INTERNATIONAL ATOMIC ENERGY AGENCY

IAEA-PDE-94/02
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PROJECT DESK EVALUATION

A DESK EVALUATION REVIEW OF PROJECT

MYA/6/015

HORMONAL STUDIES
ON PITUITARY ADRENAL DISORDERS

DEPARTMENT OF TECHNICAL CO-OPERATION

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EVALUATION SECTION

DEPARTMENT OF TECHNICAL CO-OPERATION

PROJECT DESK EVALUATIONS

Project Desk Evaluation (PDE) is an intensive review process, using agreed guidelines, of the design, implementation, and the outputs of a project. Its purpose is to convey concisely as comprehensive a picture of a project's performance as can be obtained without a specific evaluation mission to the project site. It will subsequently provide the required background information for a field evaluation review, if such a review will appear to be necessary.

Project Desk Evaluations are carried out by the staff of the Evaluation Section, Department of Technical Co-operation, with the assistance of the staff in the Agency concerned with the specific projects. Upon completion, each Project Desk Evaluation is submitted to the Deputy Director General of the Department of Technical Co-operation.

DESK EVALUATION REVIEW OF PROJECT

MYA/6/015
HORMONAL STUDIES ON PITUITARY ADRENAL DISORDERS

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EXECUTIVE SUMMARY

Snake-bite is one of the high priority health problems in Myanmar, causing high mortality and morbidity rates among the rural population. In 1982 the Department of Medical Research (DMR) of the Ministry of Health launched a research programme for the comprehensive studies of snake (Russell's viper) bites and since then various research divisions of the DMR have been actively engaged in both basic and clinical studies aimed at obtaining adequate knowledge of the biochemical, clinical and pathophysiological mechanisms to guide rational management of snake-bite cases. Also, a clinical research unit has been established in a particular area where the incidence of Russell's viper bite is quite high.

Project MYA/6/015 was initiated in 1989 with the objective of determining the incidence, facilitating early diagnosis and assessing the value of therapy in hypopituitarism following snake bite, through the measurement of pituitary and adreno-cortical hormones in serum and their changes in response to dynamic tests. The project was completed in July 1993. The review was undertaken upon request by the Asia and Pacific Section, to assess the overall performance of the project.

ACCOMPLISHMENTS

Project MYA/6/015 supplied a total of 4.1 man-months of expert services, equipment valued at $32 141, as well as a fellowship for a total of 6 months of training abroad.

A RIASTAR gamma counter was provided, installed and brought into operation. The local staff were trained in the use of the counter and associated data processing programs. Reagents and chemicals were provided regularly to conduct research.

A research programme was prepared by the expert, taking into consideration the probable effects of snake (Russell's viper) venom on the pituitary and endocrine system. The protocol for in-house assays using bulk reagents was introduced, and all the needed radioimmunoassays (RIAs) were established.

Field clinical studies were carried out in a snake-bite endemic area. In the period 1990 through 1992, a total of 50 acute bite cases, 23 follow-up cases and 31 normal controls were recruited for the laboratory investigations. All the snake-bite survivors and normal controls were studied to establish basal hormone levels. Dynamic studies were performed to assess pituitary and adrenocortical reserve capacity.

As a result of the project, the short-term and long-term endocrine effects of snake-bite were studied by the measurement of serum levels of the relevant hormones by RIA methods. The obtained results, particularly those related to human Growth Hormone (hGH), are proving to be of prognostic significance and may influence the future management of snake-bite survivors.

FINDINGS

The objective of project MYA/6/015 has been achieved. A facility has been created to study the effects of snake-bite on the hypothalamic-pituitary-adrenal axis by the measurement of basal serum levels of the relevant hormones and response to dynamic tests by RIA methods. Improved facilities and local expertise needed to conduct a hormonal study on pituitary adrenal disorders in general and in snake-bite patients in particular have been established.

The introduction of in-house assay using bulk-reagent-based methodology has taken place, obviating the technical disadvantages and high costs of importing ready-made kits. All RIA methods required for the assessment of endocrine effects of snake-bite are now available at the DMR. Through on-the-spot training by Agency experts and through training abroad, the necessary expertise for conducting research has been transferred to local staff.

Through the support provided by the project, good progress has been achieved in studying the short-term and long-term endocrine effects of snake-bites. Field and laboratory studies were conducted and the needed hormonal profiles of acute snake-bite cases and normal controls have been determined by RIA methods. The results obtained are of practical significance and may influence the future management of snake-bite survivors, and could thus yield good returns for both national health and the agricultural sector of national economy.

In summary, Myanmar is in a unique position to carry out the study on the effects of snake-bite on the endocrine system. Good progress has been made in assessing these effects and the inputs provided by the project have been well utilized. Local staff are in a position to continue the research (which may take several more years) on their own and publish their final conclusions.

RECOMMENDATION

In view of the importance of the results of the hormonal studies on pituitary adrenal disorders started under the project, these activities need to be sustained. To this end, the Agency should maintain contacts with the Department of Medical Research, Yangon, with the aim of determining possible future needs as well as ways of providing further Agency support that may be required for the continuation and further development of on-going research.

I

INTRODUCTION

Several tropical diseases, including parasitic, bacterial and viral infections, and snake bites are endemic in Myanmar. Snake bite is one of the high priority health problems in the country, causing high mortality and morbidity rates among the rural population. In 1982 the Department of Medical Research (DMR) of the Ministry of Health launched a research programme for the comprehensive study of snake (Russell's viper) bites and since then various research divisions at DMR have been actively engaged in both basic and clinical studies aimed at obtaining adequate knowledge of the biochemical, clinical and pathophysiological mechanisms to guide management of snake bite cases. Also, a clinical research unit has been established in a particular area where the incidence of Russell's viper bite is quite high.

Project MYA/6/015 was initiated in 1989 to assist the Department of Medical Research in assessing the effects of snake bite on the victims' hypothalminic-pituitary-adrenal axis. The project intended to facilitate the establishment of RIA methodology for hormonal studies on pituitary disorders in snake-bite patients. Bulk reagent based methodology was utilized to obviate the technical disadvantages and the high costs of importing ready-made kits.

The project provided a total of four months of expert services, $32 000 worth of equipment and six months of training abroad for one counterpart staff. It was completed in July 1993.

II

PROJECT UNDER REVIEW

The following section contains a Project Desk Evaluation (PDE) of the Agency's project MYA/6/015, Hormonal Studies on Pituitary Adrenal Disorders.

The review was undertaken upon request by the Asia and Pacific Section, to assess the overall performance of the project and to determine how the experience gained through it might be utilized in the implementation of similar projects. It must be borne in mind, however, that a desk evaluation review is but one element of a critical examination to which there must be a tentative approach and continual testing of its conclusions. As the Joint Inspection Unit concluded:

> "One of the most difficult problems which internal evaluation systems face is the tendency to regard them as a self-contained management technique which merely needs to be introduced into an organization to swiftly improve operation. In fact, evaluation is only a phase -- albeit an important one -- in the basic management cycle. It cannot have its full impact until it becomes part of an overall management system." (Second Report on Evaluation in the United Nations System, para. 28, Joint Inspection Unit, JIU. rep.6).

Findings and recommendations are in Sections III and IV of this report.

FINANCIAL SUMMARY

Project: MYA/6/015 HORMONAL STUDIES ON PITUITARY ADRENAL DISORDER

Recipient Institution: Ministry of Health,
Department of Medical Research,
Yangon

Counterparts: Maung-Maung Thwin (until February 1991)
Myo-Khin (as of February 1991)

Financial Data:

Current Budget ($)	1989	1990	1991	1992	1993	TOTAL
Experts	24 300	-	8 850	-	-	33 150
Equipment	25 000	-	7 014	-	-	32 014
Fellowships	4 400	-	-	-	-	4 400

Disbursements ($)	1989	1990	1991	1992	1993	TOTAL
Experts	-	18 259	563	7 695	-	26 517
Equipment	20 291	772	7 059	3 367	652	32 141
Fellowships	-	-	5 536	-	-	5 536

Total disbursements (experts, equipment and fellowships): $64 195

Project completed: 26 July 1993

APPROVED PROJECT OBJECTIVES AND ACTIVITIES

The objective of the project was to determine the incidence, facilitate early diagnosis and assess the value of therapy in hypopituitarism following snake bite, through the measurement of pituitary and adrenocortical hormones in serum and their changes in response to dynamic tests. It was planned that bulk reagent methodology should be introduced for in-house assays of the pituitary and adrenal hormones. The assays should be utilized in the measurement of hormonal status of snake bite victims for early diagnosis and prevention of sequelae on the pituitary-adrenocortical axis.

The Agency was to assist the Government in their efforts by providing the services of experts, equipment and chemicals required, and training for the local staff involved.

Intended target groups and beneficiaries of the project were the health and agricultural sectors of national economy and the population at large, particularly farmers, who were the worst affected.

PROJECT SUMMARY

In December 1987, the Ministry of Health submitted a request to the Agency for assistance in implementing in 1989-1990 a project on application of nuclear techniques in research of tropical diseases, in particular snake bite. In his technical appraisal the Technical Officer (Piyasena) supported the request as being relevant to the country's needs. He noted, however, that the request comprised two issues: (i) scientific work related to snake bite victims; and (ii) the introduction of bulk reagent methodology for non-thyroid related hormones in the laboratory. The Technical Officer considered that the first issue was more appropriate for a Research Contract, while the second one was suitable as the subject of a separate TC project. He recommended that the request be reformulated in line with his observations. A reformulated request was resubmitted to the Agency in June 1988 for the following Agency inputs: An expert in hormone assay for three months in 1989, to plan and assist in the introduction of bulk reagent methodology; some spare parts for equipment, RIA kits, bulk reagents, etc. at an estimated cost of $20 000 in 1989; and one six-month fellowship during 1990 for studying advanced RIA techniques.

Approval of the project under the 1989 Regular Programme provided for 3 months of expert services, $25 000 for equipment and six months of fellowship training.

Between September 1990 and July 1993 a total of five programme changes were made to respond to developments of the project. The total budget for the years 1989 through 1991 amounted to $69 564 and included $33 150 (4 man-months) for expert services, $32 014 for equipment, and $4 400 for a fellowship.

Total disbursements under the project amounted to $64 195, providing a total of 4.1 man-months of expert services, $32 141 worth of equipment, as well as one fellowship for a total of 6 months of training abroad. The project was closed on 26 July 1993.

IMPLEMENTATION

Experts

Expert Task 01 - Hormonal Assay

- S.L. CH'NG (MAL) May - August 1990 3.1 months
  - To install the RIASTAR gamma counter;
  - To draw up a strategy for investigation of hormonal changes in snake-bite victims; and
  - To introduce in-house radioimmunoassay using bulk reagents for the relevant hormones.

On arrival the expert found that the staff of the Department of Medical Research (DMR) were well trained and skilled in immunoassay methodology. Several excellent collaborative papers had been published on the effect of snake bites on the levels of pituitary and adrenocortical hormones.

The expert installed a new RIASTAR gamma counter and brought it into operation. All the software was tested and the staff were instructed on their use.

The IRMA (immuno-radiometric assay) for Russell's viper antigen was improved. A modification was made by using the same antibody for both immobilization on a solid phase as well as for labelling. The other assays for pituitary peptide hormones in blood and for human Growth Hormone (hGH) and free cortisol in urine were set up using imported bulk reagents. Some progress was made to initiate local reagent production but part of this work suffered because the necessary reagents did not arrive in time.

Before leaving the country, the expert provided the counterpart staff with instruction and left written protocols as to how they may proceed.

The expert's recommendations:

To the Government:

- The Nuclear Medicine Division of the DMR at the present moment is the best equipped for the future development of immunoassay technology in Yangon. The division should be encouraged to expand and develop to become the centre of excellence in the country and to form the base for devolution of immunoassay methodology to the peripheral laboratories. It should become the centre for (1) collaborative research with other clinical units; (2) screening of diseases, using immunoassay methodology; and (3) training of medical and scientific staff.

To the counterpart:

- The snake-bite project has tremendous potential for future research into medical, pharmaceutical, biochemical aspects and should be continued and supported. The recently published works are just indicators for future research development. Further fruitful areas of research are: (1) the study of the effects of snake venom on insulin and glucose metabolism; (2) the study of the effects of snake venom on gut hormones secretion (e.g. gastrin and other polypeptide hormones); (3) the study of the long-term effects of snake bite on reproductive hormone secretion; (4) the study of the effects of snake venom on secretion of atrial-natriuretic polypeptides and sodium metabolism; (5) the study of the long-term effects of snake bite on renal function (e.g. microalbuminuria).

- To carry out the initial clinical research work, the division probably has to rely initially on bulk reagents or assembled bulk reagents in kit form. The introduction of bulk reagents has to be implemented gradually in stages. The major aim of the project at the present moment is to study effects of snake bite on secretion of the relevant hormones. The second stage should consist of partial production of the labile component of the reagent, i.e. iodine labelled monoclonal antibodies for the polypeptide hormone IRMA assays, the cortisol conjugate, and standards. At the third stage, the division should attempt to raise polyclonal antibody to cortisol and hGH and immobilize these on to solid phases.

- The production of monoclonal antibody will have to await future development of the division, and the supporting units and training of its staff. The division in the meantime should carry out further study on the venom antigens and try to raise antibody to individual venom components for setting up immunoassay methodology (unique to the institute) for future clinical study of the effects of the individual components of the antigens. The division should also look into the alternative label, e.g. Europium label for time-resolved fluorescence immunoassay. This would be a fruitful area for future advance research.

- The division should also look into innovative ways (e.g. using locally available human resources and replacement parts) for future maintenance of the instruments. Additional dehumidifier and voltage stabilizers would be extremely useful to the division.

- The number of scientific staff should be increased to cope with the expected increase in work load, e.g. in-house reagent production and research activities. The staff should be given ample opportunity to go abroad for regular advanced training and conferences to update information on recent biotechnological developments.

To the Agency:

- The Agency should provide long-term support for this very important project. The support should consist of: (1) continual supply of bulk reagents; (2) training programme for the scientific and instrument maintenance staff (especially for the RIASTAR gamma counter); and (3) prompt provision of replacement boards or other parts for the repair of the instrument.

Expert Task 90 - Consultant

- R.D. PIYASENA (IAEA) April 1991 3 days
  - To evaluate the effectiveness of the Agency inputs provided, attend to any troubleshooting as may be needed, and assist in the identification of meaningful areas for future development.

The Technical Officer reported that good progress was being made in research activities of the DMR and the Agency inputs had been well utilized. It was foreseen that the loss of two key staff members should not strongly affect the implementation of the project. Two new technicians have been appointed to support the two senior technicians.

The Technical Officer recommended that a follow-up expert mission which was specifically requested be provided by the Agency in 1992 as well as reagent supplies. Local funds should be found for local travelling to the "snake bite area", 90 miles from Yangon.

Expert Task 02 - Upgrading of Radioimmunoassay Techniques

- S.L. CH'NG (MAL) May/June 1992 29 days
  - To introduce and develop radioimmunoassay for non-thyroidal hormones using bulk reagent methodology and to improve radioimmunoassay techniques;
  - To help to develop a future research programme for the Nuclear Medicine Division of DMR; and
  - To give advice in the formulation and implementation of the Technical Co-operation Programme for 1993-1994.

Several new techniques were introduced into practice at the DMR by the expert, e.g. re-equilibration immunometric assay, raising antisera in chicken, data analysis. It was found that changes in hormonal levels in urine could serve as a prognostic indicator in snake bite survivors. Long term follow up of the findings would be required to establish the clinical predictive value of this finding. Promising areas for further research were proposed by the expert.

The expert concluded that the project was well planned and carried out with precision by the local counterpart and his research team. Optimal use was being made of the equipment and material resources supplied by the Agency. However, additional equipment, such as a liquid scintillation counter and a time-resolved fluorometer, would be essential for future continuous development of the acquired immunoassay technology. A simple chromatography system could complement the immunoassay work. In order to further strengthen both the antibody production facility and the data processing facility, additional equipment, training and expert services would be required.

The expert's recommendations, as supported by the Technical Officer:

To the Government:

- The Nuclear Medicine Division is well equipped and staffed. Every opportunity should be given to the unit to assist in its development to become one of the centres of excellence in the region.

To the counterpart:

- The initial analysis of the results showed that it is possible to predict the severity of the snake bite by measuring urinary hGH output. But long-term follow-up of these subjects are important to establish the predictive value of this finding. The data is good enough for publication as a preliminary result. The data also indicated that it is important to further identify the true causative factor of the hormonal and pathological changes, especially the cytokine IL-1, IL-6, & TNF & the different components of snake venom, as this has important future pharmacological and therapeutic implications. The long-term effect of venom on serum reproductive hormone secretion in these subjects should be further studied. Other serum biochemical substances mentioned in the end-of-mission report for the first visit to DMR by the author should be further explored.

- The technique of re-equilibration assay could be applied to hGH assay in the long-term follow-up of these subjects as also to other hormonal assays. The technique of antibody production using chicken could be further developed. Data processing facility could be improved for more sophisticated analysis to detect trends in hormonal levels in long-term follow-up; (this has to await the upgrading of the computer facility in the unit). The use of other labels, such as tritiated label and lanthanide label, should also be explored in the future.

- The staff should be exposed to opportunities to continuously upgrade their knowledge in recent advances in immunoassay and other related techniques in the region, so that regional collaboration could be effectively implemented.

To the Agency:

- As the Nuclear Medicine Division of the DMR has great potential to develop into one of the centres of excellence within the region, strong support should be provided and sustained in terms of:
  (1) Additional equipment, such as liquid scintillation counter, time-resolved fluorometer, computer with software, simple chromatography system.
  (2) Reagents, as per attached list, and IL-1, IL-6, TNF assay kid.
  (3) Fellowship training for the staff.

In his assessment of the expert's report, the Technical Officer concluded that the mission had been an outstanding success, and that the technical results beginning to emerge were quite exciting, particularly the finding that changes in hormonal levels in urine could serve as a prognostic indicator in snake bite survivors. If this were confirmed by long-term studies now in progress, the finding should be published at international level.

With regard to the expert's recommendations, the TO considered that extending the studies to assays of cytokines and INF was really up to the counterpart, but seemed the logical thing to do from the results so far. However, he doubted very much whether bulk reagents were obtainable for these sophisticated assays, but commercial kits could be, and he would look into the issue. As regards the equipment, the TO stated that the LSC had already been provided. The computer, chromatography system and the reagents were all agreed to and procurement requests would be issued. Fellowships were a different issue, but the TO noted that we had trained workers from this lab, and that other applications were pending.

Equipment

The items purchased and supplied to Myanmar for project MYA/6/015 are listed on the following page:

LIST OF EQUIPMENT SUPPLIED			
Ordered	Supplier	Items	Shipped (S) Received (R)
89-02-27	Canberra-Packard, AUS	RIASTAR 5410 multiple manual gamma counter, I-129 source	89-08-29 (S)
89-02-14	Fischer Scientific Co., USA	Vacutainer tubes, needles, absorbent paper	89-04-29 (S)
89-01-20	Recom Electronics, AUS	Constant voltage transformer	89-06-29 (R)
90-07-10	Sigma, GER	Chemicals (danazol, hydrocortisone, etc.)	90-08-09 (R)
90-07-16	Metria, UK	CH IRMA Reagents	90-08-29 (R)
90-08-24	Diagnostic Product Co., USA	ACTH double antibody RIA Kits, Cortigol double antibody	90-12-07 (S)
90-10-12	Sigma, GER	Carboxymethyloxime, Methylene chloride, etc.	91-02-05 (R)
90-10-12	Metria, UK	hGH IRMA reagents, hGH antibody, purified Hgh for standard preparation, I-125 tracers	92-06-26 (R)
91-03-08	Nordion International, CAN	Radiochemicals (four shipments in 1991)	91-12-18 (S) (final shipm.)
91-03-08	University of Surrey, UK	Sheep anti-cortisol, Donkey anti-sheep, Rabbit anti-human Growth Hormone	91-04-02 (R)
91-03-08	Diagnostic Products Corporation, USA	Cortisol Bulk reagents, ACTH kits (three shipments in 1991)	91-08-13 (R) (final shipm.)
91-03-08	Southampton/South West Hampshire Health Authority, UK	Cortisol conjugate for immunization	91-04-29
91-08-26	METRIA, UK	GH IRMA reagents, prolactin IRMA reagents	91-09-19 (S)
91-11-22	Diagnostic Product Corporation, USA	Cortisol bulk reagents, ACTH double antibody (three shipments in 1992, one in 1993)	93-02-08 (S) (final shipm.)
91-11-22	METRIA, UK	GH IRMA reagents (four shipments in 1992)	92-11-17 (R) (final shipm.)

The RIASTAR gamma counter was installed by the Agency expert in mid-1990. All the software was tested and was found to be working. Some technical problems encountered at the installation were resolved by the expert.

Some delay in the shipment of reagents required for field work by the expert in mid-1990 was caused partly by the Gulf crisis. Further provision of the chemicals and reagents proceeded according to the schedule of the field and laboratory studies.

Since the funds available under the project were exhausted, the additional equipment recommended by the expert was provided under a project approved for 1993/94, MYA/6/017, Application of Nuclear Techniques in Reproductive Health.

Training

One candidate was nominated in May 1990 for project-funded training and duly awarded a Type I fellowship:

MYA/9003 KYI-THEIN, KYI-CHEN
Type I Fellowship, June/December 1991
THA - Chulalongkorn Hospital and Medical School, Bangkok 6 months
Radioimmunoassay (6B)
- o General training in radioimmunoassay with special emphasis on solid phase methodology, labelled antibody techniques, quality control and data processing.

ACCOMPLISHMENTS

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III

FINDINGS

The objective of project MYA/6/015 has been achieved. A facility has been created to study the effects of snake-bite on the hypothalamic-pituitary-adrenal axis by the measurement of basal serum levels of the relevant hormones and response to dynamic tests by RIA methods. Improved facilities and local expertise needed to conduct a hormonal study on pituitary adrenal disorders in snake-bite patients have been established.

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IV

RECOMMENDATION

In view of the importance of the results of the hormonal studies on pituitary adrenal disorders started under the project, these activities need to be sustained. To this end, the Agency should maintain contacts with the Department of Medical Research, Yangon, with the aim of determining possible future needs as well as ways of providing further Agency support that may be required for the continuation and further development of on-going research.