REPORT TO DR. J. TUINMAN, VICE-PRESIDENT (ACADEMIC),

INTO ALLEGATIONS OF SCIENTIFIC FRAUD

AGAINST DR. R.K. CHANDRA

by the

COMMITTEE OF INVESTIGATION

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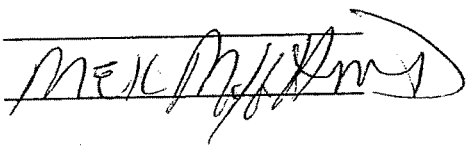
M. MOFFATT 

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TABLE OF CONTENTS

A. INTRODUCTION AND CONTEXT

The Committee of Investigation was established by Dr. J. Tuinman in April 1994 to investigate allegations of research fraud against Dr. R.K. Chandra. Such a (further) investigation was recommended by the Panel of Inquiry, consisting of Drs. J.T. Brosnan and W.L. Andrews, who first looked into the matter and reported on March 25, 1994 (Appendix 1). The allegations were made to the President of Memorial University (Dr. A. May) in January, 1994, by Dr. A.J. Davis (Professor and Chairman, Discipline of Pediatrics, Faculty of Medicine, Memorial University of Newfoundland) and involved:

1. The publication of an article (Annals of Allergy 63, 102 (1989) where Dr. Chandra claims to have recruited 72 infants into each of four groups, specifically one being for whey hydrolysate formula (NAN/HA). It is alleged that only 17 infants were enrolled in this group for study.
2. A three-year follow-up study of these infants was published in abstract form (J. Clinical Nutrition 56, 758 (1992)) but allegedly was never carried out. A similar claim is made with respect to a five-year follow-up and report.

The guidelines and procedures used in this investigation were those proposed in the "Framework for Institutional Policies and Procedures to Deal with Fraud in Research" as originally published on November 4, 1988, and re-issued on November 10, 1989 by the Association of American Universities, National Association of State Universities and Land-Grant Colleges and the Council of Graduate Schools and "Beyond the 'Framework': Institutional Considerations in Managing Allegations of Misconduct in Research" as adopted by the Executive Council of the Association of American Medical Colleges on September 24, 1992. The Committee wishes to emphasize that the fundamental principle of the investigation was to assure fairness. Every opportunity was provided to Dr. Chandra to respond to the allegations made and to provide the Committee with information or any new evidence needed to arrive at a just conclusion.

From the start of this investigation it was clear that the task would be difficult. This was for several reasons. First, the Committee's mandate was to investigate the "factual matters" of the case as outlined in the above mentioned Framework. The normal process of an investigation is to collect and examine "raw research materials and records", receive and document "testimony from all relevant sources", draw conclusions and prepare a report. In the present investigation the factual matters were difficult to assess because the essential raw materials, in this case the research files, were unavailable. Second, Dr. Chandra is a very highly regarded scientist with a strong international reputation, who has

received many awards and honours including the Order of Canada. It was, therefore, important to keep the investigation as confidential as possible, so as not to adversely damage Dr. Chandra's reputation, yet at the same time be sufficiently zealous to obtain adequate information to reach accurate conclusions. The Committee also recognized that a finding of misconduct could have wider implications for the scientific community at Memorial University and elsewhere. Third, in view of the guiding principle of fairness, it was a concern to the Committee that all necessary information may not have been provided by the respondent in a timely manner. Fourth, there was a great deal of confusion among those interviewed and who had worked with Dr. Chandra as to exactly which studies were going on in the relevant time period, who was involved with each study and the timing of each. Similar circumstances exist for the Mead Johnson files. Even Mrs. Harvey (Dr. Chandra's Head Nurse, who effectively initiated the allegation) and Dr. G. Singh (co-author on the Annals of Allergy paper in question) were not quite aware of the actual situation until after the allegations were made. It appears that there were at least three allergy-related infant formula studies in the time-frame (1987-88) in question:

1. the Mead Johnson (Bristol Myers) study, involving 221 infants, published as "Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants" by

R.K. Chandra, S. Puri and A. Hamed in the British Medical Journal 299, 228-230 (1989) with acknowledgements to M. Harvey, G. Woodford and D. Bryant;

2. the Carnation (Nestle) study, involving 288 infants, published as "Effect of feeding whey hydrolysate, soy and conventional cow milk formulas on incidence of atopic disease in high risk infants" by Dr. R.K. Chandra, G. Singh and B. Shridhara, in Annals of Allergy 63, 102-106 (1989) with acknowledgements to A. Hamed, M. Harvey, G. Woodford and D. Bryant; "Cumulative incidence of atopic disorders in high risk infants fed whey hydrolysate, soy, and conventional cow milk formulas" by R.K. Chandra and A. Hamed in Annals of Allergy 67, 129-132 (1991) with acknowledgements to D. Bryant; and "Cumulative incidence of allergic disorders in high risk infants fed whey hydrolysate, soy and conventional cow's milk formulas" by R.K. Chandra, A. Hamed, C. Prasad and G.K. Singh, which is an abstract in Journal of Clinical Nutrition 56, 758 (1992); and

3. the Ross study with 262 infants and is not published

Other papers and studies also relevant to this investigation and report are: "Influence of maternal food antigen avoidance during pregnancy and lactation on incidence of atopic eczema in

infants" by R.K. Chandra, S. Puri, C. Suraiya and P.S. Cheema in Clinical Allergy 16, 563-569 (1986) with acknowledgements to G. Woodford, B. Au and T. Lundin; and "Growth comparison of breast-fed and formula-fed infants" by A.F. Roche, S. Guo, R.M. Siervogel, H.J. Khamis and R.K. Chandra in Canadian Journal of Public Health, 84, 132-135 (1993). All of the above publications have been placed in Appendix 2.

In the allegations it appears to be assumed that the publication in question involving the Carnation study was actually based on the Ross study data. Consequently it was necessary to look at all of the above studies.

It should be emphasized that most of the focus of the investigation was on the Carnation study. This study was an assessment of the effect of feeding different infant formulas on incidence of atopic disease in a double-blind randomized controlled trial among high risk infants with family history of atopy among first-degree relatives. The study stated that 72 infants were recruited into each of 4 groups, including cow milk whey hydrolysate formula (NAN/HA), conventional cow milk formula (Similac), soy-based formula (Isomil) and exclusive breast feeding for greater than 4 months. (The breast feeding group was not randomly assigned).NAN/HA is a Carnation product, now marketed as Good Start, whereas Similac and Isomil are Ross products. It was reported that exclusive breast feeding reduces the occurrence of atopic disease and that, among those not breast-fed, the incidence

of atopic disease in infants fed NAN/HA was significantly less compared with infants fed Similac or Isomil.

B. PROCEDURE

The investigation involved a number of steps.

1. The Committee started by interviewing Dr. A.J. Davis, Mrs. M. Harvey and Dr. R.K. Chandra; co-author, Dr. G. Singh was brought in from California and thoroughly questioned. About 50 others, associated directly or indirectly with these studies, were also questioned either in person, by most of the Committee, via conference phone call or individual phone contact. A list of these people is included in Appendix 3. Records of most of the discussions were kept.

2. Contact with representatives of Carnation (Nestle) (Mr. S.R. Allen, Vice-President Nutrition, Nestle Canada; Mr. T. Ellwood, Senior Vice-President, General Counsel and Secretary, Nestle Canada; Ms. M.M. Fairchild, Senior Counsel, Nestle USA; Dr. L. MacDonald, Vice-President, Corporate Affairs, Nestle USA; and Dr. P. Guesry, Vice-President of Research, Nestle Switzerland), was established and copies of the study protocols, correspondence, reports and results, pertinent to the work in question, were submitted by them.

3. Likewise, contact with representatives of Ross Laboratories (Dr. W.C. MacLean, Vice-President, Pediatrics Nutrition Research and Development, Ross Products Division; and Mead Johnson (Mr. R. Matthias, Director, Long Range Planning and New Business Development, Mead Johnson Canada) was established and copies of correspondence and protocols were submitted by them.

4. Records of the statistical data analysis, for the relevant papers, were sought and obtained from Dr. D. Bryant (retired Professor of Biostatistics, Division of Community Medicine, Faculty of Medicine, Memorial University of Newfoundland), now living in Nova Scotia.

5. Human Investigation Records for study protocols and Human Investigation approvals were sought at the C.A. Janeway Hospital and the Faculty of Medicine, Memorial University of Newfoundland.

6. Financial records were examined in an effort to locate a group of infants, different from that in the Ross study, where compensation was made for travel expenses.

7. Attempts were also made to obtain laboratory records and hospital records, especially with respect to the Challenge Tests, to provide evidence for the existence of the missing group of infants.

8. The locked-up Ross files and the resultant analyses were carefully inspected.

9. Hospital file searches were completed, both in the Salvation Army Grace General Hospital and St. Clare's Mercy Hospital, for September, 1987; November, 1987; and February, 1988, in an effort to locate a group of infants on special formulas or formula studies.

10. Contact was made with Dr. M. Sly, Editor of Annals of Allergy, for files on the two relevant papers.

It very quickly became evident that the Committee would have difficulties in assessing "truths" in that many of those questioned have a stake in the outcome and that the stakes in this case could indeed be very high. Dr. Chandra had contacted many of the individuals involved with the studies before the Committee talked to them. Comments were frequently guarded and several had concerns about making negative comments. In the process of this investigation, there appeared to be many discrepancies and inconsistencies, in addition to the two completely different accounts of events, by Mrs. M. Harvey and Dr. R. Chandra. Mrs. Harvey states that the above mentioned studies were not carried out; Dr. Chandra insists that they were but that he cannot find the records. The Committee has not been able to find a well-defined paper trail that supports one view rather than the other. Neither has the Committee been able to identify an individual with reliable first-hand knowledge who could completely support either version.

Nevertheless, the Committee is led to believe that Dr. Chandra has committed scientific misconduct where misconduct has been defined, in the guidelines, as meaning "fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community, for proposing, conducting, or reporting research. It does not include honest error or honest differences in interpretations or judgments of data". There is no convincing evidence that the so-called Carnation study was done completely, if at all, and a substantial amount of circumstantial evidence suggests the contrary. In addition, there were questions about the way some of the data were handled and about some of the related studies. Each of the evidences is discussed in detail below:

1. the question of recruitment, timing and witnesses to the so-called Carnation group of infants and the associated hospital file search;
2. the absences of identifiable witnesses who have seen the entire set of Carnation study infant files or were aware of the study procedures;
3. the apparent zero attrition rate of the Carnation study between 6 months and 5 years;
4. significant changes in data between final reports and publication;
5. the sudden infant death syndrome (SIDS) case in both the Carnation and Ross study;

6. the apparent lack of Human Investigation Committee (HIC) approvals;
7. the question of who supplied the Ross formulas;
8. analysis of the Carnation infant growth statistics;
9. whether Challenge Tests were completed;
10. nursing records and recall; and
11. the inappropriateness of the research environment for studies of this kind.

The Committee has attempted to judge these issues according to accepted scientific standards and practices but not in any juridical sense. The question of witness motivation also was not dealt with.

Dr. Chandra has not been especially cooperative during this investigation, particularly with respect to providing the Committee with helpful requested information, documentation or new evidence. For example, only after a number of requests did Dr. Chandra give the Committee a copy of the 5-year study report, well after it was received from Nestle USA (Appendix 4).

C. EVIDENCE

The locked-up files are definitely those of the Ross study and appear to have been described correctly in the Report of the Panel of Inquiry. A Log book was also labelled the Ross Study and contained numbers and names which corresponded to charts in the

filing cabinet. The Log book indicated that about 332 infants were recruited over a period of 2 years at a maximum rate of 26 per month. The Committee counted the files in the cabinet. There were files in 7 different colours or types, each representing a different type of formula.

Colour	No. of Files	Formula	Identification per Mrs. Harvey
White - legal	18	NAN/HA	Carnation Good Start
Red	48	Ross HF	Alimentum
Green	48	IS	Isomil
Blue	49	SW	Similac
White - normal	81	BR	Breast
Dark Blue	9	BR-SW	Breast/Similac
Yellow	11	BR-HF	Breast/Alimentum

Because there seemed to be fewer charts than patients listed in the green Log book (i.e. 332), the Committee went through the Log book comparing subjects who were assigned to the HF formula (for example). There were 21 patients assigned to HF who did not have files. Of these, 9 represent a situation in which the mothers had changed their minds and withdrew from the study before the two-month visit. The other 12 had at least some follow-up and 7 of

these actually completed 6 months of follow-up. There were also 3 red (HF) files in the cabinet for which the Committee could not find a corresponding entry in the Log book.

Some of the consent forms were modified. The consent form in the files mentions only 6 months of follow-up and 2 blood tests (at 2 and 6 months). There is no mention of 12 and 18 month visits although the files contain results of these visits and the laboratory Log book has some results of blood tests. On one randomly pulled chart the words "12m and 18m" were penned in above the 6-month follow-up on the consent form.

Close analysis of the Ross study allergy data shows reasonable similarity with the Carnation study data when substituting Alimentum for NAN/HA. It appears, however, that the Carnation study was not based on the Ross data.

It is the Committee's opinion that a principal investigator has full responsibility for data in a scientific study. It is his responsibility to maintain records with backup copies to avoid the difficulty arising from inadvertent loss or destruction of files. It should be noted that the Ross data were backed up in a computer with computer files available from Ross. It is remarkable that a comparable backup system was not done in the Carnation study.

1. Recruitment Timing, Witnesses and Hospital File Search

Much effort has gone into seeking evidence that a group of about 216 infants were actually recruited into the 3 formula groups for the Carnation study in the time-frame claimed by Dr. Chandra.

Dr. Chandra claims that almost all of the recruitment for the Carnation study was done before Mrs. Harvey was on board (i.e. the end of November, 1987) or at least before initiation of the Ross Study at the end of January, 1988. There is a letter from Ms. M.C. Cheney (Chief, Nutrition Evaluation Division, Health and Welfare Canada), dated July 17, 1987, acknowledging that it would be acceptable to use NAN/HA in a study and then use of NAN/HA was actually approved by the HIC on August 20, 1987 (Appendix 5). A July 1, 1987 letter from Dr. Chandra to Dr. P. Guesry (Nestle Switzerland and who was Dr. Chandra's initial Nestle contact) requests information as to whether everything is in order for the study to commence in early August as planned. Guesry's response comes on August 6, 1987 confirming agreement for the study and in which he outlines conditions for the collaboration (Appendix 5). Nestle has submitted records of NAN/HA shipments beginning of October, 1987, middle of October, 1987 and December, 1987. Dr. P. Guesry, Switzerland has confirmed that he could find no evidence of NAN/HA shipments before October, 1987. He stated, however, that it is possible that 1 box (12 cans) was sent earlier for analysis of nutritional composition. In a November, 1988 protocol and summary to Nestle, it appears that only about one-half of the Carnation study had been completed, namely "In this on-going study, there are currently growth data on 34 infants in Group 1, 30 infants in Group 2, and 30 infants in Group 3. A minimum of 60 infants per group will be required to complete the study". Dr. G. Singh, who was a Research Fellow in Immunology with Dr. Chandra from August, 1987 -

July, 1988, denies taking part in the recruitment procedure (as claimed by Dr. Chandra). He claims that patients would have been enrolled in early 1988 and does not recall separate papers for a Carnation study. The Committee, in fact, cannot locate anyone, including former hospital nurses and nursing managers, who clearly remembers recruitment of infants in this time-frame other than with Mrs. Harvey. Dr. Chandra, nevertheless, adamantly insists that recruitment, for the Carnation study, started in June/July, 1987 and finished around the end of 1987, i.e. when Mrs. Harvey came on board. Dr. Guesry felt that recruitment possibly could have been done within this time-frame.

The Committee consequently requested hospital file searches, at both the St. Clare's and Grace Hospitals, for the months September, 1987, November, 1987 and February, 1988, to locate infants on special formulas and studies (Appendix 6).

The results for St. Clare's Hospital are as follows:

	Total Number of Births	Number on Special Formula or Feeding Study
September, 1987	167	0
November, 1987	116	0
February, 1988	97	6

On comparison with the locked-up Ross files, of the 6 cases, in the last column in February, 1988, at least 5 correspond to the ones in the Ross study since the formula codes were clearly identified.

The results for the Grace Hospital are as follows:

	Total Number of Births	Number for which Formula is not indicated or Feeding Study
September, 1987	202	10
November, 1987	163	11
February, 1988	132	8

The total of 29 in the last column were noted as "formula-type not indicated". Six of these were involved in a study by Dr. J. Friel; another 5 were below 2500 gm, which is the cut-off for Dr. Chandra's study. It is not clear whether the remaining 18 are in any kind of a study or not. About 3 of these 18 do not fit the weights noted in the Carnation study. Fifteen, in any case, is a very small number over 3 months (if indeed they were involved with the Carnation study). One would have expected, approximately, 30 infants per month during this time period.

The results of the hospital file search does not in any way support Dr. Chandra's claim concerning the timing of the Carnation study; in fact, it suggests that essentially no such study, or, at least, very little of the study, was done in the latter part of 1987 or the first part of 1988. Dr. Chandra, at one point, claimed that some of the infants were recruited through physicians' offices. A check with several identified physicians revealed little, if any, evidence of this and, furthermore, such infants would have been delivered at one of the hospitals and started formula at birth (and would therefore have been recorded in the hospital files). It is, in fact, incredible that there are no hospital records evidencing a substantial group of infants, in the noted timeframe, but there is evidence for a study by Dr. J.H. Friel and the Ross study (Feb. 1988)

2. Evidence of the Existence of Carnation Study Files.

Drs. A. Hamed, B. Shridhara, G. Singh and C. Prasad were co-authors on the three relevant Carnation papers. The Committee was surprised that only one individual, namely Dr. Hamed, remembered a large Carnation study and the three others did not.

Dr. A. Hamed (graduate student, May 1988 - end of 1990) recalled the Carnation and Ross studies and stated that she could have 5 or 6 clinics per week, seeing approximately 6 or 7 children in each clinic. She recalled there were many patients in 1 of the studies. When Dr. Hamed read the manuscript (later published in Annals of Allergy) the numbers quoted seemed to her to be correct.

She further stated that in each feeding group there were approximately 65 babies with ages of approximately 5, 6 and 18 months with many 3 year olds in 1990 and stated that all the recruiting was done by Mrs. Harvey. This is not consistent with Dr. Chandra's testimony if Dr. Hamed means Carnation study. She was vague on the distinction of Ross patients versus Carnation patients and thought, in fact, that the Ross study may have started at the end of 1989. She also recalled that Mrs. Harvey kept the files and records of the study. Dr. Hamed reviewed only the clinical part of the work. She did not review any statistical work or compare data with files. It is interesting to note that her name appears, as a co-author, in the Mead Johnson paper but she does not recall the specifics of the study. She did not see or review any data relevant to this study. Dr. Hamed stated that she always knew Dr. Chandra as an honest and kind person.

It appears that no one interviewed (other than Dr. Chandra) has seen all of the raw data for the Carnation study. Dr. Chandra claims that Dr. B. Shridhara (post doctoral fellow, October 1988 - December 1988) copied data from the files to prepare the paper. Dr. Shridhara was not entirely sure which study he was involved with and stated that his role was in examining the infants for evidence of allergy, that Dr. Chandra wrote the manuscript in question, and that the study involved 60, 70 or maybe 80 infants, ranging from 3 - 6 months of age. He further stated that he had not seen tabulated data and that as of December, 1988 there was still follow-up to be completed.

Dr. G. Singh (post doctoral fellow, August 1987 - July 1988) thinks that he was only involved with the Ross study. He recalled an information meeting at St. Clare's Hospital with Dr. Chandra around the end of 1987 or early 1988. He did not perform any skin tests (this was done by Dr. Chandra). Patients were presented to him by Mrs. Harvey. He saw patients both in Clinics and in the Immunology Centre but stated that he never recruited patients (as claimed by Dr. Chandra). Dr. Singh saw the Annals of Allergy paper with his name on it, while attending a Pediatrics Conference, after it was published. He did not do any writing nor did he see any raw data. He never saw any ledgers on Carnation or Ross studies and never saw separate papers for a Carnation study. Dr. Singh was interviewed a second time at his own request where he stated "that he and others at the Janeway knew there had been files, probably in the vicinity of 70, certainly no where near 280 charts". Concerning two letters sent to Dr. Singh (as submitted by Mr. Lavers to the Committee), Dr. Singh does not recall ever having received the letter of February 8, 1989 (Appendix 8). He feels that the letter of November 6, 1989 is a modified version of the one he received.

Dr. C. Prasad's (post doctoral fellow, 1990 - 1991) name is on the abstract (American Journal of Clinical Nutrition); she did not write the abstract. Dr. Prasad did not know whether a Carnation product had been used and could not specify how many babies were being assessed. She once questioned Dr. Chandra about the ethics of rigid and restricted diets to pregnant mothers but

she did not get any response to her question. Dr. Prasad stated that when you are a foreign graduate endeavouring to succeed, you ask very few questions and just do the job assigned to you in an efficient manner. She kept her opinions to herself. She stated that in retrospect, she has formulated her own opinions (about the work) and did not wish to share them with the Committee.

Dr. C. Collins-Williams (retired Professor, Hospital for Sick Children, University of Toronto) visited St. John's in 1991 (well after the publication of Annals of Allergy paper) in connection with a Nutrition and Immunology Seminar. He remembers reviewing records of 288 patients divided equally into 4 groups who were followed for 18 months for signs of atopic disease in a May 12, 1994 letter to Dr. Chandra (as submitted by Mr. J. Lavers, Dr. Chandra's Legal Counsel). When further elaboration was sought regarding the review, Dr. Collins-Williams replied to Dr. Kiefte (Appendix 7) that "You realize, of course, that this is now three years ago. I was not viewing our meeting, held in my hotel room, as if I were a critic or an accreditation inspector from the Royal College, but simply as a friend meeting another friend to talk over a subject of mutual interest and make last minute revisions to our papers (chiefly my paper) so that there would be no overlap ... Therefore, my recollections are not as vivid as they would have been had I been acting as a critic or an inspector". He also elaborated that Dr. Chandra came with a pile of charts about 1½ to 2 feet high. Dr. Collins-Williams continued "I did not count the charts (Why should I have?) nor ask if they represented the whole

study. (Again why should I have?) Naturally I simply took them for what he said they were since the purpose of our meeting was to finalize our presentations, not for me to judge the research he had been doing."

Mr. S.R. Allen (Nestle Canada) writes to Dr. Chandra on May 13, 1994 that Dr. R.J. Merritt (previously with Nestle Canada) visited Newfoundland in August 1991 and said that "He was very impressed with the organization of the NAN/HA trial, the completeness of the work, the progress made and the prospects for follow-up in the infants who had been enrolled (288 initially)... Dr. Merritt was completely satisfied by the way the study had been conducted." It should, however, be clearly pointed out that the first (18 month) follow-up was submitted in November 1990 and published in August 1991. In discussion with Dr. Merritt, he doesn't think that he examined case records but does recall seeing periodic statistical analysis and bits and pieces of data form time to time. Dr. Merritt was asked to write a formal letter but declined to do so.

Ms. T. Lundin (Nutritionist, January 1986 - March 1990) was involved in a Carnation study which was connected with a research group at the University of Toronto. She stated that the number of patients recruited was probably less than 20 - between 10 and 15. Ms. Lundin recruited these babies from prenatal clinics at the hospitals. This was an entirely different study than the Carnation study in question. Infants, who were fed Carnation evaporated milk by parental choice, were studied. She also recalled a study with

expectant mothers on a restrictive diet in which she acted as a consultant. She also recalls Mrs. Harvey passing out the formulas in the Ross study but could not recall any other formulas being passed out prior to the Ross study. She knew most of the post doctoral fellows and felt that they were not passing out formulas. Predominantly Mrs. Lundin worked with the elderly patients (with Ms. B. Roebothan, Nutritional Biochemist). Ms. Roebothan always had difficulties recruiting patients and according to Mrs. Lundin, they both often wondered where Dr. Chandra got his subjects. Mrs. Lundin was acknowledged in Dr. Chandra's 1986 Clinical Allergy paper which was submitted for publication on February 1, 1986, whereas she began work in January 1986. This paper mentions 101 mothers on restricted diets. Ms. Lundin felt that these numbers would be impossible.

Dr. H. Hafiz (post doctoral fellow, June 4 1991 - April 16 1994) stated that once he received a license to practise, he examined patients in Dr. Chandra's clinics (no skin tests). He stated that there were some 3 and 5 year old patients, maybe a couple of 5 year olds and 10 or 15 3 year olds. He never went to the hospitals to recruit babies. In fact, very few, if any, 3 - 5 year old patients were noted by anyone, with the exception of Dr. Hamed. It remains unclear, however, as to which of the 3 and 5 year olds, if any, were in a study. He was not sure of a Carnation study but does mention whey hydrolysate in a May 11, 1994 letter to Mr. Lavers.

Dr. S. Puri (post doctoral fellow, 1984 - 1985) did literature searches for Dr. Chandra and helped in the writing of a paper (most likely the Clinical Allergy paper, 1986, but she also co-authored the British Medical Journal paper) and recalls a study where mothers were on a special restrictive diet. She did not recruit any babies nor did she know who recruited them. Regarding the writing of the paper, she said everything had been done previously, i.e. the results had been analysed and, based on those results, conclusions were made. She never examined the records of mothers and infants.

Dr. C. Suraiya (post doctoral fellow, June 1985 for 9 months) then worked with Dr. W. Andrews for 3 months and was not involved in writing a paper and could not recall analyzing the data. She recalled an allergy study at St. Clare's involving pregnant women and breast feeding where some were on special anti-allergic diets. The babies were followed for 3, 6 and 12 months. The study, however, did not commence until she was taking up a position in Stephenville, Newfoundland. She recalled visiting St. Clare's with Dr. Chandra for an information session related to the study.

Dr. C. Daza (retired representative, WHO Centre, Geneva, Switzerland) did not see any raw data or charts to any studies, on his visit to Dr. Chandra in February, 1989.

In addition to the Carnation study, a number of workers e.g. Dr. D. Callahan/Dyer (Family Practice Physician), Ms. K. Matthews, (School of Nursing, Memorial University of Newfoundland), Dr. C. Prasad, Ms. T. Lundin very much doubted that such a large number

of pregnant mothers would accept as rigid a diet as described in several other publications (Clinical Allergy, 1986 and British Medical Journal). Ms. Lundin tried to recruit for such studies and managed to recruit only one mother and baby.

3. Attrition Rate

The Committee had very real concerns about the low attrition rate reported in the Carnation study and the reports of follow-up at 18 months, 3 years and 5 years. In the first paper (Annals of Allergy, 1989) the attrition rates are only 12.9% in the three formula-fed groups over the first 6 months. This includes many who exited because they had an adverse outcome (15/28). In many clinical studies adverse outcomes are not a reason for leaving the study and, indeed, in this study it seems that complete withdrawal would not have been essential although it might have been clinically indicated. The attrition in the breast-feeding group was 19.4% but apparently does not include some subjects who breast-fed for less than 4 months (a number not quantified, as they were replaced). These rates were felt to be extraordinarily low for this type of study. The Committee was unable to identify any unique individual who could have been responsible for recruitment and retention in Dr. Chandra's study. It is well known to epidemiologists that such a person is critical to the success of clinical studies like these.

Of even greater concern is the attrition rate in the two follow-up reports of the subjects at 18 months (Annals of Allergy

1991) at 3 years (Journal of Clinical Nutrition) and at 5 years (unpublished manuscript submitted to Nestle, Appendix 4). In these manuscripts the reader is led to believe that all of the subjects who were in the study at 6 months were followed through to five years of age with no losses. The legend under Figure 1 in the 18-month report says "The total number of infants examined until 18 months in the different groups was the following: breast - 60; whey hydrolysate - 68; soy - 68; and cow milk - 67". The same numbers are mentioned in the 5 year paper with losses from the 72 patients in each group having exited prior to 6 months. There is no mention of any losses between 6 months and 5 years. In both of these papers, figures are presented for the cumulative incidence of significant atopic problems for each group. In Committee discussions Dr. Chandra argued that talking about cumulative incidence is not the same as saying that all of the children were followed. He implied that possibly some children were not followed. If this is so, then both papers are misleading and breach fundamental rules of clinical research design. Cumulative incidence has no meaning unless the number followed is reported. Incidence is a rate and one cannot count in the denominator those who have been lost to follow-up. If more of the children in the cow milk and soy groups were followed than in the NAN/HA and breast groups, the number with atopy would be higher, and the incidence, based on original denominators, would be lower in the latter two groups. Dr. S. Witherly, now at Nutralite but who was at Nestle

at the time of the study and Dr. P. Guesry recall that there had been questions about the attrition rate.

It also appears most unusual that all weight and length data are available for all infants at 0, 2, 4 and 6 months for the Roche study (Canadian Journal of Public Health, 1993). There is not one missing piece of information.

To establish the expected norm for attrition in this type of study the Committee did the following:

(i) approached three leading Canadian pediatric clinical epidemiologists: Dr. M. Kramer, McGill University; Dr. B. Pless, McGill University; and Dr. W. Feldman, University of Toronto, who have done clinical trials with children regarding what they would expect in a hypothetical trial where infants were given formula from birth to 6 months and then followed, without incentive, to age five (Appendix 9). The minimum attrition that any of them felt achievable was 10% to 15% with extremely intensive follow-up using creative methods. Two felt that without intensive efforts the attrition rate would be as high as 40% by 18 months. The Committee could find no evidence that intensive efforts were made in the Carnation study under question that would lead to a zero attrition between 6 months and 5 years;

(ii) reviewed the 1989 Volume of the 2 leading Pediatric Journals (Pediatrics and Journal of Pediatrics) for

longitudinal studies which followed groups of children for 2 to 24 months (with one exceptional study which followed children for 84 months). The mean attrition rate was 14% over varying periods of time in 18 studies (Appendix 9). This included 3 studies which reported zero percent. However, of those 3 studies, 1 was a study of 29 children undergoing liver transplant (these children depend on the clinics for life-sustaining medications) and the other 2 left the suspicion that the studies were reported improperly (that is only those who stayed in until the end were counted as having started). When those 3 studies are eliminated, the mean attrition rate was 21%. There were 4 studies which reported attrition rates of 12% or less but they were all special cases. One studied survivors of neonatal intensive care in a special clinic, another was part of a national birth cohort in Holland, a third followed poverty children in Jamaica from birth to 18 months by means of intensive and frequent home visits and the fourth treated short children with growth hormone, a product which they could only get through the study. The studies which followed ordinary children without the aid of special clinics or services had attrition rates from 15% to 42%. These numbers contrast sharply with attrition rates of Dr. Chandra;

(iii) because Dr. Chandra has frequently stated that Newfoundland is a special case for research due to a small stable homogeneous population, the Committee talked with several people who have done clinical research in St. John's. Only one agreed that it was possible that attrition rates would be lower in Newfoundland than elsewhere. Nobody had experiences comparable to Dr. Chandra. In a study done in St. John's at about the same time by Dr. J. Friel, in which premature babies recruited from the same maternity wards, were provided with formula, 30/80 subjects were lost over a 12-month period (see also Appendix 9). Dr. Friel had a single person co-ordinating recruitment and retention;

(iv) examined the files of the Ross study which the Committee knows was carried out in a somewhat similar manner to the study in question. When these files are carefully examined, the attrition rate at 18 months appears well over 30%. More important, the attrition rate between 6 and 18 months is over 20% in the Ross study (as opposed to zero percent for the Carnation study) . The Committee would have expected a comparable attrition rate in the Carnation study which was also carried out in Newfoundland;

(v) noted the following statement, concerning the Carnation study, from a protocol and letter of Dr.

Chandra to Dr. E. Strapazon (Vice-President and General Manager, Nutritional Products, Nestle USA) on October 3, 1988: "Target enrolment is 72 infants per cell to allow for an expected attrition rate of 35 - 50%" (Appendix 9). Dr. Chandra denies ever stating this and it was not included in the November 1, 1988 revised version of the protocol and summary.

When all this information is carefully considered, the Committee feels that the attrition rates reported at 6 months are theoretically achievable but unlikely in the circumstances. The low attrition rates between 6 months and 5 years were felt to be impossible and represent either misleading reporting or a fundamental lack of knowledge of clinical research design.

4. Changes in Data and Statistical Analysis

Re: Annals of Allergy, 1989 paper, a letter to Dr. E. Strapazon, dated March 9, 1989 (Appendix 10) was attached to a draft of the Annals of Allergy paper and the paper was submitted to the Journal on March 25, 1989, 16 days later. In Table 2 of the draft are data which differ from the corresponding Table 4 in the final paper. The numbers in the draft Table 2 are exactly the same as the handwritten set of numbers present on Dr. D. Bryant's June 14, 1994 submission (Appendix 10). A comparison of the draft Table 2 numbers and the Bryant numbers versus the final manuscript (Table 4) shows that the number of breast fed babies increased from

58 to 60 and the number of Similac babies increased from 66 to 67. However, the number of breast fed babies with atopic symptoms decreased from 14 to 12. As can be seen from Dr. Bryant's calculations, some of the original findings were not significant, but these changes produced significance by the chi-square method. Most notable is that the number of infants with atopic symptoms decreased but number of infants in the same breast fed group increased. There are two possible explanations.

(i) All the data were reviewed by Dr. Chandra and a few new cases were added. This review of data led to a decrease in atopic symptoms being noted, which means that the submitted data to his statistician were incorrect.

(ii) The finding that Similac versus breast fed babies had no statistical differences in atopic symptoms was not regarded as acceptable by the investigator and the numbers were deliberately altered without reference to any data.

Re: British Medical Journal paper, there is second evidence of important changes from the time of statistical analysis by Dr. Bryant and the publication of data in the British Medical Journal. Table 1 of Dr. Bryant's submission (letter of March 29, 1989) (Appendix 10) versus the British Medical Journal Table 1 is summarized below. Dr. Bryant's numbers are shown, and in brackets

and bold are the numbers observed in the British Medical Journal paper (Table 1) where these change from the original.

Group	No. of mothers (babies)	Mean Eczema Score	Babies With Eczema	
			No.	Mean Score
Dietary precautions	46 **(49)**	5	10 **(11)**	23 **(22)**
No precautions	45 **(48)**	15 **(17)**	19 **(21)**	36 **(34)**

It is to be noted that number of mothers (babies) increased and mean eczema score increased in the "no precautions" group. This latter change from 15 to 17 is very important. At first glance, this appears to be a minor change but in fact the additional 2 babies in the "no precautions" group would have needed a mean eczema score of 70 to change the overall mean score from 15 to 17. This is highly improbable as the mean eczema score of 3 babies added to the "dietary precautions" group stayed as exactly 5, i.e. unchanged from the earlier mean. In this context, it is also

interesting to note that Table III of the British Medical Journal paper is exactly the same as Dr. Bryant's Table 2. Here the results (Table III of British Medical Journal paper) showed statistical difference, whereas the initial calculations of Dr. Bryant on the results of "dietary precautions" vs "no precautions" group failed to show statistical significance. The addition of small number of babies to both the "dietary precautions" and "no dietary precautions" groups could have been real except for the enormously important change in mean eczema score. It is also highly unlikely that SD (standard deviation) value of the eczema score would remain identical (SD = 4.1) in both Dr. Bryant's data and the British Medical Journal paper, inspite of the fact that "N" values (sample numbers) and means were changed.

All the above facts taken together - the changes observed in the very short time-frame between statistical analysis by Dr. Bryant and submission dates for both publications; the fact that these changes converted non-significant data to significant; that the mean eczema score change representing recruitment of 2 babies with enormous amount of eczema; and that the SD values remained constant even though patient numbers have changed - lead to the conclusion that the results as presented are hard to believe. It should also be pointed out that Dr. Bryant never saw any individual data.

The above information on statistics (and other issues) has been independently assessed by Dr. J. Harnett, (Associate Professor

of Medicine and Clinical Epidemiology, Memorial University of Newfoundland) who concluded that "this change in figures over a short time span resulting in a statistically significant difference directly relevant to the study's main conclusion is disturbing and difficult to explain" (Appendix 11). In summary, Dr. Harnett also suggested that "in my opinion, scientific misconduct is one explanation for these issues. Alternative explanation will depend on more detail being provided by the investigator".

5. Sudden Infant Death Syndrome (SIDS) Cases

In the interim report to Carnation (November 1, 1988) Dr. Chandra describes a child who died of SIDS in the Similac group at 7 weeks of age. When interviewed Dr. Chandra could not identify the child or provide any further details. When Mrs. Harvey was asked if there were any deaths from SIDS in the Ross study, she immediately recalled and identified a child (born in March, 1988) who died just 2 days before the 2 month visit. The child was in the Similac group. Considering the fact that 11 and 8 Newfoundland children died from SIDS in 1987 and 1988 respectively and only 2 in the right time frame at age 2 months, it is highly coincidental, to say the least, that both children would be in a Similac group. It is, in fact, unlikely that the "other" child would have been in any study of this kind at all. This is strongly suggestive that there was no separate complete Carnation study.

6. Human Investigation Protocols and Approvals

The Clinical Allergy, 1986 paper was received by Clinical Allergy on February 3, 1986. This particular proposal was approved at a meeting of the Memorial University of Newfoundland Faculty of Medicine HIC on February 20, 1986. This finding clearly indicates that the entire study preceded ethical approval by the HIC.

On July 6, 1987, Dr. Chandra requested to the HIC Chairman that a new hypoallergenic formula be added to the earlier approved project. There is unequivocal evidence that the new formula referred to was NAN/HA. Thus, the 2 studies published in Annals of Allergy , 1989 and 1991, and the subsequent Abstract in Journal of Clinical Nutrition would have had to be based on the 2 HIC approvals that are mentioned. It is, however, absolutely apparent that neither the Annals of Allergy papers nor the Abstract had the same experimental design as the HIC submissions. A new HIC approval should, therefore, have been submitted. From the HIC records, there is no evidence for such a submission. This means the various studies mentioned never had formal HIC approval.

In 1989 Dr. Chandra published a paper in the British Medical Journal. There is no evidence in the HIC records that this particular study was ever submitted for ethical approval.

It is possible that the various studies could have been approved at the particular hospitals involved in the studies. The Committee, however, was unable to obtain such evidence from the Grace and St. Clare's Hospitals. The HIC records at these hospitals appear to be poorly kept and the Committee, therefore,

cannot exclude the possibility of hospital approval without Medical School HIC approval. Nevertheless, it is normal practice to obtain University HIC approval prior to hospital approval.

During the investigation period, Dr. Chandra submitted to the Investigation Committee an HIC application dated January 8, 1987 and with a covering letter to the HIC and with a title and protocol completely consistent with the 2 Annals of Allergy papers. Review of the HIC Minutes and other HIC documents, however, provide no evidence that this particular proposal was ever submitted to the HIC for review. Moreover, such a submission is not consistent with the documents held by the HIC indicating that NAN/HA should be added to the Mead Johnson study.

7. Ross Formula Supplier

Dr. Chandra claims that the Ross products, Isomil and Similac, were supplied by Nestle for the Carnation study. Nestle, however, has no record of this. Nevertheless, it is possible (typical according to Mr. Allen) that a company like Nestle would directly supply a competitor's product for clinical trials.

8. Infants Growth Statistics

The Committee performed a birth weight analysis for both the Ross and the Carnation study (from the Roche paper in the Canadian Journal of Public Health) by plotting a 100 gm interval histogram. The histogram for the Ross study was, as expected, a relatively normal distribution peaked at the Newfoundland mean of about 3500

gm and tapering down to 2500 and 4500 and more on either side. The histogram for the Carnation study looked somewhat surprising in that it had a second strong peak at about 3000 gm and virtually no entries above 4000 gm. The latter point appears to be more unusual.

9. Challenge Study

There were Challenge Tests of about 12 symptomatic babies in 1990 in the Carnation study. Skin tests (based on milk or soy) were done in the clinic, sometimes in the office. If they react positively showing the symptoms, they were kept for observation for about 15 or 20 minutes. Hospitalization was necessary only in rare instance, only when there was a history of anaphylaxis. To quote Dr. Chandra regarding hospitalization: "It must have been a very rare instance. I don't think the majority of children would need hospitalization". Information was sought to obtain those 12 names of patients who were observed closely in the clinics or in the hospital. It was expected that the physician may remember the parents or patients in this situation of close contact. If the names were available, one can get the evidence that they were on formula in the right time period and they were not people in the Ross study - this would constitute 1 piece of evidence to indicate that the Carnation study was indeed done. The 5 year follow-up study, in fact, suggested that 60 patients had received Challenge Tests between ages 13 to 60 months. Surely some would have been done towards the end of the study and should be fresh in the memory

of investigators (for identification purposes). One Committee member suggested that only 1 patient was identified so far. In response to this, Dr. Chandra replied "Well, I'm sure if I dig through all my files, I will find a few more", but he wanted to be sure what number would be enough to satisfy the Committee. Dr. Chandra, however, did not provide any other name for the Challenge Study. The other issue is related to requests for funds, by Dr. Chandra to Nestle, for hospitalization of infants in the Challenge Study. A letter of Dr. Chandra to Dr. Witherly on June 14, 1990, comments about "cost over-runs to challenges in symptomatic infants and with cow's milk allergy" (Appendix 12). Actually $18,475 was received for the hospitalization of the infants for 1 - 2 days or longer follow-ups.

10. Nursing Records and Recall

In a telephone conversation, Mrs. F. Downey, Director of Neonatal Unit at the Grace Hospital, indicated that her first work with Dr. Chandra was when Mrs. Harvey came to the Grace Hospital and she does not recall an earlier study of similar type. She mentioned that the Neonatal Unit Annual Report dated April 1, 1987 - March 31, 1988, indicated that "Dr. Chandra and his research nurse had begun an allergy study". Review of the Annual Reports for the 3 previous years reveals no mention of a research study involving Dr. Chandra. She would expect such mention, had a study been performed.

Ms. J. Georghiou, who at the time of the study was Co-ordinator of the Prenatal Education Program at St. Clare's and the Co-ordinator of the Breast Feeding Support Clinic, does not think that she had anything to do with Dr. Chandra before Mrs. Harvey arrived. Mrs. D. Whittle, (retired Nurse/Manager of the Neonatal Intensive Care Unit, St. Clare's) and Mrs. E. Thomas (retired Supervisor of Postpartum Unit, St. Clare's) recall no recruiting activity before Mrs. Harvey. Ms. E. Nash (retired Assistant Director of Nursing at St. Clare's, from 1985 - 1988,) remembers a study in conjunction with Mrs. Harvey. She checked the Nursing Hospital Annual Reports from 1986 - 1989 and found no records of studies by Dr. Chandra.

11. Research Environment

The Committee of Investigation felt very much disturbed by the research environment under Dr. Chandra in the WHO Centre and elsewhere. Following are some of the concerns.

(i) This is not an educational environment in the accepted sense. Post doctoral and clinical fellows are not receiving proper training in research methodology and are mostly not encouraged to carry out independent investigation beyond reviews of the literature.

(ii) There is a remarkable lack of communication and openness, which are hallmarks of a good research environment.

(iii) It is most unusual that the co-authors, in the papers in question, know so little about what was in them or that they had not seen the appropriate files. There appears to be no substantive reason as to whose names appeared as co-authors or as acknowledgments.

(iv) The important step of taking clinical research from the individual patient file to the finished product is not being taught to the associates and nobody other than Dr. Chandra seems to have any part in this process. There are inevitably problems when the data is held by only one person.

(v) There are no meetings in which research methods, proposals, problems and day to day progress are discussed.

(vi) Why have no Canadian and North American trained medical graduates been attracted to do post doctoral fellowships with such a well known Institution?

(vii) Dr. Chandra's frequent absences make it very difficult to carry out the studies in an efficient manner, particularly since none of the team has a full knowledge of each individual study.

(viii) Dr. Chandra's practice of throwing away the files and raw data after publication is not a healthy one.

(ix) It is unusual that computers are not used to handle data in research of the type under investigation.

D. CONCLUSIONS

With the evidence presented, the testimony of many witnesses, and the fact that absolutely no raw data (or files) of any kind were exhibited, the Committee cannot accept that the Carnation study was done anywhere near to the completeness or with the accuracy reported in Annals of Allergy and Journal of Clinical Nutrition. For that matter, the same can probably be said for the Mead Johnson work as published in the British Medical Journal. In fact, the Committee cannot identify anyone who did the recruiting, cannot identify anyone who did or remembers a significant amount of the work, and the co-authors of the papers had little or very likely nothing to do with the work. In addition, the question of attrition rate and changes in data on publication and the noted SIDS case(s) situation are major concerns of the Committee. Moreover, it is unbelievable that there are essentially no hospital records to support the study in question (in the timeframe stated by Dr. Chandra). With respect to the allegations, the Committee is, therefore, led to conclude that scientific misconduct has been committed by Dr. Chandra in this matter.

As an implication from this investigation, the University research community at Memorial must take a lesson from these unfortunate events. Building of a research enclave with very few day-to-day research consultations, group discussions, group

seminars, and exposure of research fellows to the larger community of research should not be allowed to happen again.

Dr. Chandra's research activity was very much operated as a pyramid system where only one person at the top had access to all the final raw data. The research personnel functioned mainly as physician-technicians and had or were shown little insight into experimental objectives, design and procedures. There should have been more openness and communication. Most research personnel were not around long enough and it was thus difficult for them to detect wrong-doing. The exception is Mrs. Harvey who was there for 6 years. The Committee has found no reason to doubt the allegations and Mrs. Harvey's testimony. From the interviews, the Committee was, in fact, impressed by Mrs. Harvey's sincerity, dedication, thoroughness and compassion towards the mothers, infants and community at large.

E. ENCLOSURES IN APPENDIX

The following documents are enclosed.

Appendix 1 : Final Report of the Panel of Inquiry into Allegations of Scientific Fraud against Dr. Ranjit Chandra

Appendix 2 : Six relevant publications

Appendix 11: J. Harnett submission

Appendix 12: Letter to S. Witherly