) for the red cells and their precursors, but an even wider term is required.

Regarding the blood, then as a fluid tissue, it need not surprise that a neoplastic condition of one of its elements does not always result in actual tumours, and that the effects of such a neoplasm, although benign in the sense in which it is here used, may nevertheless have far-reaching effects.

The chronic leukaemias are characterized by a proliferation of essentially mature cell types, which have their identical counterparts in the normal. Much time has been spent endeavouring to demonstrate a biochemical or cytological deviation from these normal counterparts, but it may be fairly said that no convincing difference has so far been demonstrated, and this is as might be expected of the cells of a benign neoplasm. As regards their invasive properties, it is agreed by histopathologists that the cells of the chronic leukaemias have little if any, true invasive power, their presence in all organs and tissues being merely an expression of the ubiquity of blood as a tissue.

The course, too, of the chronic leukaemias, suggests a benign neoplasm, but here a change appears to have occurred in recent times, and it is this change which has led to the development of this hypothesis. Previously, it appears, the usual termination of the chronic leukaemias was for the patient to succumb to an intercurrent infection or a thrombotic episode or to die from anaemia and exhaustion. The possibility of termination as a typical acute leukaemia is mentioned in the older texts, but it is clearly indicated that this was regarded as a rather rare event. Shimkin *et al.* (1951) state that one quarter of the cases of chronic myeloid leukaemia they studied over a 40 year period, died in a terminal acute phase, but these were *post mortem* diagnoses. What does more recent experience show? Out of 19 cases of chronic myeloid leukaemia observed by us until demise, in the past 3 years, no less than 15 (over 75%) terminated as an acute myeloblastic leukaemia, both clinically and haematologically. Of the 4 others, 1 died of coronary thrombosis, 1 of post-operative infection, and 2 of anaemia and exhaustion.

In considering the reasons for this, the possibility that therapeutic measures may be increasing the likelihood of malignant change has been considered. Haddow and others have shown that most of our therapeutic agents are carcinogenic e.g. X-rays, nitrogen mustards, the epoxides, 'myleran', urethane, and others (Haddow, 1953). The following table shows the various agents used to treat these cases, but no special significance can be attached to the figures.

DXT alone	5
DXT + Myleran	7
Myleran alone	2
Urethane alone	1

The course of chronic lymphatic leukaemia is somewhat different from that of chronic myeloid leukaemia in that the prognosis is better and it but rarely terminates as an acute leukaemia. Thus Shimkin found an acute termination in only 2 out of 137 cases of chronic lymphatic leukaemia (Shimkin *et al.*, 1953). Nevertheless I think there is evidence from our material that the character of the disease does sometimes change from a benign to a malignant neoplasia terminally.

It is unusual to perform bone-marrow aspiration biopsies on terminal cases of chronic lymphatic leukaemia, but we have done so on 3 cases. In each case there was what is termed in the American literature 'marrow block'—a state in which the bone-marrow is crowded with cells so that aspiration is difficult and results in only a drop or two of material. This material in the cases studied did not consist of mature lymphocytes such as were still present in the peripheral blood, but was almost entirely primitive lymphoid reticulum cells. Now 2 of these 3 cases had received T.E.M. as treatment at 2 months and 3 months before death, and the 3rd case 2 courses of nitrogen-mustard therapy 6 months and 3 months before death. There was no clue from the peripheral blood that invasion of the marrow by primitive cells had occurred, there being merely severe anaemia, thrombocytopenia and the leucocyte picture of a chronic lymphatic leukaemia. The fact that they do not terminate as acute 'lymphoblastic' leukaemia gives some support to the view held by Naegeli, Rohr and Moeschlin, with which I am in agreement, that acute lymphoblastic leukaemia has no existence in fact, unless possibly during childhood.

A further point which may have some bearing on the apparently infrequent acute termination to chronic lymphatic leukaemia is the fact that this condition is more often treated conservatively than chronic myeloid leukaemia, with usually only sufficient radiation to cause the lymph nodes to regress.

These cases lend some support to the hypothesis here put forward, but clearly further investigation of chronic lymphatic leukaemia in its final stadium must be carried out.

Finally, a concept which has arisen of late years helps I think to keep the matter in a proper perspective. I

refer to the concept of the myelo-proliferative diseases which are shown in Fig. 1. These diseases could, I think, be regarded as benign neoplasms, and the grounds for this concept of myeloproliferative disease is the agreed

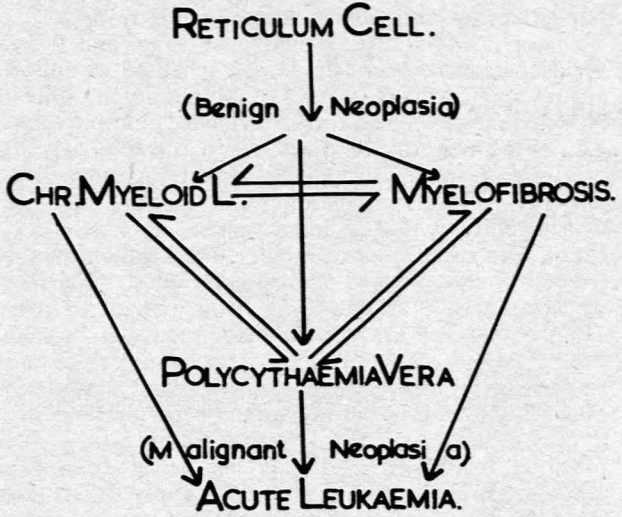

Fig. 1. A schema showing the myelo-proliferative diseases and their interrelations. Chronic myeloid leukaemia, myelofibrosis and polycythaemia vera are regarded as benign neoplasms and acute leukaemia as a malignant neoplasm.

multipotentiality of the primitive reticulum cell, enabling benign neoplasia to occur along the various developmental lines and often along more than one simultaneously, leading to known associations of these conditions. Thus polycythaemia has an association with chronic myeloid leukaemia, and with myelofibrosis. Myelofibrosis may be the end-result of a chronic myeloid leukaemia or of a polycythaemia. Any may terminate as the malignant form, to wit, acute myeloblastic leukaemia. This has been known for some years now to occur more commonly after treatment of polycythaemia with ^{32}P than in untreated cases.

CONCLUSION

To conclude then, the following suggestions are made:

1. Leukaemia is a true neoplasm.

2. The chronic myelogenous and chronic lymphatic forms are benign neoplasms which, on account of the ubiquity of the tissue affected, have far reaching and ultimately fatal effects. (In this sense they are not benign.)

3. Acute myeloblastic leukaemia is the malignant neoplasm corresponding to chronic myelogenous leukaemia, and a lymphoid reticulum cell neoplasm is the malignant neoplasm corresponding to chronic lymphatic leukaemia.

4. This view of the leukaemias is in keeping with the concept of the myeloproliferative diseases.

5. The change from benign to malignant neoplasms is being seen more frequently now as a result of the use of carcinogenic therapeutic agents.

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