INTERNAL BONE SEEKING RADIONUCLIDES AND MONOCYTE COUNTS

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ABSTRACT

Statistically significant monocyte depression is reported in four populations with internal exposure to bone-seeking radionuclides (uranium, radium, thorium, lead 210, strontium 90 and plutonium) at relatively low dose levels. Both the proportion of the population with monocytopenia and the severity of the depression appear dose related. The purpose of this paper is to alert others to the effect and solicit their experience and interpretation. It is important to extend these observations on monocyte counts to other communities exposed to bone-seeking radionuclides, for example in uranium mining areas, areas near nuclear reprocessing plants and communities in the Arctic exposed to Chernobyl and weapon testing fallout. Persons exhibiting monocytopenia need to be medically observed until cellular immunity is restored since their ability to resist or survive diseases such as tuberculosis or meningitis appear impaired.

INTRODUCTION

A normal healthy community has an average count of 350 to 400 monocytes per cubic millimetre of blood. Homeostatic controls maintain the count for the individual between 200 and 800 M per cubic millimeter (1).

Monocytes are now thought to originate in bone marrow. Their transit time there is only 2.5 to 5 days. About four hundred million monocytes are delivered to the blood daily and about half migrate from the blood to tissue every 70 hours. The life span of monocytes in tissue is several months. Monocytes are able to divide outside of the bone marrow, have a phagocytic function, participate in delayed hypersensitivity and in viral immunity.

> "The monocyte-macrophage may be regarded as a cellular mediator in the hemopoietic system, interacting with kinin, complement and clotting systems, and modulating production and destruction of red cells, granylocytes, lymphocytes and bone. It also influences the central nervous system through endotoxin-mediated pyrogens. The complexity of its functions approaches that of the hepatocyte." (2)

It is also known that monocytes are required to process and present antigen to T and B lymphocytes, which in turn are stimulated to proliferate and differentiate into mature plasma cells that secrete specific antibodies. In particular, T lymphocytes mature into the helper/inducer T subsets and the suppressor cytotoxic T cells needed for effective immune response. A defect in any of these cell interactions results in alteration in immunoreactivity. While current research has focused on T and B lymphocyte response to radiation, there has been little research into monocyte response. Medical literature on hemotological response to radiation therapy and military radiobiological discussions deal with monocytopenia together with general reduction in number of all leukocytes. However these experiences are at relatively high dose levels.

In older texts the term "reticuloendothelial system" (RES) was used to describe the phagocytic system of the body thought to originate in the connective tissue. The more recent term for the phagocytic system is "monocyte-macrophage system" (MMS) reflecting the finding that the principal macrophage cells originate in bone marrow. This MMS has a capacity for rapid killing and destruction of bacteria and for "indefinite storage of particles such as silica, carbon and thorium dioxide" (3)

An increased monocyte count may indicate bacterial infection, protozoal infection, virus infection, malignant conditions, collagen diseases, chronic ulcerative colitis or regional enteritis. Monocytosis has been traditionally one of the diagnostic signs of tuberculosis. Some authors consider an absolute increase of monocytes to more than 500 per mm^3 as a monocytosis indicative of occult disease. Others use a cut off of 800 M per mm^3. The clinical significance of decreased monocyte count is unknown. However it has been observed in patients with disorders causing marrow replacement or marrow aplasia, and after radiation therapy or radiomimetic drugs.

Further insight into the role of monocytes comes from studies of the role of neuropeptides, produced by nerve cells in the brain, and their receptors. These neuropeptides include natural analogs of psychoactive drugs and even hormones, such as insulin, and the chemical substance angiotensin, which mediates thirst. According to researcher Candace B. Pert: "The new discovery I want to

emphasize here is that every neuropeptide receptor that we have looked for is also on human monocytes."(4) Absense or depletion of monocytes may have far reaching unexpected results on a human organism.

Case 1: MCCLURE CRESCENT

A residential area within Scarborough, a suburb of Toronto, Canada, was contaminated with radium and its decay products. Contamination was about one-tenth as concentrated as one would expect to find in uranium mine tailings, but two to three times higher than normal North American backyard soil. According to an engineering firm hired by the Canadian Atomic Energy Control Board, there was one "hot spot" where a radium source was buried, several pieces of property with other buried radioactive debris and other property either uncontaminated or having minor surface contamination. The government's estimate of radiation exposure to the average resident was 200 to 300 millirem (2 to 3 mSv) per year.

Fifty-eight children (15 years of age or under) were given three sequential complete blood counts (CBC) and differential testing in the course of a month. Thirty-six (62.1%) had at least one monocyte count less than 200 M/mm^3. All tests were conducted by the same laboratory, with one supervisor to assure uniformity. The children were examined for fever or sore throat, and eliminated if symptomatic. Age, sex and race were recorded for controlled

analysis. Blood tests were all conducted by the MDS Laboratory, which had no knowledge of the exposure status of the residents.

Those children living on property identified as having radioactive debris actually buried on it were classified as having high exposure. Those children living on property with no radioactive debris or only surface contamination were classified as low exposure. Children's high mobility in the neighbourhood argues against a "no exposure" category. Unfortunately the most popular spot for children to play in the neighbourhood was the backyard with the radioactive hot spot.

There were 34 children living on property with buried radioactive debris and 24 with no detectable or only surface detectable debris.

[INSERT GRAPH 1]

The background line in Graph 1 shows an expected frequency distribution for monocyte counts in a randomly selected normal population. No more than 10% of such a population would be expected to be below 200 M or above 800 M per cubic millimeter of blood due to chance. Stated in another way, 90% of a population would be expected to have a monocyte count between 200 and 800 M per cubic millimeter of blood. Since our population was selected for good health, we expected less than 5% to have a monocyte count below 200.

In contrast, 38.6% of the tests of higher exposure children, and 18.8% of the tests of lower exposure children, were found with monocyte counts below 200 per cubic millimetre of blood.

The tabulated results underlying Graph 1 are as follows:

	Higher Exposure	Lower Exposure
# of Children:	34	24
# with at least 1 low M count	26 (76.5%)	10 (41.7%)
# with at least 2 low M counts	11 (32.4%)	2 (8.3%)
# with 3 low M counts:	2 (5.9%)	None
# with a zero M count:	8 (23.5%)	None
Total # of observations:	101	64
Observations with low M count:	39 (38.6%)	12 (18.8%)

In addition sixty-one adults were tested three consecutive times within a month's time. Each was screened for infectious disease. Age, sex and race were controlled in the analysis. The abnormal monocyte counts for those with higher and lower residential contamination against a background of normal are given in Graph 2.

A summary of the findings indicates:

	Higher Exposure	Lower Exposure
# of Adults	30	31
# with at least 1 low M count	16 (53.3%)	11(35.5%)
# with at least 2 low M counts	7 (23.3%)	1(3.2%)
# with 3 low M counts:	None	None
# with a zero M count:	2 (6.7%)	None
Total # of observations	84	78
Observations with low M count:	23 (27.4%)	12(15.4%)

Further examination of this data, this time using three exposure groups was undertaken. Those whose property had no elevated radiation measurements were designated "low exposure"; those with surface radioactive debris on their property were designated "medium exposure"; and those with both surface and buried radioactive debris were designated "high exposure". We found the following age adjusted average blood counts in these groups:

Mean Age Adjusted Blood Counts

Exposure Group	No. of Persons	All White Cells	Monocytes
Low	22	7465	381.1
Medium	32	6791	352.9
High	65	6571	305.5

A statistical test of trend was conducted using these three exposure categories. The F test of linear trend with exposure yielded the following results:

All subjects combined (Age Adjusted):

All White Blood Cells: F = 4.82 (Prob: 0.02)

Monocytes: F= 6.39 (Prob: 0.006)

It is possible to reject the hypothesis that there is no trend toward lower WBC with increasing chronic low dose radiation exposure at a 5% level of statistical signigicance. The hypothesis of no trend for monocyte levels can be rejected at a 1% level of statistical significance.

Even with this small sample size there is a statistically significant trend toward lower total white blood count and monocyte count with radiation exposure within currently permissible ionizing radiation exposure levels (0.5 rem or 5 mSv per year).

One child living on residential property with buried radioactive debris died of meningitis at age 16. He was 11 years old at the time of this study and had abnormal blood parameters. Unfortunately neither health authorities nor the family physician followed up on our findings and this child had no medical examination between age 11 and the terminal illness five years later.

Case 2: MALAYSIAN CHILDREN

Sixty children in 1987 and forty-four children in 1988, with suspected exposure to thorium hydroxide and lead sulfate waste from the Asian Rare Earth Company (A.R.E.) in Bukit Merah, Malaysia, were given CBC with differential and blood lead testing. The CBC's were conducted in a uniform way by the Clinostic Laboratory in Ipoh, Malaysia and venous blood lead levels were done in a uniform way at Chemlab, in Selangor, Malaysia. There was one supervisor at each laboratory to assure the quality of results.

The A.R.E. plant had been closed by court order in 1985 and ordered to construct a temporary storage building. Construction was completed and A.R.E. resumed operation in early 1987. The children tested in June 1987 were exposed to about 4 months of continuous plant operation. Those tested in June 1988 were exposed to about 16 months of continuous plant operation after resumption. In addition to its radioactive liquid and solid waste products, the

plant emits two radioactive gases, radon and thoron. Monocyte count for the 1987 and 1988 testing are presented as frequency distributions in Graph 3 against an expected normal background distribution.

[INSERT GRAPH 3]

There is an obvious shift toward lower monocyte counts with more prolonged exposure. In addition to the 93 Bukit Merah children tested, 171 Malaysian children from Carey Island of comparable socio-economic status were tested. These children were found to have lower nutritional status than the Bukit Merah children but better health as measured by blood tests and physical examination. While 39% of the Bukit Merah children suffered from a triad of mild lymphadenopathy, congested turbinates and recurrent rhinitis, less than 4% of the Carey Island children presented with these problems. The Carey Island children were exposed to chemical effluence from a palm oil plant, pesticides and herbicides, but to our knowledge, not radioactive wastes. Monocyte counts for the Carey Island children relative to the Bukit Merah children are presented in Graph 4.

[INSERT GRAPH 4]

Only children from Bukit Merah and Carey Island in a relatively healthy state, i.e. active and apparently normal, were included in

the study. All medical testing was under the supervision of Dr. T. Jayabalan, a licensed Malaysian physician.

Findings with respect to the children's monocyte counts were as follows:

Characteristic	Carey Island	Bukit Merah	
	1987	1987	1988
# of children	(171)	(60)	(44)
M < 100 per mm^3	0 (0%)	6 (10.0%)	13 (29.5%)
M < 200 per mm^3	19 (11.1%)	29 (43.9%)	25 (56.8%)
Average blood lead level	N.A.	12 μg/dl	27 μg/dl

Because of the possibility of lead toxicity from the A.R.E. waste, since lead sulfate and thorium hydroxide wastes are combined, Bukit Merah children whose parents worked in gasoline stations, or as plumbers, battery workers or paint factory workers had been excluded from the monocyte study. Lead is known to affect white blood count, and we were not sure whether or not it would affect monocytes.

Since we had excluded known parental exposure to lead, and since there was no obvious change in automobile traffic, use of canned food or oil based paints between 1987 and 1988, we were able to conclude that the 1988 increase in lead reflected the increased production at the ARE plant. Since the lead sulfate waste reached the children, we assumed the thorium hydroxide waste also reached them.

Because of expense, it was not possible to conduct venous blood lead level testing on the Carey Island children. Malaysian physicians are now routinely testing for blood lead in children to provide a Malaysian base-line.

To see whether the blood lead level in the Bukit Merah children was related to depression of the bone marrow and monocyte count, a subset of eleven children tested both in June 1987 and June 1988 was examined. There is no indication that increase in blood lead level corresponds with a decrease in monocyte count. Table 1 gives the findings for the self-matched sample.

[INSERT TABLE 1]

Of the eleven children, one child had the same blood lead level in 1988 as in 1987, but the monocyte level increased. Of the five children who experienced an increase in blood lead level, three experienced an increase in monocyte count and two experienced a decrease. Of the five children with decreased blood lead level, four experienced decreased and one increased monocyte counts.

Parents whose children had depressed monocytes in the 1987 testing were advised to send them away from Bukit Merah on weekends and school holidays. In the 1988 testing there were

33 "new" children, i.e. they were not tested in 1987. These children were not advised to spend time away from Bukit Merah, although some parents may have adopted this as a precautionary measure because of their neighbours. This may account for the bimodal nature of the Bukit Merah 1988 frequency function.

Case 3: ASIAN RARE EARTH WORKERS

Adult male workers at the A.R.E. company were given CBC's by the company physician. The biological laboratory used for this testing was not identified by the A.R.E. company. Full blood counts for forty-three workers were released for outside inspection. Each of the 43 A.R.E. workers had blood tests in 1986 and in 1987. Their year of first employment was given. Twenty-five were hired between 1980 and 1984; eighteen in 1985 or 1986. Of the twenty-five who had worked three and a half or more years at A.R.E., fourteen (56%) had one or more abnormal monocyte counts (one had both an abnormally high and an abnormally low count in successive years). Of the eighteen who worked between one and a half and three and a half years, fourteen (77.8%) had at least one abnormal monocyte count. Five (20%) of those who worked three and a half or more years had two abnormal monocyte counts (1986 and 1987), while only one (5.6%) of those hired since 1985 had two abnormal counts. Graph 5 gives the abnormal monocyte count distribution for A.R.E. workers.

[INSERT GRAPH 5]

It is to be noted that unlike the McClure Crescent adult males who left the contaminated property daily to go to work in a relatively uncontaminated environment, these men worked with the bone-seeking radionuclides. There is a large turn-over of workers at A.R.E. and self-selection out of the industry is a possible mechanism for those who experience ill health. The selection of only two-thirds of the workers may also be skewing the results. No job descriptions were given, and years of employment may not be a good indicator of exposure level. Workplace monitoring was not done and film badges were not worn during these two employment periods.

A follow-up of the Malaysian workers and children was undertaken. It became apparent in early 1989 that the community around the A.R.E. plant was experiencing even more severe haematological problems. Two children ages 5 and 11 were diagnosed with acute leukemia, both were born in Bukit Merah. A 19 year old man, born in Bukit Merah and a life-long resident was also diagnosed with acute leukemia. This young man worked in a cottage industry located near the plant. A two-year-old child living within the 10 km radius of the plant died of septicemia and a 22 year old A.R.E. worker died with a diagnosis of meningoencephalitis. In neither of the last two cases was a bone marrow test undertaken. On admission to the

hospital, the worker's blood count was abnormally low in view of his overwhelming infection, 6600 white cells per cubic millimetre of blood. His monocyte count is not known.

According to the official 1986 Malaysian statistics, leukemia of all types and for all ages occurs at a rate of 0.83 per 10^5 persons per year in peninsular Malaysia. About 23% are in those under 20 years of age, giving a rate of about 0.19 per 10^5 persons. For Bukit Merah, with a population of approximately 15,000, one would expect 0.03 cases a year. This means a case roughly every 30 years. Three cases diagnosed within six months is highly significant with the probability that it happened by chance equal to 0.00003 (3 chances in 100,000).

Case 4: **RONGELAP CONTROL POPULATION**

After a nuclear test of a 15 megaton hydrogen bomb at Bikini Atoll on March 1, 1954, there was serious nuclear fallout on Rongelap Atoll, an inhabited downwind group of islands. With U.S. Congressional funding, the Brookhaven National Laboratory on Long Island undertook medical follow-up of the Rongelap people who were on the atoll at the time of the fallout. Brookhaven scientists also chose an age-matched group of Rongelapese not on the atoll at the time of the fallout to use as a comparison population. This second group is called the

"unexposed" control population. Their exposure to the nuclear fallout was undoubtedly less than that of the group on Rongelap Atoll. However, it has never been established that this population had "no exposure" to the fall-out. In all, 66 atmospheric tests were conducted in the Marshall Islands between 1946 and 1958.

There were 134 people in the "unexposed" control group, who returned to the contaminated Rongelap Atoll in 1957 with the returning "exposed" Rongelapese. The yearly CBC and differentials for "unexposed" (five tests each) for 1957 to 1966 were released by Brookhaven to IICPH in February 1988. Brookhaven has refused to release the blood test results for the "exposed" population.

The average monocyte count for this control population was 169/mm^3, below the 200 M/mm^3 considered the lower limit of normal. By 1962 to 1966, the number of "unexposed" living on Rongelap had increased to 158, and their average monocyte count increased to 200 M/mm^3, meaning a substantial fraction were still below normal. All laboratory tests were conducted by the Brookhaven National Laboratory (BNL).

In 1982-1986, 69 "unexposed" persons were living on the Atoll, and their monocyte count average, according to BNL, had risen to 328 M/mm^3.

There is no reason to believe the Rongelap people have abnormal monocyte counts due to heredity. Because of weathering and increased reliance on food imported from North America, residual nuclear radiation exposure to the Rongelapese has gradually declined since 1957. This is the presumed explanation of the return to more normal monocyte counts in the 1982-1986 period. Comparison of the "exposed" Rongelapese with the Brookhaven "unexposed" has been important for decisions on compensation. It appears justified on the basis of this analysis to consider this control population exposed to radiation, albeit at a lower dose level than those Rongelapese in the direct fallout.

Out of 76 "unexposed" Rongelapese tested between 1957 and 1961, sixty (78.9%) had one or more monocyte counts below 200 M per cubic millimetre of blood. In 1982-1986, fifty (57.0%) out of eighty-nine "unexposed" had counts below 200 M. In the 1957-1961 period twenty (26.3%) had at least one zero monocyte count, and in the 1982-1986 period eight (9.0%) had at least one zero monocyte count. Graph 6 gives the frequency distributions for monocyte counts of Rongelapese children and adults in the 1957-1961 period.

[INSERT GRAPH 6]

The Brookhaven research team added to the "unexposed" control population over the years as some Rongelapese were lost to

follow-up. The Brookhaven "unexposed", all adults in 1982-86, had a more normal monocyte distribution.

[INSERT GRAPH 7]

We found fifty-eight persons with medical records in both the 1957-61 and 1982-86 time periods, with one or more low monocyte counts in the early period and no other blood abnormality. Of these 58 Rongelapese with monocytopenia in 1957-1961, we found in 1982-1986:

8 (13.7%) had normal blood parameters
39 (67.2%) still had monocytopenia
8 (13.8%) had monocytosis
3 (5.2%) had normal monocyte counts but other abnormal blood parameters

The same 58 individuals who had normal blood counts except for monocytopenia in 1957-61, were examined for subsequent neutropenia and lymphopenia.

In 1982-1986 we found:

7 (12.1%) with neutropenia
4 (6.9%) with lymphopenia
3 (5.2%) with both neutropenia and lymphopenia

One of the individuals had a total white count of 1800 cells per cubic millimetre (310 N, 1390 L, 0 M, and 500 E).

FURTHER RESEARCH NEEDED

Sensitive immunological testing of children with monocytopenia is now being undertaken in an attempt to elucidate the biological mechanism of cellular immune depression with radiation exposure. Implications of monocytopenia for diseases involving neuro-transmitters may also prove important.

Monocytopenia in other radiation exposure populations, especially those exposed to particulate bone-seeking radionuclides, should be examined.

ACKNOWLEDGEMENTS

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2. Ibid. p. 249.

3. **Hematology**, edited by William S. Bede, MIT Press 1985, p.27.

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TABLE I

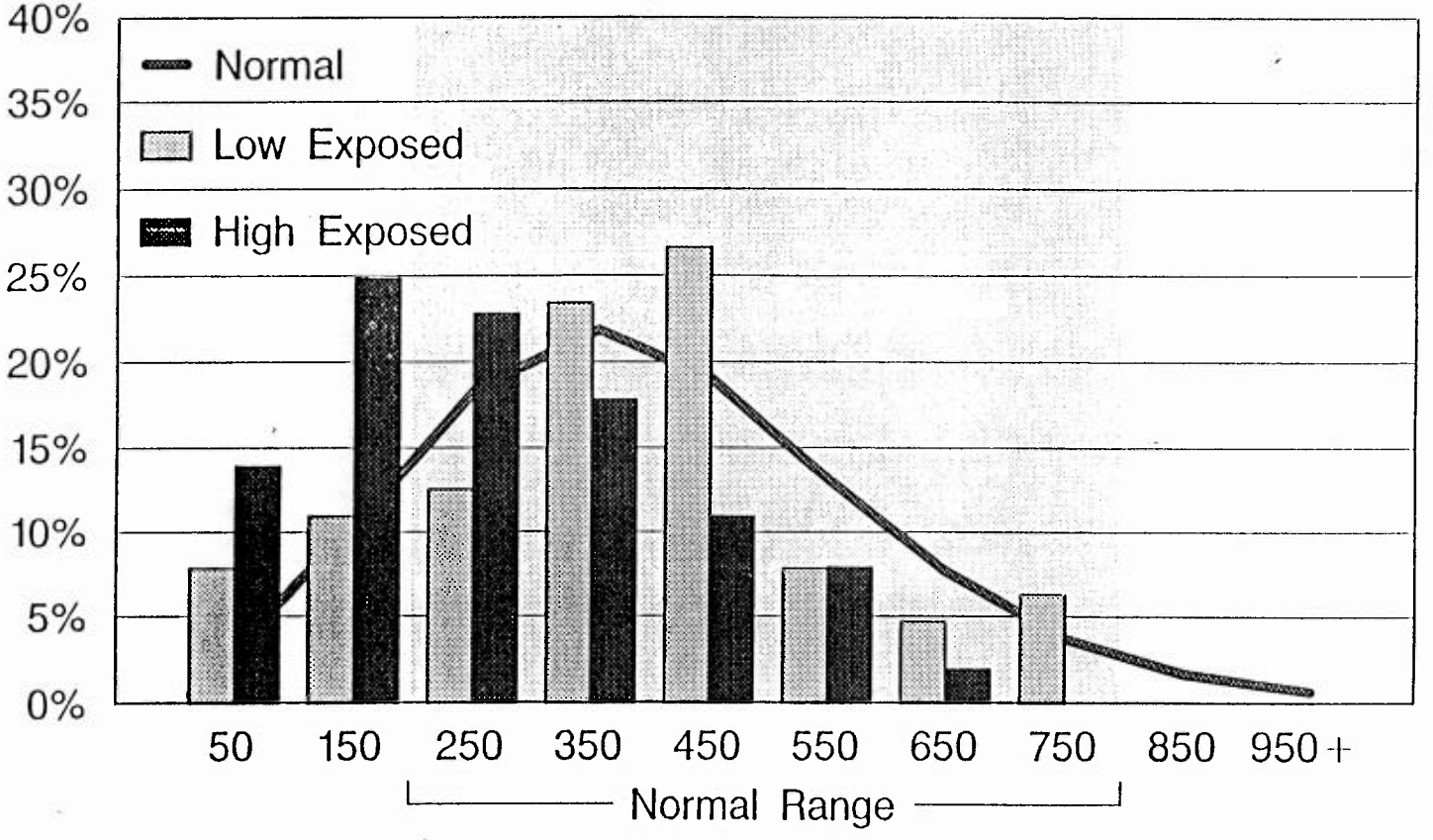
Repeat Tests for 11 Children from Bukit Merah

June 1987 and June 1988

Age	Monocyte Counts M per cubic millimetre		Blood Lead Micrograms/decilitre	
	1987	1988	1987	1988
8 yrs	240	86(-)	12	14(+)
9 yrs	80	180(+)	18	11(-)
10 yrs	273	158(-)	18	12(-)
5 yrs.	376	188(-)	24	9(-)
8 yrs	136	85(-)	12	11(-)
12 yrs	83	170(+)	9	12(+)
11 yrs	166	230(+)	7	13(+)
10 yrs	73	142(+)	11	11(0)
11 yrs	225	43(-)	9	25(+)
9 yrs	224	246(+)	10	22(+)
10 yrs	308	240(-)	15	14(-)
Total	2184	1768	145	154
Average	198	161	13.2	14

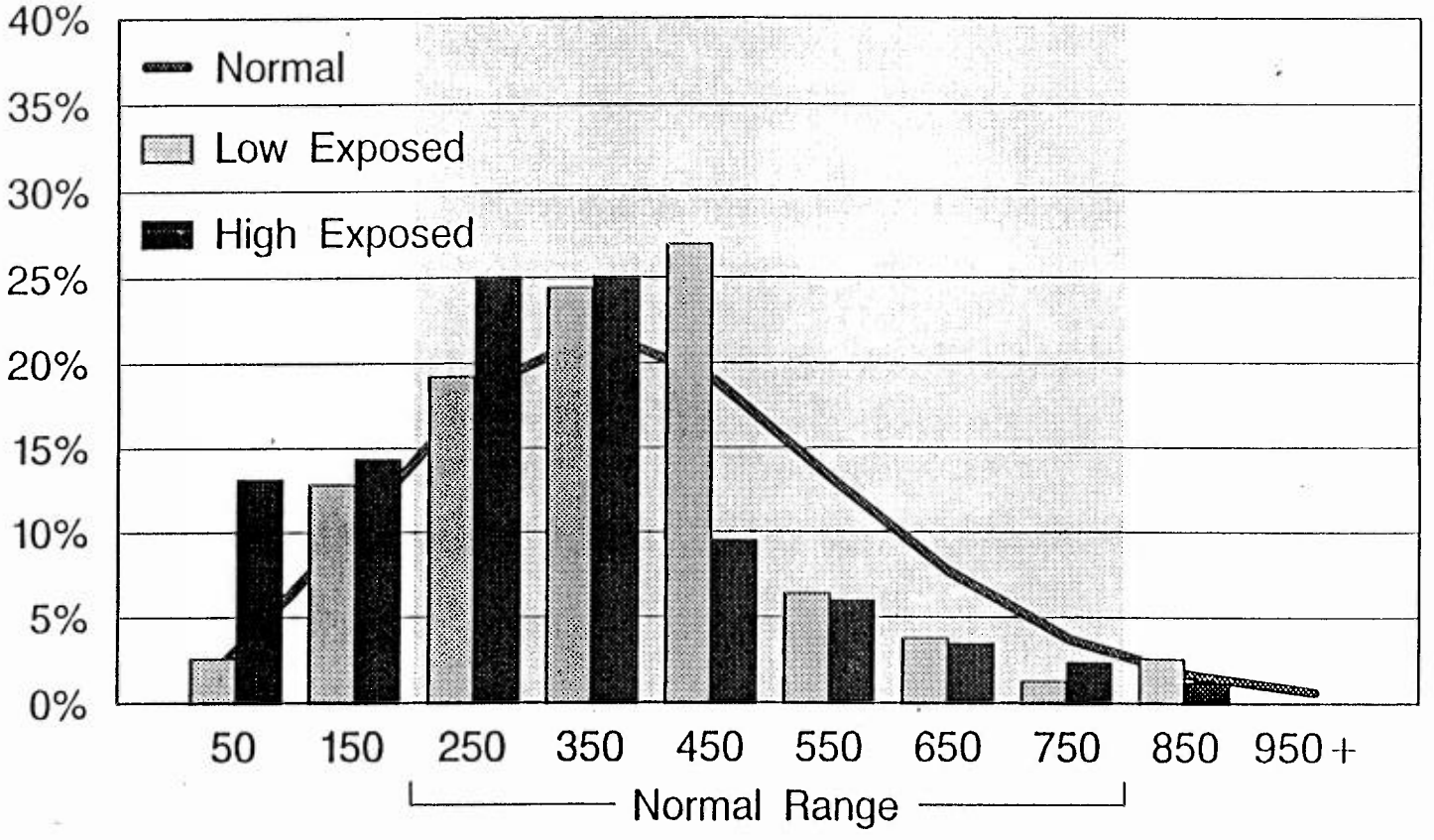
McCLURE CRESCENT
EXPOSURE OF CHILDREN

% Population with Monocytes per cc. Blood



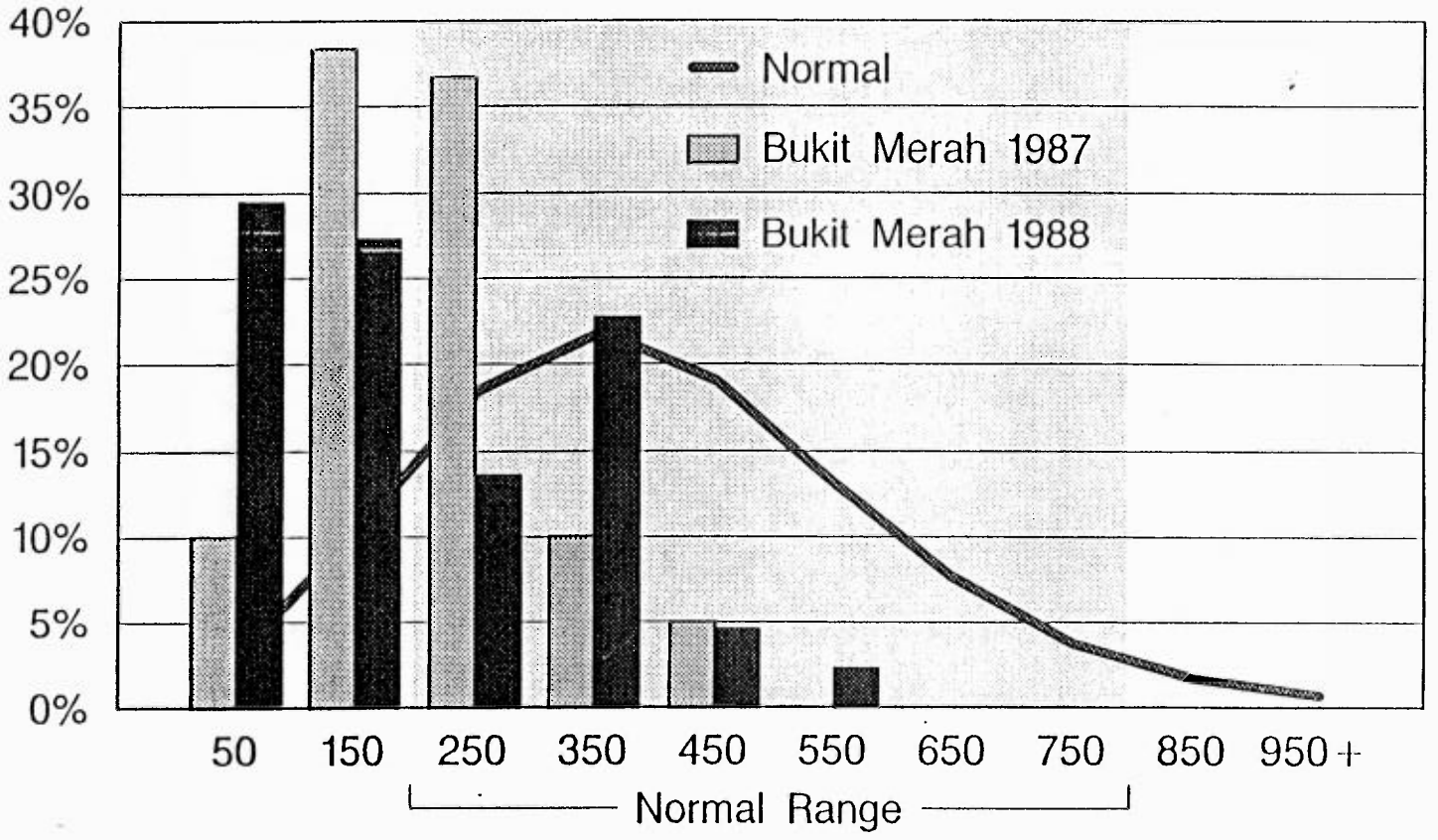
McCLURE CRESCENT
EXPOSURE OF ADULTS

% Population with Monocytes per cc. Blood



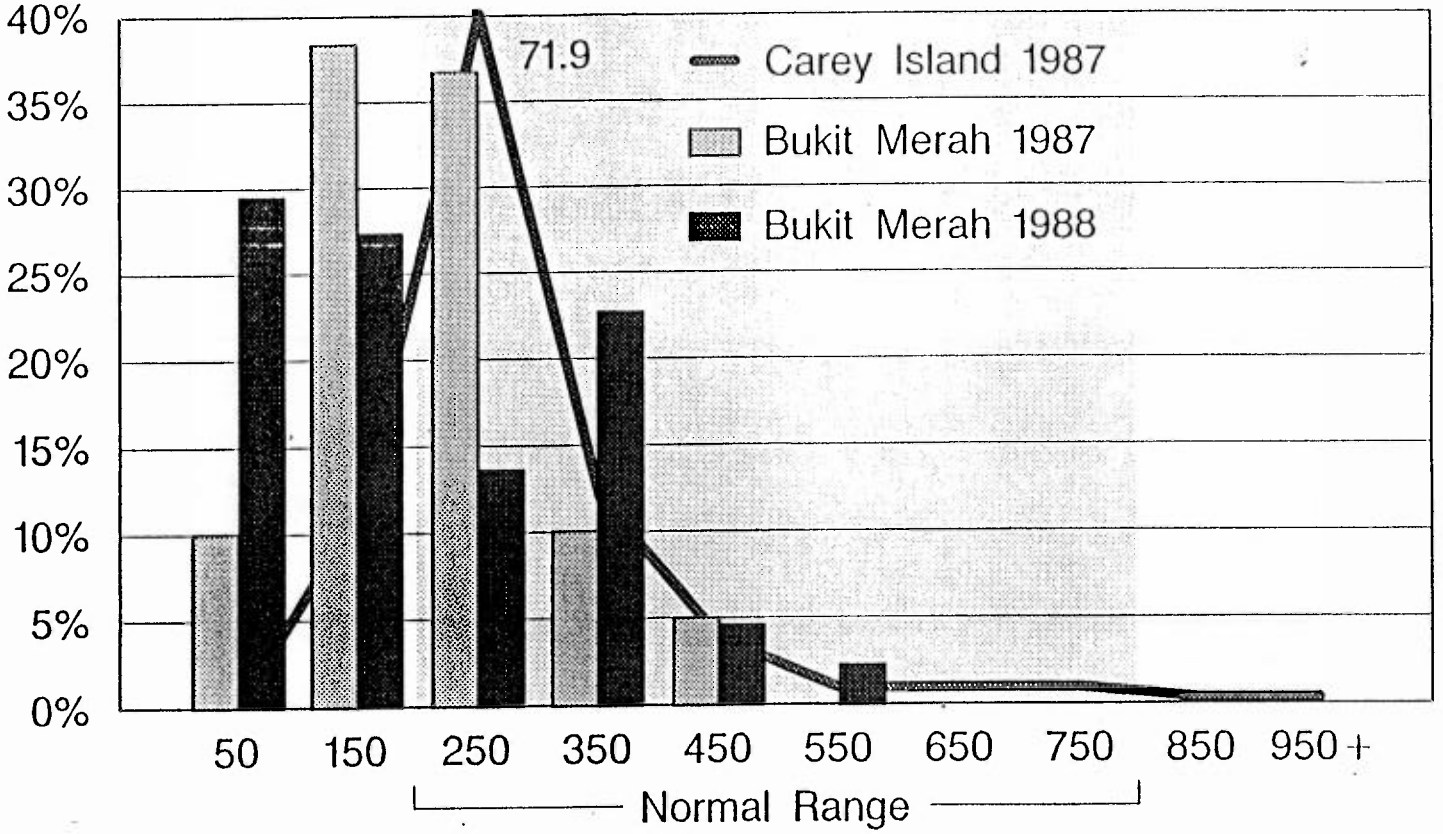
MALAYSIA
EXPOSURE OF CHILDREN

% Population with Monocytes per cc. Blood



MALAYSIA
EXPOSURE OF CHILDREN

% Population with Monocytes per cc. Blood



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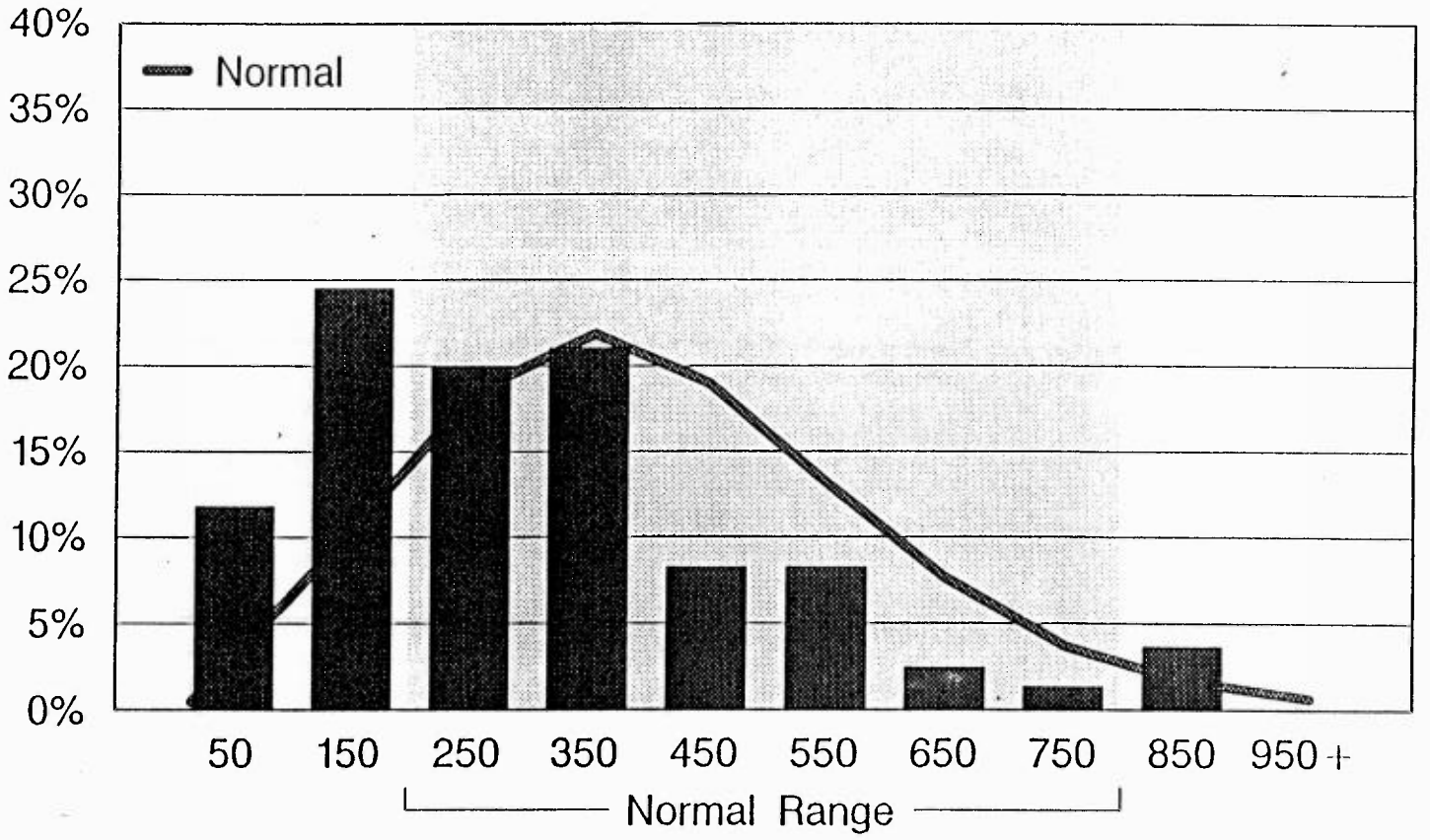
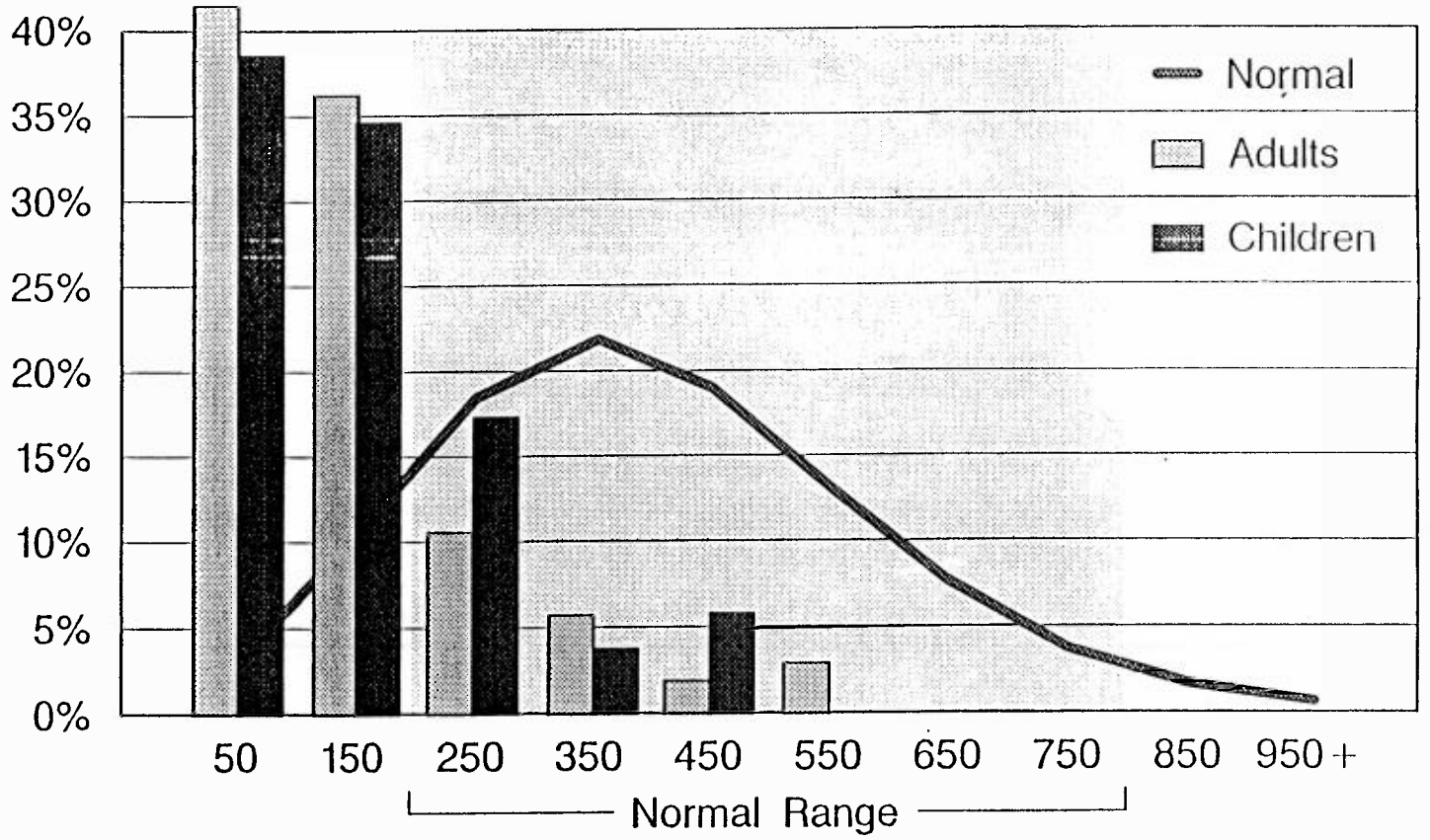
MALAYSIAN
RARE EARTH WORKERS 1986-87

% Population with Monocytes per cc. Blood



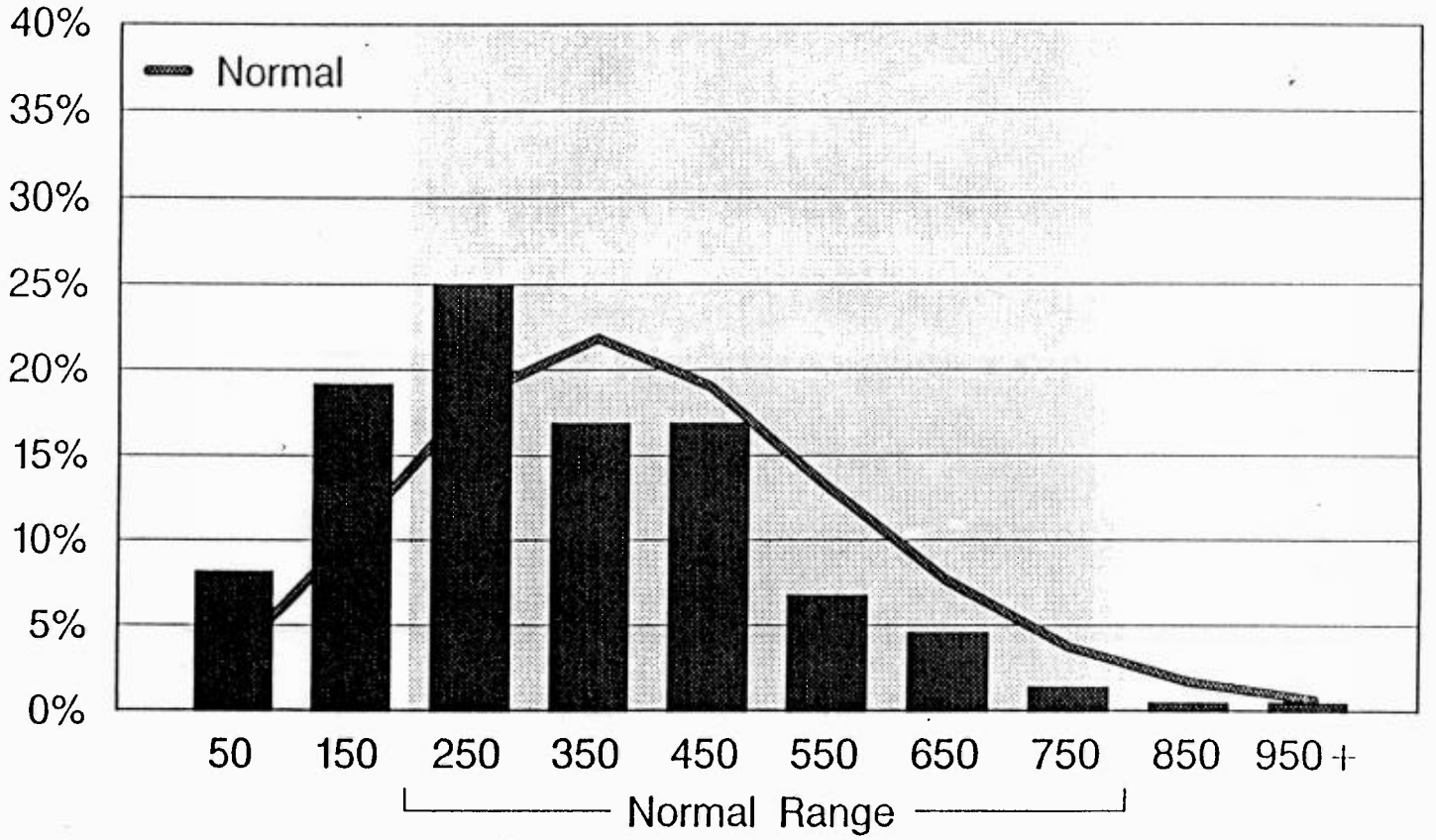
MARSHALL ISLANDS
EXPOSURE OF POPULATION 1957-61

% Population with Monocytes per cc. Blood



MARSHALL ISLANDS
EXPOSURE OF ADULTS 1982-86

% Population with Monocytes per cc. Blood



7