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## CONTROLLED FIELD TRIAL WITH ALUMINIUM PHOSPHATE ADJUVANT CHOLERA VACCINE IN CALCUTTA, 1975-1976

The rationale for large-scale use of any vaccine in the prevention of an infectious disease lies in the demonstration of its effectiveness in man by properly designed controlled field trials. It is essential for such a field study to include vaccinated and controlled groups<sup>1</sup>.

Cholera vaccine has been greatly over-rated as a preventive measure against the disease. This impression of effectiveness was built up on several earlier observations and field studies without adequate controls.

### EARLIER CONTROLLED FIELD TRIALS (1963-1973):

Several controlled field trials with varieties of conventional cholera vaccine were conducted in three countries namely India, Philippines and Bangladesh.

The first field trial in Calcutta was initiated in the year 1964, where five different cholera vaccines and a control TAB vaccine were used. "The trial could not give any unequivocal answer to the question of efficacy of cholera vaccine, although the three agar grown vaccines showed 30-40% effectiveness"<sup>2</sup>.

The second trial was conducted in 1965 in two phases<sup>3</sup>. During the first phase of the trial an agar grown vaccine from the Central Research Institute, Kasauli was compared with a casein hydrolysate vaccine from the Haffkine Institute, Bombay. The agar grown vaccine showed an effectiveness of 40%. However, the

duration of protection could not be determined as there were only a few cases of cholera that year.

During the second phase an agar grown classical cholera vaccine and an *El Tor* (haemolytic) vaccine were used to determine whether *El Tor* and classical cholera vaccine give cross protection. There was little difference in the incidence of cholera in all three groups-including the control, in the first three months, thus leaving the question unanswered: Does *El Tor* vaccine protect against classical cholera infection?

### FOUR CONTROLLED FIELD TRIALS IN THE PHILIPPINES:

The first trial was carried out on about 584,000 people in Negros Occidental Province in 1964. The aim of the trial was to determine the effectiveness of a classical cholera, a cholera *El Tor* and an oil-adjuvant vaccine<sup>4</sup>. The trial showed that both classical cholera and *El Tor* vaccines afforded protection of about 50% but showed a varying duration of effectiveness. The immunity conferred by *V. cholerae* vaccine declined rapidly after three months whereas that of *El Tor* continued up to six months. An oil-adjuvant vaccine, prepared by the Chiba Serum Institute, Japan, conferred the highest degree of protection for a longer period of time, but owing to the severe reactions caused by the vaccine, its use could not be recommended.

The second trial<sup>5</sup> was initiated in 1966

in an attempt to improve the over-all effectiveness by administering cholera *El Tor* vaccine in three different doses: one injection with  $8 \times 10^9$  organisms per ml, two injections of the same vaccine and a single injection of a double dose ( $16 \times 10^9$  organisms per ml.). No improvement in protection, which was statistically significant, was observed with one or two doses of the single strength or with the one injection of double strength vaccine.

The third trial in the Philippines<sup>6</sup> was conducted with monovalent *Ogawa* and *Inaba* vaccines prepared from classical and *El Tor* strains of *V. cholerae*. The results indicated that all four vaccines tested offered a significant degree of protection which varied from 58-71%.

The fourth field trial<sup>7</sup> was conducted between July 1971 and February, 1972 to assess the relative effectiveness of the intradermal and subcutaneous routes of administration of the same cholera vaccine. The trial showed that both these routes were effective and gave significant protection against cholera. In the 1-5 years age group, the vaccine afforded a more lasting protection when given subcutaneously (6 months) than when given intradermally (4 months).

Four controlled field trials were undertaken in East Pakistan (now Bangladesh) between 1963 and 1969. The first trial was initiated in November, 1963. An agar grown phenol killed commercial classical cholera vaccine (CRL vaccine) with high mouse potency was used along with a control TAB vaccine. During the first year of study<sup>8</sup> the incidence of cholera in the vaccinated group was 1.7 per 1000, whereas in control group it was 6.1 per 1000. In a follow-up study<sup>9</sup> it was observed that the effectiveness was 76% during the first cholera season (December, 1963 - June, 1964) and 62% during the second cholera season (July 1964 - June 1965) following vaccination. However, many of the children under five years lost protection during the second cholera season. The high mouse potency (CRL) vaccine produced untoward reactions among adults.

During the second trial a whole cell vaccine (CRL) and an *Ogawa* fraction purified antigen were used. The results of these two trials showed that: a high potency vaccine can give significant protection upto 18 months; more than 70% protection could be obtained

during the first 7 months but beyond that period protection fell in the age group below 5 years; and the vaccine had no effect on asymptomatic carriers in family contacts of cholera patients. The purified *Ogawa* antigen afforded significant protection to adults against *Inaba* serotype.

The third trial<sup>10</sup> was conducted during 1966-67 and children aged 3 months to 14 years were inoculated with a commercially made classical cholera vaccine with one and two dose schedules. During the 8 months cholera season following immunization, a single dose produced 46% and 2 doses provided 64% protection. The single dose was virtually ineffective in children. The enhanced effect of 2 - dose schedule was presumably due to the booster effect in children under 5 years. Duration of significant protection even with 2 doses did not extend beyond the first 3 months.

The fourth field trial<sup>11</sup> in rural East Pakistan (now Bangladesh) was conducted in 1968-69 with a monovalent whole cell *V. cholerae Inaba* vaccine, a monovalent whole cell *V. cholerae Ogawa* vaccine and a purified *Inaba* antigen. A total of 45,711 children in the age group 0-14 years were inoculated. Inoculations were given annually for 2 years just before the start of the cholera season and follow up was continued for one additional year. All the cholera cases that occurred were due to *Inaba* serotype, so that protection could be studied only against that serotype. Two annual injections of the whole cell *Inaba* vaccine gave the highest level of protection, averaging 84% over the 3 years of follow-up; a single injection of the purified *Inaba* vaccine gave less protection (51%). Two annual injections of the whole cell *Ogawa* vaccine failed to protect children under 5 years but gave 48% protection to children in the age group 5-14 years against *Inaba* cholera. Hence, monovalent vaccine cannot be recommended for general public health use as it gives relatively low protection to infection with a heterologous strain.

The following facts have been brought out by the results of the above field trials:

The degree of protection afforded by the vaccines now available does not exceed 50 to 60 per cent and for a period of 3-6 months only.

Longer protection was observed with an oil-adjuvant vaccine in the Philippines and with a high mouse potency vaccine in Dacca. These two vaccines could not be recommended for mass immunization as they produced severe reactions.

Cholera vaccines did not modify the severity of the symptoms in vaccinated cholera patients.

Vaccination did not reduce the frequency of inapparent infection.

The rate of protection was lowest among 0-4 years old children.

Duration of significant protection, even with 2 doses did not extend beyond 3 months in the cholera season. The degree of protection of the groups immunized with 2 doses of  $8 \times 10^9$  and  $16 \times 10^9$  vibrios did not differ significantly.

Vaccine-induced protection against cholera depends upon the development of type-specific immunity.

#### RECENT DEVELOPMENTS:

A great deal of research is now in progress in many laboratories throughout the world to develop more effective immunizing agents against cholera and a few of them are being tried in large-scale controlled field trials. A brief outline of these trials is as follows:

##### Cholera Toxoid:

It is now fully established that the severe fluid and electrolyte loss in cholera is caused by an enterotoxin elaborated by *V. cholerae* during its multiplication in the gut. This toxin has been purified and converted to toxoid. One such product, the glutaraldehyde toxoid is being used for a controlled field trial in Bangladesh. The objective of the study is to determine the role of antitoxic immunity in protecting against cholera. The follow-up of the trials is not yet completed.

##### Aluminium hydroxide adsorbed cholera vaccine:

A controlled field trial with the aluminium hydroxide adsorbed cholera vaccine was undertaken in Surabaya, Indonesia with the joint collaboration of the World Health Orga-

nization and the Government of Indonesia. The final results of the trial are not yet available.

#### PRESENT TRIAL BY ICMR CHOLERA RESEARCH CENTRE:

Aluminium compounds are generally recognised as the safest adjuvants and their use is based on wide experience with other vaccines<sup>12</sup>. A cholera vaccine (containing 4000 million organisms of classical *V. cholerae* of both *Ogawa* and *Inaba* serotypes per 0.5 ml) adsorbed with aluminium phosphate as adjuvant has been used in a controlled field trial in Calcutta during 1975-76 by the ICMR Cholera Research Centre. Tetanus toxoid was used as placebo. Volunteers above 5 years received 0.5 ml (8000 million vibrios) and those below 5 were administered 0.25 ml of the vaccines given intramuscularly as a single dose. Children below 1 year were not included in the trial.

#### STUDY AREA & CHOLERA INCIDENCE:

The study area comprised 17 Municipal Wards of Calcutta and two adjoining Wards of South Dum Dum Municipality with a total population of above 500,000. The above area was selected on the basis of a high incidence of cholera during the past 10 years. The average annual incidence was 0.5 per 1000, and it was estimated that a minimum of 100,000 volunteers should be inoculated with each vaccine to ensure a statistically significant result.

#### PREPARATORY PHASE:

During the preparatory phase 150 health assistants were recruited and were trained for the programme. Each volunteer was inoculated with a separate sterile needle following a strict random allocation. The vaccine bottles were identical and were coded as "A" and "B". The identity of the vaccines during the vaccination phase was not disclosed. The vaccination team consisted of one recorder and one vaccinator. Four such teams were closely supervised by one health inspector who had previous experience of similar controlled trials conducted in Calcutta. Two physicians were constantly supervising and assessing the vaccination programme.

#### STUDY POPULATION & VACCINATION PHASE:

The vaccination phase was completed in 45 working days. A total of 203,170 volunteers were vaccinated on a random basis during the inoculation phase, of which 101,096 received



the adjuvant cholera vaccine and 101,030 were given placebo (tetanus toxoid). Out of a total enumerated population of 529,580 about 69.6% could be contacted. Of the 69.6% contacted, only 38.4% could be vaccinated by repeated home visits: 24.7% refused to accept vaccination while 6.5% were found to be ill. During the cholera field trials in Calcutta in 1964 and 1965 about 36% and 35% of the study population respectively could be vaccinated. The refusal rate was high which is to be expected in an urban population. Out of the total of 14,291 vaccinated in 1-4 year age-group, 7,159 received the vaccines and 7,132 the placebo. Similarly of 46,956 volunteers in the 5-9 years age-group 23,481 were given cholera vaccine and 23,475 placebo. Overall figures show that 101,096 were given the vaccine and 101,030 the placebo. The male:female ratio was 1000:766 among the vaccinated volunteers and reflects the overall sex ratio of the study area which was 1000:726 according to the 1971 census.

#### REACTIONS TO VACCINE:

Assessment of reactions following vaccination shows that there was little significant difference between those in cholera vaccine and placebo groups. The reactions looked for were erythema, pain, local tenderness and swelling, headache, fever and vomiting. It was, however, observed that the adjuvant vaccine produced a rise of temperature in 21.7% of volunteers as compared to 11.3% in placebo group. The fever was mild.

#### FOLLOW-UP PHASE & RESULTS:

The follow-up of the vaccinated volunteers was started 7 days after the start of the vaccination phase. It was decided to continue the follow-up phase for a period of 2 years.

Since the incidence of cholera in the study area was calculated on the basis of hospitalised cases, it was decided to restrict the follow-up to the hospitals. A hospital follow-up is less cumbersome, economic and more acceptable since only genuine cholera cases, acute enough to be hospitalised, are encountered. The follow-up at the home level stands the occasional risk of including sub-clinical infection, on whom the cholera vaccine has no effect. All acute cholera cases in Calcutta and its suburbs are admitted mainly to the Infectious Diseases Hospital which is situated within the study area. No other hospitals in Calcutta admit cholera

patients. Round-the-clock vigilance was employed at the hospital so that every cholera case coming from the study area for admission was sampled before any antibiotic is administered. In case of any doubt the houses of the cholera cases are visited to determine their vaccination status.

The results of the first 90 days period of follow-up showed that of 27 cholera cases detected during this period 5 belonged to vaccine group and 22 to placebo group. The overall protection offered by the adjuvant vaccine was 77.3% which was statistically highly significant ( $P < 0.01$ ). When the period of follow-up was extended upto 180 days the overall efficacy of the vaccine appeared to be 60.6%, a figure which is statistically significant ( $P < 0.01$ ).

It is interesting to note that children between 1 and 4 years of age were protected by the adjuvant vaccine at the rate of 100% for 180 days, which was statistically significant. Trials conducted earlier in Bangladesh, Philippines and Calcutta with conventional cholera vaccines had shown a poor degree of protection in this particular age group. Considering the fact that it is this young age group which is mostly affected by cholera in endemic areas, the high degree of protection offered by the aluminium phosphate adjuvant vaccine may be regarded as an important finding. It may be noted that, in a similar trial with aluminium hydroxide adjuvant vaccine conducted in Indonesia, better protection was found amongst children below 4 years of age.

Considering the results obtained so far in the present trial, it may be concluded that the aluminium phosphate adjuvant cholera vaccine, if administered prior to an epidemic season, may be able to modify the course of the epidemic by effectively reducing the number of cholera cases, particularly among children below 4 years.

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## ABSTRACTS

Some Research Projects completed in 1975

### BIOCHEMISTRY

#### *Biosynthesis and metabolism of phospholipids in chicken*

Studies on  $^{32}\text{P}$  incorporation into chicken liver under *in vivo* conditions showed that its incorporation reached a maximum at 6 hrs after injection and that estrogen injected simultaneously accentuated the rate of incorporation by 80%. The incorporation of  $^{32}\text{P}$  into liver phospholipids of estrogen-treated birds (treated for 10 days) was also greatly enhanced. There was a simultaneous increase in the synthesis of neutral lipids. The hormone-treated birds secreted these lipids into serum at a much faster rate than the controls. The results also suggested an increased rate of conversion of phosphatidyl ethanolamine into phosphatidyl choline.

Cyclic AMP was found to inhibit the synthesis of fatty acids from acetate at higher concentrations while at very low concentrations this synthesis was activated. The cyclic nucleotide specifically inhibited the acetate incorporation into triglycerides as compared to other lipids. There was no indication of an enhanced lipolysis.

Cyclic AMP also inhibited the incorporation  $^{32}\text{P}$  into phospholipids under *in vitro* conditions and this effect was found to be not due to a decreased  $^{32}\text{P}$  incorporation into the precursors of phospholipids.

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#### *Studies on the kidney glutaminase*

Earlier studies<sup>1</sup> on albino rats showed that adrenalectomy caused diuresis, negative nitrogen balance, acidosis and excess excretion of both sodium and potassium. Amongst the nitrogenous products, there was a marked increase (about three to four fold) in ammonia excretion. Chemical analysis of the adrenalectomized rat kidneys showed there was hypertrophy, increased RNA and protein. The enzymatic analysis, in particular the enzymes involved in the formation of ammonia like amino acid deaminases, glutamic-dehydrogenase and glutaminases, showed that there was a phenomenal change in the activity of kidney glutaminases but almost no change in other ammonia forming enzymes.

The enzymatic analysis of the ammonia forming enzymes of adrenalectomized rat kidney showed that there was increase in the activity of kidney glutaminases. Kidney glutaminase exists in three forms (i) phosphate dependent (pH optima 7.4), (ii) phosphate independent (pH optima 7.4) and (iii) glutaminase II (-ketoacid dependent, pH optima 8.5). The activity of the above three increased under adrenalectomized condition and the additional observation was that a new peak appeared at pH 6.0. This peak was due to the combined activities of the three forms of glutaminases. When adrenalectomized rats were injected with adrenal extract or a mixture of corticosteroids, the pH 6.0 peak did not appear and there was no increase in urinary ammonia. A phosphate dependent pH 6.0 glutaminase studies was isolated. Kinetic studies and optimum temperature showed that the enzyme was different as compared to the normal phosphate dependent glutaminase. The above experiments showed that as a response to acidosis, due to the adrenalectomy, these glutaminases are formed to help to maintain homeostasis<sup>2</sup>. When adrenalectomized rats were fed with added pyridoxine (3 mg per rat per day) diet, the pH 6.0 glutaminases did not appear and there was no diuresis, acidosis and the ammonia excretion was normal.

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#### *Functional role of urea cycle intermediates in brain*

The distribution of argininosuccinate synthetase and argininosuccinase, arginase and synthetic capability of urea in the cerebellum, cerebral cortex and brain stem were studied. The cerebral cortex showed high argininosuccinate synthetase, argininosuccinase and synthetic capability of urea from aspartic acid and citrulline. Of the three regions the cerebellum had a high arginase activity. The activities of the enzymes transaminidase and ornithine aminotransferase involved in the metabolism of arginine and ornithine in pathways, other than urea formation, were studied in the three regions of the rat brain. The activity of creatine phosphokinase in the three regions was the same. The carbamylphosphatase activity was highest in cerebellum. Cerebral cortex had a high activity of aspartic acid transcarbamylase. The brain stem amongst the three regions had the lowest activities of glutamine synthetase and glutaminase. The activities of the above enzymes in the different regions are discussed in relation to urea production and the utilisation of the urea cycle intermediates.

Intraperitoneal injection of large amounts of citrulline brought about a rise in glutamine synthetase activity of the cerebellum and brain stem and a rise in ornithine aminotransferase in the cerebral cortex and liver. The results, are discussed in relation to the mechanism of action of citrulline in

alleviation of toxicity in hyperammonemic states.

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#### ICMR NEWS

##### ICMR/DGHS SEMINAR ON CHOLERA CONTROL

A Seminar on Cholera Control is being held from May 20-28, 1976 at the Cholera Research Centre, Mohammad Ishaq Street, Calcutta. The objective of the seminar is to review the recent trends in epidemiology, diagnosis and

methodology of treatment. The seminar will consist of lectures discussions, demonstrations and field visits. Twenty to thirty participants chosen from cholera endemic States and Union Territories are expected to attend the seminar.

##### ICMR/WHO NATIONAL COURSE ON 'PREPARATION AND STANDARDISATION OF SALMONELLA DIAGNOSTIC SERA' HELD AT THE DEPARTMENT OF MICROBIOLOGY, LADY HARDINGE MEDICAL COLLEGE, NEW DELHI FROM APRIL, 12-17, 1976

The course was a sequel to the ICMR/LHMC workshop-cum-seminar on 'Microbiological Investigations in the Epidemiology of Enteric Infection' held at Lady Hardinge Medical College, from 9th to 14th December, 1974. In a survey carried out on the availability of salmonella diagnostic sera, it was found that some centres had stopped producing these sera and among those, which were producing antisera, many did not absorb the antisera. This meant great hardship to the peripheral laboratories.

The faculty consisted of 5 members and included Dr. Benard Rowe, WHO consultant. Dr. Rowe is the Director of the Salmonella Shigella Reference Centre, Central Public Health Laboratories, Colindale, London. The 12 participants selected, came from existing salmonella sera production centres.

The recommendations of the workshop are given below:-

- I. As a first priority the following centres will produce a basic set of adsorbed salmonella sera comprising of 0=2, 0=9, H-a, H-d and Vi antisera:

1. Central Research Institute, Kasauli

2. Indian Veterinary Research Institute, Izatnagar
3. Haffkine Institute, Bombay
4. King Institute, Guindy
5. Institute of Preventive Medicine, Hyderabad.
6. Vaccine Institute, Baroda.
7. Laboratory of the Serologist to the Govt. of India, Calcutta
8. Pasteur Institute, Shillong
9. Public Health Laboratory, Poona
10. National Institute of Communicable Diseases, New Delhi.

These laboratories must submit their sera for quality control to the Salmonella Reference Centre, Central Research Institute, Kasauli, before supplying the antisera.

Information regarding the availability of these sera must be published in the NICD

bulletin. These sera should be available within one year.

II. After this basic set of sera is available, the Salmonella Reference Centre, C.R.I., Kasauli should prepare polyvalent O and H sera, absorbed O and H factor sera and rapid diagnostic sera for H antigens.

III. The manufacturing laboratories should motivate the laboratories to whom they

supply sera, to take part in the National Salmonella Surveillance Programme.

The aim of the recommendations was to establish a network of salmonella surveillance in the country and to step up the production of diagnostic sera.

The Manual of Procedures for Salmonella Serology & Production of Diagnostic Sera prepared for this course is compact, comprehensive and very useful for anyone taking up production of diagnostic reagents for salmonella work.

#### THE CENTRAL JALMA INSTITUTE FOR LEPROSY (ICMR), AGRA

This leprosy centre was established in Agra in 1967 by the Japanese Leprosy Foundation, Tokyo, in collaboration with the Central and the U.P. Government.

The centre consists of a complex, which includes an administrative set up and a supporting laboratory for a 50 bedded hospital alongwith an out patient department. For the last 10 years this Institute has done considerable work in establishing an active centre for the care of leprosy patients. The JALMA team commenced its clinical activities in 1966, on a comparatively small scale. These activities gradually expanded and in 1968 there was an out patient department in the centre and clinics at Ghatampur, Etawah & Mathura. By 1969 the centre was running a 40-bedded hospital. The laboratory is very well equipped. With the help of the Colombo Plan staff a small beginning was made in research on immunology of leprosy in 1972.

JALMA centre has been extremely well maintained and caters for leprosy patients free of cost. The total laboratory space comprises about 12 big laboratories, apart from the self contained Out Patient Department Laboratory.

The centre was taken over by the Ministry of Health & Family Planning on April the 1st, 1976 and placed under the ICMR.

On April 18, 1976, an inaugural function was arranged at JALMA, Agra. The Chief Minister of U.P., the Minister of Health & Family Planning, the Japanese Ambassador, the Chief of the JALMA, the State Minister of Health, The Director-General of Health Services and the Director-General, Indian Council of Medical Research were present.

Dr. Karan Singh, Union Minister for Health & Family Planning was presented a giant symbolic key by Mr. Ueda, Chief of JALMA. The key was in turn presented to Dr. C. Gopalan, Director-General, ICMR. The function was very well attended.

A Scientific Advisory Committee, consisting of experts in various fields of leprosy, has been constituted by the ICMR. Detailed plans for future work at this centre will be drawn up by the Scientific Advisory Committee, in consultation with the Director and the Technical Committee of the ICMR. The Council plans to develop JALMA into a laboratory centre for certain special type of work in leprosy i.e. immunology, microbiology and chemotherapy etc., making use of the clinical facilities already established at the centre. The Director has been selected and is expected to take up his post shortly. Other staff is being recruited. The centre will be known as the Central JALMA Institute for Leprosy (ICMR):

# COUNCIL'S TRAINING PROGRAMMES FOR 1976-77

## (A) EXISTING ANNUAL TRAINING COURSES:

### Nutrition & Endocrinology:

At the National Institute of Nutrition, Hyderabad.

- (1) Annual Certificate Course in Nutrition; (December 1, 1976 to February 28, 1977)
- (2) M.Sc. (Applied Nutrition) Course: (June 1, 1976 to February 28, 1977)
- (3) Annual Certificate Course in Human Nutrition for Teachers in Agricultural Universities: (August - October, 1976)
- (4) Annual Training Course in Endocrinological Techniques and their Application:

### Reproductive Biology and Fertility Control:

At the Institute for Research in Reproduction, Bombay.

- (1) Annual Certificate Course in Reproductive Biology and Fertility Control: (November 1, 1976 to April 30, 1977)
- (2) Annual Training Course on Hormone Assays: (February 1, 1977 to March 31, 1977)
- (3) Annual Training Course in Endocrinology and Fertility Control: (October, 1976)
- (4) Annual Training Course in Cytology and Cytogenetics: (September, 1976)

### Haematology:

At the Blood Group Reference Centre, Bombay.

Comprehensive programme in Blood Banking Technology and Basic Haematology: (For a period of 3 months from February 15, 1976)

### Immunology:

At ICMR/WHO Research and Training Centre in Immunology, Department of Biochemistry, A.I.I.M.S., New Delhi.

\*Annual Training Course in Immunology

## Animal Technicians Training:

At the Laboratory Animals Information Service, National Institute of Nutrition, Hyderabad.

Ninth Annual Animal Technicians Training Course: (For a period of three months from September 1, 1976)

### Biostatistics:

At the National Institute of Nutrition, Hyderabad.

\*Third Training Course in Biostatistics for Statisticians and Medical Research Workers.

## (B) NEW TRAINING COURSES DURING 1976-77:

### Virology:

\*At the Virus Research Centre, Poona. Diploma course in Virology.

### Amoebiasis:

At the School of Tropical Medical, Calcutta.

Technician's Training Course in the field of Amoebiasis: (For a period of three months from April 1, 1976)

### Occupational Health:

At the National Institute of Occupational Health, Ahmedabad.

#### (1) \*Pneumoconiosis:

This course, meant for the medical practitioners to be organised in co-operation with Directorate of Mines Safety, Dhanbad.

#### (2) \*Diploma in Occupational Health for the year 1976-77 under Gujarat University.

### Pharmacology and Drug Trials:

At Dr. U.K. Sheth's Unit, Seth G.S. Medical College, Bombay.

#### (1) \*A short-term course for four weeks' training.

(2) \*A long-term course for twelve weeks' training.

(C) COURSES FOR TALENT SEARCH SCHEME FELLOWS:

Haematological Techniques:

\*At the Department of Haematology, Post-graduate Institute of Medical Education and Research, Chandigarh.

Biochemistry & Instrumentation:

At the National Institute of Nutrition, Hyderabad. March 1-10, 1976.

Cell-Biology and Cyto-Genetics:

At the Indian Institute of Science, Bangalore. April 12-21, 1976.

Principles & Methods in Medical Statistics:

\*At the Tuberculosis Chemotherapy Centre, Madras.

Courses in Immunological Techniques:

\*At the Department of Biochemistry, AIIMS, New Delhi.

\*Dates to be announced later

INDIAN COUNCIL OF MEDICAL RESEARCH  
TECHNICAL REPORT SERIES

1. Research in Medical Education 1970
2. Research in Health Practices 1970
3. Acute Encephalopathy Syndrome in Children 1970.
4. Technical Review on Pneumoconiosis in India 1970
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