

Studies on the Toxicology of the Palmyrah Palm (*Borassus flabellifer* L.) Part III. Development of Malignant Lymphomas in Rats after Prolonged Feeding of Palmyrah Flour.

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Abstract: Palmyrah flour which is consumed by humans in some Asian and African countries, has previously been reported to produce acute and chronic toxic effects in rats. This report describes the characteristics of neoplasms which developed in rats which were either fed directly on a 20% flour diet or were the offspring of palmyrah fed females. Single or multiple malignant lymphomas of varying degrees of differentiation were the commonest tumour; their predominant location was the small intestinal mesentery. Thymic and pulmonary lymphomas and lymphomatous nodules attached to the spleen and kidney were also present in some of these cases. A cervical fibrosarcoma and an intra-abdominal tumour of possibly pancreatic origin were also included in this series. Hind limb paralysis was observed in three tumour bearing rats, one of which had an atrophic spinal cord. The toxic effects of this flour, notably aberrations of immune competence, are discussed in relation to the pathogenesis of these tumours with special reference to a possible aetiological role of C-type viruses.

1. Introduction

Feeding of flour from the young shoot of the palmyrah palm, which is consumed by humans in some Asian and African countries, was reported to produce hepatotoxic and neurotoxic effects in short term feeding experiments¹, hepatic veno-occlusion with hepatic fibrosis¹⁵ and depression of humoral and cell-mediated immune competence² after prolonged feeding in rats. The partial purification of a neurotoxin from this flour was reported by Greig *et al.*⁸

During prolonged feeding trials for the investigation of a possible hepatocarcinogenic effect of this flour, it was found that malignant tumours, notably malignant lymphomas developed after 2 to 7 months of feeding of a 20% flour diet;^{1,6} terminally some of these tumours became infected.

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This report describes the characteristics of these tumours and discusses their possible pathogenesis together with their relevance to malignant lymphomas in rodents and in humans in Sri Lanka with special reference to aberrations in immune competence as a pathogenetic factor.

2. Experimental

2.1 Flour

Flour was obtained by grinding boiled and sundried, recently harvested shoots of the palm; the flour was stored at 4°C to prevent microbial spoilage. This flour showed no contamination with the commonly used agrochemicals (chlorinated hydrocarbons, organophosphorus compounds or paraquat) or with aflatoxin; nitrosamines and pyrrolizidine alkaloids were not detected in this flour.

2.2 Rats

Four batches of male, random bred, Wistar rats (150-200 g) were used, each batch having consisted of 10 test rats, free fed on a 20% flour-pellet powder mixture with water *ad lib.* and 5 control rats in each of the 4 batches, free fed on standard rat pellet powder with water *ad lib.* A total of 40 test rats and 20 control rats were thus used. Each cage housed 5 rats, test or control.

Included in this series, are 3 tumour bearing rats (No. 10, 17 and 18) which were not directly fed the flour diet but were the offspring of females which were fed the test diet during pregnancy in separate experiments. The offspring were fed normal rat pellets after weaning while the mothers were fed the normal diet after parturition.

2.3 Histology

Representative portions of the tumours and other organs were fixed in 10% formal-saline. Sections 5 μ in thickness, of paraffin blocks were stained with haematoxylin and eosin (H & E), reticulin stain and Gram's stain. With infected tumours, the walls of the abscesses especially at the sites of attachment, were examined microscopically for neoplastic tissue.

On account of the obscurity of the disease when first encountered, no specimens such as blood or bone marrow smears, lymph nodes, which were considered relevant in retrospect, were examined.

2.4 Ultrastructural studies

Multiple pieces of tumour from the abdominal and thymic lymphomas in rat N. 12 were processed in glutaraldehyde, osmium tetroxide and Epon for electron microscopy. These specimens were examined by Dr. Robert J. Huebner (National Cancer Institute, Bethesda, Maryland, USA).

2.5 Bacteriology

At necropsy done as soon as possible after death or under ether anaesthesia of moribund rats, the tumour was exposed aseptically; the pus from the 5 infected tumours was examined by Gram's and Ziehl-Neelsen stains and cultured on sheep blood agar which was incubated aerobically and anaerobically at 37⁰ C for 2 to 3 days. Standard bacteriological tests⁴ were used to characterise and identify the isolates.

3. Results

This series comprised 18 rats with tumours or abnormal histology which was suggestive of neoplasia. Of these, 15 rats from the 4 batches (40 rats) which were directly fed the test diet, developed tumours. The remainder of the test diet fed rats, died spontaneously without evidence of neoplasia. Three rats (No. 10, 17 and 18) were not directly fed the test diet but were the offspring of females which had been on the test diet during pregnancy in separate experiments, None of the control rats (nor stock rats in the animal facility) fed the same standard pellet diet developed neoplasia.

3.1 Time of appearance of tumours

The tumours were first detected between 2 and 7 months of the commencement of feeding of the test diet.

3.2 Location of tumours

The location and number of tumours in each of the 18 rats is shown in Table 1.

Except in 3 rats, the site of origin of the single and multiple intra-abdominal lymphomas was not obvious, although the mesenteric lymph nodes could have been the site of origin. These tumours were associated with the small intestinal mesentery and adherent to the adjacent viscera and intestines. In 3 rats, one lymphoma was retroperitoneal on the infrarenal posterior abdominal wall. In 2 other rats, single large lymphomas were diffusely adherent to the posterior abdominal wall in the paravertebral region.

3.3 Macroscopic appearances

The uninfected intra-abdominal lymphomas were thin walled, multinodular, cystic and haemorrhagic in some areas and solid in others, with marked vascularity in restricted zones. The large infected tumours had thick walled fibrous capsules and contained viscid or caseous yellowish pus; the haemorrhagic cysts contained brownish material.

The pulmonary lymphoma in rat No. 4 was a small well defined nodule within the lung tissue. In rat No. 18 the apical pulmonary lymphoma was confluent with the

thymic mass. An ill defined indurated area in the lung of rat No. 12 consisted of diffuse lymphoid cell infiltration.

Table 1. — The distribution according to site and number of tumours or lymphoid tissue abnormalities, in palmyrah treated rats.

Number, site and nature of tumour	Experimental number of rat
<i>directly fed rats</i>	
1 intra-abdominal lymphoma	1, 2, 3, 6, 7, 16
1 intra-abdominal lymphoma with 1 pulmonary lymphoma	4
1 intra-abdominal lymphoma with 1 lymphoma on ventral surface of base of heart	14
3 intra-abdominal lymphomas; 1 thymic lymphoma	9
4 intra-abdominal lymphomas; 1 on upper pole of right kidney, adherent to liver; 1 thymic lymphoma; a lymphoma on posterior thoracic wall	12
1 cervical lymphoma of obscure origin	5
1 axillary lymphoma of obscure origin	15
1 cervical fibrosarcoma (Figure 2) of ill defined origin	11
1 intra-abdominal tumour of possibly pancreatic origin	13
<i>progeny of palmyrah fed mothers</i>	
2 intra-abdominal lymphomas; 1 in gastro-splenic omentum	10
1 thymic lymphoma confluent with apical pulmonary lymphoma	18
abnormal thymic tissue	17

Table 2. — The Provincial incidence of malignant lymphomas in Sri Lanka (1973-1977). Total number of malignant tumours examined, 11844. Total number of malignant lymphomas 739.

Province	malignant lymphomas per 100,000 population
Northern	13.8
Southern	2.0
Western	22.8
Eastern	2.6
North Central	0
North Western	3.2
Central	3.3
Uva	5.1
Sabaragamuwa	3.4

The thymic lymphomas were solid, thin walled, well defined masses.

The intra-abdominal tumour of apparently pancreatic origin in rat No. 13 was a large (5 cm diameter) hard, fibrous, coarsely multinodular, non-infected tumour which in comparison with the intra-abdominal lymphomas was relatively vascular.

Serous pleural effusions were present in rat No. 12 with multiple (mesenteric, thymic and pulmonary) lymphomas and in rats No. 3 and 13; pleural and peritoneal effusions were present in rat No. 16.

Hind limb paralysis was present in 3 rats - No. 7 which had a single mesenteric lymphoma, No. 12 which had multiple intra-abdominal lymphomas together with a thymic lymphoma, and in No. 14. The spinal cord of the lumbar region was macroscopically atrophic in rat No. 12; the cords in rats No. 7 and 14 were not available for study.

3.4 Microscopic appearances

Intra-abdominal mesenteric lymphomas. A noteworthy feature of these tumours was the variation, between rats and within the tumour of an individual rat, of the degree of differentiation of the lymphoid cells, from poorly differentiated, large pleomorphic cells (Figure 3) with a large, indented, single nucleus and numerous mitotic figures, to smaller cells with scanty cytoplasm which were more typical of mature lymphocytes. Giant cells were occasionally present, especially in the less differentiated tumours. Five lymphomas had a predominantly lymphoblastic morphology while 6 had appearances of mixed (lymphoblastic and lymphocytic) patterns; one was predominantly lymphocytic. In 3 tumours with infection, a clear identification of the pattern from the residual lymphoid tissue, was difficult although neoplastic lymphoid cells were present in the wall. In two infected intra-abdominal tumours (rat No. 7 and 8) which were closely adherent to the posterior abdominal wall lymphoid cell infiltration into the muscle of the wall was noted.

Thymic lymphomas. These were multinodular with a thin fibrous encapsulation. The cortical-medullary pattern was replaced by a mass of lymphomatous cells; in some areas, the cells were pleomorphic, poorly differentiated and resembled lymphoblasts while in other areas, the cells were more differentiated, resembling lymphocytes. The overall appearances were those of a mixed cell lymphoma. There were areas of necrosis without haemorrhage or infection. Scattered giant cells were present.

In rat No. 17 the enlarged thymus had lost its normal architecture, which was replaced by well differentiated lymphomatous cells without evidence of infiltration. In rat No. 18 the thymus showed a normal histological pattern in some areas; in other areas which were confluent with the pulmonary lymphoma, bizarre cells with a pleomorphic morphology suggestive of lymphoblasts, were present.

Dr. Robert J. Huebner (personal communication) reported on the ultrastructure of the thymic lymphoma in rat No. 12 as ".....packed thymus tumour cells having no evidence of type-C virus".

Pulmonary lymphomas. In 3 rats (Nos. 4,9,16) the alveolar septa were diffusely infiltrated with lymphoid cells which were well differentiated and distinct from the peribronchial masses of lymphocytes seen in normal rats. One of the tumour bearing rats (No. 4) had a localised, 4 mm lymphomatous nodule in addition. The pulmonary lymphoma in rat No. 18 was poorly differentiated and had infiltrated the pulmonary veins. In rat No. 9 microscopic collections of lymphoid cells were present in the alveolar septa. Vascular congestion and alveolar oedema were noted in rat No. 8 and 13.

The lymphoma in the posterior thoracic wall of rat No. 12 was of the more differentiated lymphocytic type but more haemorrhagic than its abdominal counterpart, and had infiltrated the muscles of the thoracic wall (Figure 4).

Renal lymphomas. The lymphoma in the anterior pole of the right kidney in rat No. 12 had a mixed lymphoblastic-lymphocytic pattern with a predominance of more differentiated cells.

Fibrosarcoma. The single large fibrosarcoma in rat No. 11 (Figure 2) was a mesenchymal, malignant tumour with wide variations in histological appearances (Figure 5). In solid areas the tumour was vascular and cellular with large, elongated pleomorphic cells containing bizarre nuclei and many mitotic figures. Other areas were cystic with haemorrhages and necrosis without infection, and were more fibrotic. Infected areas showed a neutrophilic cell reaction.

The reticulum pattern was that of connective tissue with no evidence of an adenomatous structure. Cellular differentiation into fibroblasts with myxomatous change in the stroma was present in some areas. The peripheral blood smear showed a normoblastaemia with polychromasia of the red cells.

The liver. In rats Nos. 6, 12, 13, 14 and 15, the liver showed vascular abnormalities which were similar to those described in earlier reports¹⁵ viz., central and portal venous subendothelial oedema or occlusion with fibrous tissue. In rat No. 12 which had 4 intra-abdominal lymphomas and a thymic lymphoma, well marked veno-occlusive reactions were present with extensive tracts of fibrous tissue which bridged portal tracts, with scattered areas of hepatocellular necrosis (Figure 6) and hyperplasia of the hepatocytes with multinucleated cells. Infiltration of the liver by lymphoblastoid cells was seen in rat No. 16.



Figure 1. Thymic lymphoma (arrow) at base of heart (H) in rat No. 12. x 1.8



Figure 2. Cervical Fibrosarcoma (arrow) in rat No. 11. x 3/4.

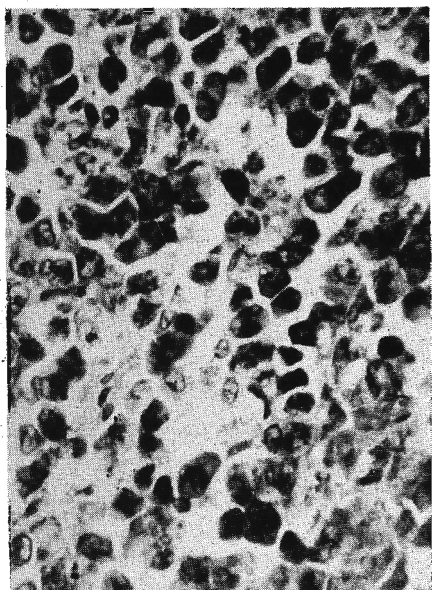


Figure 3. Poorly differentiated lymphomatous cells in single mesenteric lymphoma in rat No. 5. H&E, x 18000.

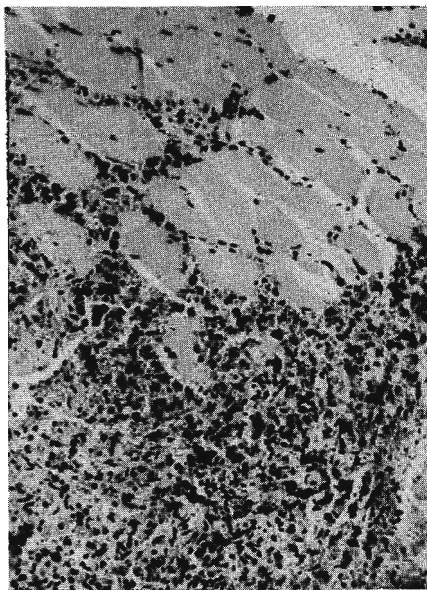


Figure 4. Site of attachment of pulmonary lymphoma to posterior thoracic wall, showing lymphomatous cell infiltration into muscle. H&E, x 210

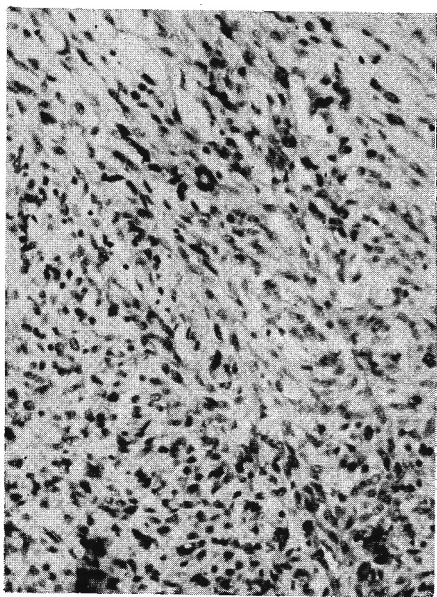


Figure 5. Uninfected cellular region of cervical fibrosarcoma of rat No. 11. H&E, x 210.

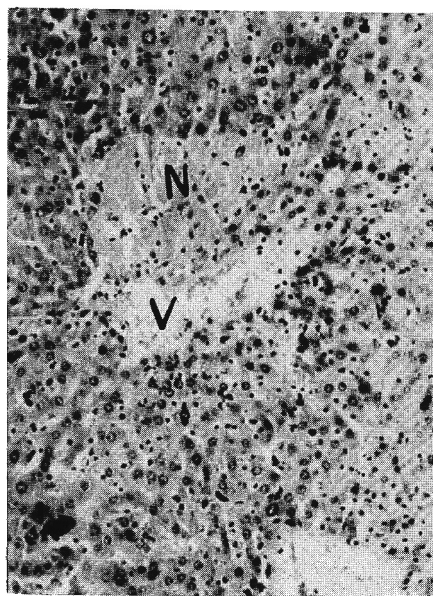


Figure 6. Commencing central venous occlusion (V) and hepatocellular necrosis (N) in rat No. 11. H&E, x 120.

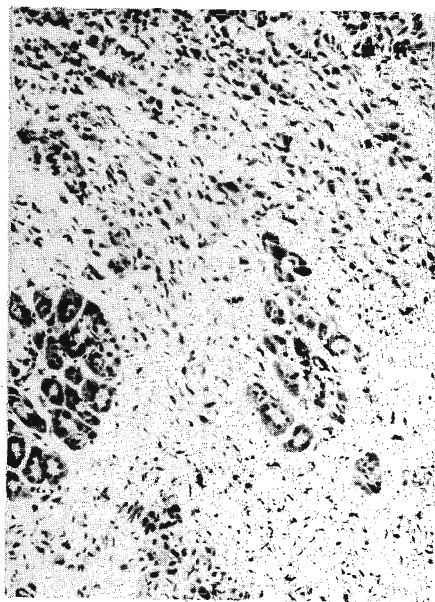


Figure 8. Loss of follicular pattern in spleen in rat No. 10 with 2 intra-abdominal lymphomas. H&E, x 100

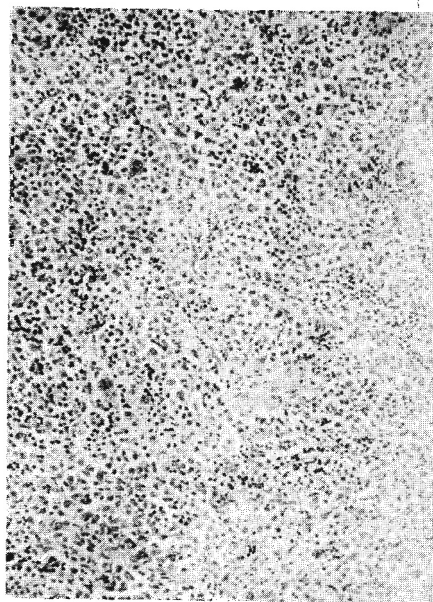


Figure 7. Lymphomatous cell infiltration into pancreas in rat No. 16. H&E, x 650.

The pancreatic tissue was infiltrated by lymphomatous cells in rat No. 6 (Figure 7).

The intra-abdominal tumour in rat No. 13 had a fibroadenomatous structure; proliferating acini, both tubular and solid were scattered in a densely fibrotic mass. The tumour was of uncertain origin although it bore some resemblance to the well differentiated pancreatic adenocarcinoma described and illustrated as 'Figure 5' by Roe and Roberts²¹; no evidence of cell infiltration was noted in our tumour.

Spleen. In rat No. 10, the large 8 cm infected lymphoma was accompanied by a small 1 cm lymphoma in the gastro-splenic omentum, closely attached to the spleen which itself was of normal dimensions. The spleen however showed loss of architecture (Figure 8) in most of its tissue which was replaced by large, poorly differentiated lymphoblastic cells.

Axillary lymphoma. In rat No. 15, the axillary lymphoma had no follicular pattern but consisted of a diffuse mass of mixed-lymphoblastic and lymphocytic-cells in equal proportions.

Bacteriology

Of 7 infected tumours, pus from 5 was available for bacteriological examination. Two yielded no bacterial isolate. Pus from the solitary lymphoma in the neck of rat No. 5, yielded *Klebsiella aerogenes* as did one intra-abdominal lymphoma in rat No. 7. An unidentified *Corynebacterium* species was isolated from one of the mesenteric lymphomas in rat No. 9.

4. Discussion

Spontaneous lymphocytic neoplasms, described as rare in rats³ have been reported in experimental and wild rats and their occurrence is regarded as strain and colony dependent.²⁸ The latter authors reviewing the literature on lymphoid neoplasms in the rat reported that the intra-abdominal location was common with lymphosarcoma in Wistar rats, many of them arising in the ileocaecal mesentery. The histological appearances of lymphocytic lymphomas (lymphosarcomas) in the rat as reviewed by Swaen and van Heerde²⁸ are similar to those in our tumours including the variation in their differentiation from lymphoblastic to lymphocytic with mixed appearances even in the same animal. No splenic tumours were noted in our animals; this compares with reports¹³ that the spleen is not involved in chronic rodent lymphomas in contrast to myeloid leukaemias.

Data on the development of malignant lymphomas in humans and animals, naturally or experimentally, suggests several possible pathogenetic mechanisms for the induction of lymphomas in our rats.

- (i) The predominance of lymphoreticular tumours amongst the mesenchymal neoplasms in immunodeficient hosts^{18,27} led to a modification of the concept of immunosurveillance and its corollary that immunodeficiency predisposes to neoplasia, to regard disordered immunoregulation as the operative mechanism. This view^{20,23} considered that in the presence of partial immune-suppression, persistent antigenic stimulation induces lymphomas *via* viral activation and proliferation of transformed lymphocytes.^{11,24,26} Habeshaw⁹ regarded non-Hodgkin lymphomas as representing abnormal immune responses (see also^{14,25}).

In a brief communication Panabokke and Arseculeratne¹⁶ hypothesised that the lymphomas in palmyrah fed rats and their secondary infection resulted from immunosuppression produced by the toxic constituents of the flour. Arseculeratne *et al.*² reported aberrations of the immune competence of rats, after 7 and 32 weeks of feeding of a 25% palmyrah flour diet. In 7 week fed animals, a depression of humoral and cell mediated immune competence was found; after 32 weeks some rats (Arseculeratne, unpublished data) showed a depression while others showed enhanced humoral and cell mediated responses. Augmentation of humoral responses as found in rats after 32 weeks of palmyrah feeding could conceivably produce antibody or immune complex mediated enhancement of tumours;^{10,27} see also.⁵ This differential response (enhanced humoral or cell mediated reactions or their depression) may explain the development of malignancy in only some of the test animals of the present series.

Swaen and van Heerde²⁸ referred to an association between chronic infections as an initiating event and lymphocytic tumours in rodents. In our rats, the chronic infection *supervened* on advanced tumours and was not a determinant or precedent of the tumours; they were probably opportunistic infections with an immunodepressed state. On the other hand, in relation to a possible source of persistent antigenic stimulation as a synergistic factor with disordered states of immune competence in the development of neoplasia, we can only speculate that the chronic hepatic lesions which we have earlier described in palmyrah fed rats (and which we found in some of the tumour bearing rats of the present series) could have resulted in a diminished capacity of the Kupfer cells to sequester antigens from the intestinal tract or to the release of antigens after liver damage.⁶

- (ii) An alternative hypothesis for the origin of our lymphomas is the activation of latent endogenous viruses by the chemical constituents of the flour as has been suggested of some chemical leukemogens.¹³ Gardner *et al*⁷ described a C-type virus disease in wild mice, which bears some resemblance to that in our rats - the predominance of malignant lymphomas, the development of fibrosarcoma, hind limb paralysis and spinal cord degeneration. The acute neurotoxic effects produced by palmyrah flour are attributable to its neurotoxin.⁸ Although the chronic neurotoxic effects, if any, of this neurotoxin are as yet unknown, it is possible that the hind limb paralysis in addition to the tumours were a part of the disease induced by C-type viruses. Dr. Huebner commented on the absence of ultrastructural evidence of C-type viruses in the thymic lymphoma of rat No. 12 as follows: "The absence of rat Type-C virus is not unusual in carcinogen induced cancers. The rat virus is expressed after 15 or 20 subtransplants into new syngeneic hosts. When cultured *in vitro* the rat virus may appear in the cells after 20 or more subcultures."

The development of lymphomas in the progeny of our palmyrah fed females, is consistent with reports of vertical transmission of murine leukemogenic viruses¹³, either through gonadal tissue or milk.

- (iii) It has also been suggested that chromosomal damage may be an alternative mechanism for the induction of neoplasms by chemical agents.¹⁷ The immunosuppressive agents azothiaprime and 6-mercaptopurine which increase host susceptibility to neoplasia are also known to cause chromosomal damage. In view of the clastogenic effect of palmyrah extracts on human lymphocytes,¹² this mechanism would also remain a possibility in our flour induced tumours.

While it is difficult to identify one mechanism as the basis of the pathogenesis of our lymphomas, it is perhaps more likely that several factors such as aberrations of immune competence, the activation of C-type viruses and clastogenic activity were synergistically involved.

Of what significance are our findings to the human situation? It is in the Northern Province of Sri Lanka that this palm is most extensively grown and its flour consumed. From a study of the geographic pathology of malignant disease during a 5-year period (1973-1977) in Sri Lanka, Panabokke (1980 - unpublished data) found the incidence of malignant lymphomas in the 9 provinces of this country, as shown in Table II. Excluding the data from the Western Province which has the country's

only cancer hospital- data from which may therefore be biased- it appears that the incidence of malignant lymphomas in the Northern Province is approximately 4 times higher than the mean incidence in the 7 other provinces. The natural environmental radiation levels in the Northern Province are not higher than in the rest of the country and the possibility remains to be investigated that the relatively higher incidence of malignant lymphomas in this province is aetiologically related to the high consumption of palmyrah flour, a situation which parallels that in our experimental rats. Plouffe *et al*¹⁹ reported immune suppressive effects of a lectin from the navy bean and noted a clustering of cases of Hodgkin's lymphomas in humans living in the vicinity of a navy bean processing mill.

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