CASES OF CRYPTOCOCCOSIS AMONG 1067 CASES OF PRIMARY MALIGNANT AND POTENTIALLY MALIGNANT DISEASES OF THE LYMPHORETICULAR SYSTEM

Lymphoreticular disease	No. of cases	No. of cases complicated by cryptococcosis	Percentage of cases with cryptococcosis (to nearest integer)
Hodgkin's disease:			
Ordinary type	423	8	2
Indolent type	63	0	0
Reticulum-cell sarcoma ..	269	2	1
Lymphosarcoma	222	3	1
Follicular lymphoma ..	90	0	0
Total	1067	13	1

do not indicate incidence, since the 5 patients with this association were referred as cases of cryptococcosis and are not from a consecutive series of cases of sarcoidosis. Admitting that these figures are influenced by personal interest in diseases of the lymphoreticular system, which therefore figure more largely in my records than otherwise they would, there seems to be no doubt that patients with certain types of systemic disease of this system have a greater than average liability to develop cryptococcosis. The incidence of this infection among the 423 patients with the ordinary type of Hodgkin's disease in my own series (see table) was about 2%, and among over 1000 cases of Hodgkin's disease in the files of the Armed Forces Institute of Pathology, Washington, D.C., it was about 1%.[5] The available evidence does not suggest that conditions other than systemic lymphoreticular diseases are particularly liable to predispose to cryptococcosis: however, the possibility of this infection developing in the presence of other debilitating conditions that tend to lower resistance to potentially " opportunistic " fungi should not be overlooked.

Low though it is, the 1–2% incidence of cryptococcosis among patients with predisposing lymphoreticular diseases is very much higher than the recognised frequency of this infection in the population in general. Even so, it is so small that there may be a temptation to disregard the risk rather than face up to the problem of how to protect patients from infection by a fungus that grows in a medium as unavoidably ubiquitous as dried bird droppings. Let us hope that those in a position to do so may think it worth while to work out ways of effectively reducing the hazard to those who are most at risk—the patients in bird-polluted hospitals who are suffering from diseases that predispose to cryptococcosis. As Dr. Partridge and Professor Winner have repeatedly indicated, it seems only prudent, to say the least, to take such steps.

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CHROMOSOME BREAKAGE AND LEUKÆMIA

SIR,—The comments made in your annotation (Jan. 7, p. 36) about the association between certain genetically determined disorders and the presence of chromosome abnormalities in cultured cells are undoubtedly apposite. Yet certain comparisons which are drawn with chronic granulocytic leukæmia might be called in question. The abnormalities observed in Bloom's syndrome,[6] ataxia-telangiectasia,[7] and Fanconi's syndrome [8] are non-specific in that they do not involve particular chromosomes. They take the form of breaks and subsequent rearrangements and may involve different chromosomes in each damaged cell whether from the same or a different patient. The damage is of the same general type as that produced by radiation and viruses, and between 10% and 50% of the cells are affected. In no sense has a particular marker chromosome been identified. On the other hand the abnormality in chronic granulocytic leukæmia is specific, because the same chromosome is always involved, even in different patients. The abnormality is restricted to the bone-marrow, where it is present in almost every cell. In the Bloom [9] and Fanconi [8] syndromes the cells of more than one tissue have shown chromosome abnormalities indicating some generalised sensitivity to chromosome breakage. Nevertheless, we do not wish to detract from the important point made in your annotation that these inherited conditions in which chromosome abnormalities can be detected are associated with malignancy.

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ORIGIN OF PH[1] CHROMOSOME

SIR,—I should like to venture a different explanation from that of Dr. Mastrangelo and Dr. Zuelzer (Dec. 3, p. 1250) on the origin of the Ph[1] chromosome. As I have pointed out,[10] it is in my opinion a general rule that absence of some particular inhibitor causes disintegration of corresponding genes—located in the " upper " part of chromosome no. 21 in chronic granulocytic leukæmia. It is not incomprehensible that loss of one of the combination of inhibitor, enzyme-systems, and genes, should affect the remaining ones.

Judging from what persists after the Ph[1] chromosome has been formed, the normal one may consist of " upper " and " lower " curved structures, which are interlinked as shown in the accompanying diagram. Disintegration of some special gene—that is, of a number of nucleotides—may well spread through the complete chemical spiral, resulting in loss of the " upper " curve, thus forming the Ph[1] chromosome. At any rate, disintegration of a number of nucleotides would cause a break in the " upper " curve, leaving two parts of it unattached which may or may not translocate.

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MYCOPLASMA AND DOWN'S SYNDROME

SIR,—Epidemiological studies assuming an infectious ætiology of Down's syndrome have led to contradictory opinions,[11–13] and therefore the investigations of Dr. Allison and his colleagues [14] are of great interest. We have worked on the same problem, and we give here unpublished findings which are at variance with their results.

In our in-vitro experiments we infected human diploid lung cells (RIV_2 strain) with *Mycoplasma hominis*. Analysis of 400 cells from control cultures and 265 cells from infected cultures between the 19th and the 32nd passages did not result in a significant increase in numerical or structural chromosomal aberrations. There was also no increase in polyploidy. We did not find a consistent loss of chromatin material of the short arm of chromosomes 21 and 22 in cells of infected cultures. Variation in size of the short arms may occur in the karyotypes of both inoculated and control cultures. Moreover the chromosomal aberrations found by Fogh et al.[15] were based on experiments with a cell-line in which the chromsome complement is known to be abnormal at the beginning of the experiment. It is even possible that an existing aneuploidy may change into a normal diploid pattern, as we have observed in a patient with melanoma after treatment with antimitotic drugs (particularly nitrogen mustard). In our further experiments in which the action of cytotoxic drugs on the chromosomes of cells was studied in vitro as well as in vivo, it seemed to be easier to induce chromosome changes in cells in vitro.

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At present in our opinion results obtained from in-vitro experiments cannot yield an explanation of the in-vivo mechanism of the origin of Down's syndrome.

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VITAMIN-B_{12} DEFICIENCY IN PSYCHIATRY

SIR,—May we add a few belated comments to the controversy regarding vitamin-B_{12} deficiency and psychiatry, which followed the publication of the paper by Dr. Henderson and his colleagues on the antigastric-antibody (A.G.A.) test as a screening procedure.[1]

We endorse the views of Mr. Hansen and his co-workers [2] and Dr. Reynolds and Dr. Matthews [3] that the A.G.A. test must not lead to neglect of search for causes of vitamin-B_{12} deficiency other than addisonian pernicious anæmia. This is borne out by our own findings in the rhesus monkey fed on vegetarian diets:[4] such animals quickly develop low levels of vitamin B_{12} in their serum [5-7] and degenerative lesions in the nervous system similar to those found in human vitamin-B_{12} deficiency soon become apparent—on one occasion within 8 months. Such lesions are easily recognised histologically in the peripheral nerves, spinal cord, and occasionally brain, often without previous detectable neurological signs in life. Furthermore, when normal animals are compared with vitamin-B_{12}-deficient animals, changes in the peripheral blood are *not* found, although our recent unpublished findings show that, when individual animals are followed, " longitudinally " before and after treatment, minor but statistically significant changes, particularly in the mean corpuscular volume, can be demonstrated. Dr. Varadi's premise [8] that inspection of blood-films is an adequate screening procedure is certainly not confirmed by our studies; in this respect we agree with Reynolds and Matthews [3] and Dr. Schrumpf.[9] We have now extended our observations to other species of monkey and are forced to conclude that at least some neurobiological research (past, present, or future) on such animals maintained on traditional vegetarian diets is suspect. We also believe our findings to be relevant to the human situation.

We do not understand the comment of Mr. Hansen and his colleagues [2] to the effect that the significance of vitamin-B_{12} deficiency in psychiatry is conjectural. An early clinical sign of the deficiency is an altered E.E.G. pattern,[10] and recently the psychiatric significance has been expressed cogently in this journal.[11] Possibly some aspects of the behaviour of rhesus monkeys in captivity on vegetarian diets (e.g., their apparent aggressive and morose personalities) may be associated at least in part with deficiency of the vitamin—here the appropriate behavioural studies have yet to be performed.

As regards the earliest detectable structural lesions in man, reliable and detailed neuropathological studies do not appear to have been made on patients dying with vitamin-B_{12} deficiency in the absence of clinical neurological signs; indeed, it is difficult to envisage these studies ever being possible, since such patients would almost certainly show other vitamin, mineral, or metabolic defects together with the complicating factor of another associated lethal disease. Thus the closest available approximation to the human situation seems to be dietary deficiency in captive primates, in which lesions of the nervous system, clinically occult, are common. Even in this experimental model we cannot, of course, be sure that other dietary defects are not present (for instance, although the animals receive adequate amounts of protein, little of this is in the form of animal protein [12]) or that the lesions are not induced as a result of alterations in cyanide-thiocyanate metabolism.[13] The important points are: first, that experimental lesions resemble those known to occur in florid human vitamin-B_{12} deficiency; second, that these neural lesions are not found in the absence of low serum-vitamin-B_{12} levels; and third, that in several paralysed animals objective clinical improvement followed parenteral vitamin-B_{12} therapy.[4] Though this may be a far cry from psychiatric manifestations, the situation as a whole is not irrelevant.

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THE PLACE OF THE PRIMARY PHYSICIAN

SIR,—Dr. McWhinney is undoubtedly right when he states in his article last week (p. 91) that primary medical care should be carried out by the general practitioner with his focus at the hospital. It is unfortunate that present trends appear to be in the opposite direction. Local authorities, backed it seems by Ministry of Health policy, are encouraging him to throw in his lot with them and to practise from scattered premises, built by them for the purpose, in association with ancillaries, who are not under his direct control, and whose crumbs of help are only available to him in so far as they are not thought to be needed at the table of the local health authority. Laboratory and radiological help, essential though these are for primary medical assessment, will not be available at these points, and the pen-and-stethoscope era of the past will be perpetuated. There is nothing like bricks and mortar to keep in being obsolete practice, and it is sincerely to be hoped that Dr. McWhinney's perspicacious article will do something to reverse the present tendency.

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A CHILDREN'S WARD IN THE TROPICS

SIR,—It is relevant to compare the figures of Dr. Lawless and his co-authors [14] with those reported from pædiatric wards in other parts of Africa, particularly in relation to the number of beds available to the population. Musoke [15] published data from Mulago hospital, where 50 beds were available for Kampala (population about 45,000) and environs. In the first year after independence in the Congo Yarom and I [16] presented data from Luluabourg hospital, where 150 beds were available for the town of 50,000 and environs. The figures of Dr. Lawless and his co-authors are for about 75 beds for a population of more than 114,000. The beds/population ratios are therefore Luluabourg > Kampala > Kitwe, and mortalities of major disease-groups, as percentages of admissions, may be considered in that order, as follows:

Disease-group	*Luluabourg*	*Kampala*	*Kitwe*
Respiratory	10	17	24
Gastroenteric	7	15	16
Malnutrition	13	20	40
Malaria	6	13	10
Overall	10	17	14

It will be seen that for each major disease-group (excepting malaria, which is limited to one season at Kitwe) the mortality is lower where more beds are available. The overall mortality departs from this sequence because of the different incidences of the diseases: if admissions for malnutrition and malaria had

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