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29 August 1980

REGIONAL REFERENCE CENTRE ON HEAD AND NECK AND URINARY BLADDER CANCER, MEDICAL RESEARCH INSTITUTE, ALEXANDRIA

by

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The work on the using of Alpha Esterase in Urine is still going on. We are now moving into the Pilot Field study at the Beheira Governorate, but the available data and the study period is not sufficient enough to come into any conclusions.

Other useful tests :

1. Serum and Urinary Ribonuclease enzyme activity :

The results revealed an increase in serum and urinary ribonuclease of bilharzial bladder cancer patients. However, the statistical analysis revealed insignificant correlation between the incidence of bladder cancer and the enzyme activity of serum or urine samples.

11. Fibrinogen degradation Products :

These studies have not been carried since we have not received the chemicals of this test.

111. The separation of alpha esterase isoenzymes :

This study needs a special Gel Electrophoresis technique which is not available at the Institute.

The Development and Evaluation of a New Screening Test for Early Detection of Carcinoma of the Bladder

Principal Investigator :

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Proposed Starting Date : 1981
Proposed Duration in months 36 month. (three years)

Personnel in charge of the Project :

Principal Investigator : Prof. M.E.A. El-Kharadly
Prof. of Oncology & Dean M.R.I.

Collaborators

Field Work Supervisor & Epidemiologist	R.N. Bedwani, Assoc. Prof.
Biochemist	S. El-Sewedy, Assist. Prof.
Urologist	A. Arafa, Assist. Prof.
Cytologist (s)	
General Practitioners for Clinical exam. and interviewing patients and controls in the field.	Five
Laboratory technicians for routine examination of urine and stools and for biochemical and cytological lab., X-ray technicians.	Ten
Administrator	One
Secretaries	Two
Clericals	Two

Objectives:

This project aims to fulfil the following objectives:

- The development of a new screening test for early detection of Bilharzial carcinoma of the bladder using the alpha esterase activity in the urine and testing its sensitivity and specificity in the field.

2- Comparison of the efficiency and technical feasibility of this method as well as its cost in terms of manpower and facilities with those of urine cytology by :

a) all cases with positive esterase activity and a random sample of the negative alpha esterase cases will have also urine cytology test.

b) Comparison of the results and the technical simplicity of the alpha esterase test against that of urine cytology technique used as a massscreening in the project conducted by the Cancer Institute in Cairo.

3- Evaluation of the alpha esterase test by :

a) early : Comparison of the clinical stage at detection by the screening test with the clinical stage of cases presenting with symptoms.

b) late : Comparison of the total mortality or age specific survival rates in cancer bladder cases in the screened population with those of the control group.

The National Importance of the Project

1- The Magnitude of the Problem :

Bilharziasis is an endemic disease which affects 60-85% of the population in some rural areas of Egypt. It affects the socio-economic standard of the population as it affects their productivity.

Carcinoma of the bladder is the most challenging cancer problem in Egypt. In our statistics it is the second commonest type of cancer after breast with a relative frequency of 11 % and the most frequent in males (17%). Its association with bilharziasis is an established fact, but the nature of the cause effect relationship is still the subject of extensive investigations.

2- The rationale and prospects of the Project:

It may seem logic from the last statement that the most promising approach would be primary prevention by control or eradication of schistosomiasis . Inspite of the extensive efforts and campaigns undertaken by the Egyptian health authorities, this has proved so far a very difficult if not an impossible task, which is in line with the universal experience with parallel measures for environmental cancers. Thus it was decided to explore the possibility of developing a test for early detection (secondary prevention). Such a test is of particular importance in schistosomal bladder cancer, as symptoms of schistosomal cystitis may merge insiduously with those of cancer, with the result that when the patient presents the condition, may be too advanced for effective treatment . It has been estimated through our cancer registry that the average survival time of diagnosed cancer bladder cases to be only 1.5 years.

With the universal acceptance of cervical cytology as a screening test, our first attempt was to use urine cytology for the same reason, however, our experience was not satisfactory . This is due to the difficulties in recognising cancer cells amidst inflammatory and other cells, besides the fact that

this technique is time consuming, needs well trained cyto-technologists and cytologists and difficult to apply in mass screening programmes.

A histochemical study, conducted at our Institute, revealed that alpha esterase, an estrolytic enzyme, is present in the bladder urothelium in very low concentration, but in higher concentration in leukoplakia and in other urinary schistosomal manifestations, and in still greater concentration in bladder cancer. These findings have raised hopes of early detection of new or recurrent cases of bladder cancer through the use of an easier, reproducible biochemical test depending on urine analysis.

In comparison to other biochemical markers in urine and serum, it was found that urinary alpha esterase enzyme activity was consistently increased in all cases with bladder cancer and promised to be the ideal test.

A study of the enzyme activity in serum and urine was conducted at the cancer chemistry department. The preliminary results are summarised in the following two tables :

Table 1

Group	Enzyme Activity + S.D.		Serum/Urine
	Serum (Units/ml)	Urine (Units/L)	Ratio X10^3
1. Healthy Controls (22)	6.22 + 2.24	46.63 + 3/59	174
2. Schistosomal bladder cancer (35)	8.84 + 2.31	219.86+30.25	39
3. Schistosomiasis patients with other urologic diseases (92)	8.97 + 2.52	79.12 +35.88	107

Table (2)

Enzyme Activity (Units/L)	Schistosomal Bladder Cancer	Schistosomal Non-Bladder Cancer	Total
> 150	33	3	36
< 150	2	89	91
Total	35	92	127

a- False Positive = 3.37 %

b- False Negative = 5.71 %

$P < 0.001$

Material and Methods :

Two rural areas in Beheira Governorate (South east of Alexandria) with well defined populations of nearly equal size, fairly similar in their characteristics and with a nearly similar prevalence of bilharziasis (85% of population in this area are infected with bilharziasis), will be the material of the study. The first area will be chosen for testing the validity of the proposed screening test, the other area will act as a control. Assuming that the prevalence of schistosomiasis is the same, the total risk of developing bladder cancer would be equal.

The high risk group (in both populations will be defined as those individuals who had a history of treatment of bilharziasis, above age of thirty and professional farmers.

The first group (the test population) will be subjected in the first year to the following :

1- Routine urine analysis for bilharziasis and biochemical estimation of urinary alpha esterase activity.

2- Biochemically positive cases (with high alpha esterase activity) will be confirmed by means of cytology and urological investigation including pyelography and cystoscopy. The proved cancer cases

will recieve the appropriate treatment. The other cases, which are biochemically positive but non confirmed by other means will be kept under close observation with frequent biochemical, cytological and clinical follow up.

3- Random sample of the biochemically negative cases (with low alpha esterase activity) will be subjected to cytological and clinical examination. Cytologically positive cases will be subjected to clinical and urological workup, and the proved cases will receive the appropriate treatment. Cytologically negative cases will be rescreened periodically (yearly).

The Second group (the control population) will be followed in the ordinary way, i.e. all cases with symptoms suggestive of bladder cancer will receive a complete urological workup. The study will continue in the second and third year, while the negative cases in the test population will have a yearly rescreening.

Budget Project Proposal

		1st. year	2nd. year	3rd. year
A.	Salaries and Wages			
	Principal Investigator			
	Professional Persons			
	Technical Personnel			
	Other Personnel			
	Total Salaries and Wages			
B.	Staff Benefits			
C.	Total Salaries, Wages & Staff benefits	15,000	15,000	15,000
D.	Travel	5,000	5,000	5,000
E.	Permanent equipment			
	Biochemical Appliances	10,000	15,000	15,000
	Pathology and Cytology appliances	5,000	7,000	8,000
	Mobile Laboratory Car	10,000	20,000	20,000
	Total permanent equipment	25,000	42,000	48,000
F.	Expandible equipments and supplies	2,000	2,000	2,000
G.	Other project costs	2,000	2,000	2,000
	Total project Costs			
H.	Total Direct Project Costs	49,000	66,000	72,000
I.	Other allowable costs administrative expenses	3,000	3,000	3,000
	Operation and maintenance expenses	3,000	3,000	3,000
	Total other allowable costs	6,000	6,000	6,000
	Total Amount Requested (in local currency)	55,000	72,000	78,000

Equipments Requested for the Project

عدد الاجهزة المطلوبة للمشـــــــروع

1-	Spectrophoto -,Flourimeter	One	واحـــد
2-	Centriguge	Four	اربعـــة
3-	Deep-Freez	Two	اثنـــين
4-	Shaking Water bath Incubator	Two	اثنـــين
5-	PH-meter	One	واحـــد
6-	Electric balance Analytical	One	واحـــد
7-	Refrigerator	One	واحـــد

Annex 1

The DEVELOPMENT OF A CANCER SCREENING TEST WITH SPECIAL REFERENCE TO CARCINOMA OF THE BLADDER

By

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Introduction

Carcinoma of the bladder is the most challenging cancer problem in Egypt. It is the second commonest type in females, after cancer of the breast with a relative frequency of 11 per cent, and the most frequent in the male (17 per cent). Its association with schistosomiasis is an established fact, but the nature of the cause/effect relationship is still the subject of extensive investigations (3).

It may seem logical from the last statement that the most promising approach would be primary prevention by control or eradication of schistosomiasis. In spite of the extensive efforts and campaigns undertaken by the Egyptian health authorities, this has proved so far a very difficult if not an impossible task. This is in line with the world experience with parallel measures for environmental cancers. Thus it was decided to explore the possibility of developing a test for early detection (secondary prevention) without any illusion that this will prove an easy task. Such a test is of particular importance in schistosomal bladder cancer, as symptoms of schistosomal cystitis may merge insidiously with those of cancer, with the result that when the patient presents the condition may be too advanced for effective treatment.

In developing a screening test the following steps should be taken into consideration :

1. Identification of the potential test or tests.
2. Determining their sensitivity and specificity.
3. Identification of the high risk group (screened and control).
4. Problems of implementation.
5. Evaluation of the test (Cost versus benefit and risk versus benefi

1. Identification of a Screening Test

With the universal acceptance of cervical cytology as a screening test, our first attempt was to use urine cytology for the same reason. This started at our Institute as well as in other centres in Egypt. Our experience, however, was not satisfactory. In cases with proven carcinoma of the bladder, there was a positive cytological diagnosis in only 68 per cent of cases (i.e. the sensitivity of the test is 68 per cent). This is due to the difficulties in recognizing cancercells amidst chronic inflammatory, pyogenic ,red, atypical transitional and squamous cells as well as schistosomal ova. The recognition of the cells may be easier in early cases, but it should be remembered that a screening survey is needed to detect also some undiagnosed disease at a more advanced stage (Prevalent as well as incident cases). The result could be improved by using more than one voiding. The sensitivity of the test may rise from 54 per cent with one voiding to 80 per cent with use of three voidings [10]. On the other hand 15% of schsitosomal cystitis non cancer cases showed positive cytology tests, i.e. a specificity of 85 per cent. Crabb [2] reported cases with positive urinary cytology in which tumours were not at first demonstrated, but eventually appeared within period varying from five months to five years.

A histochemical study conducted at our Institute revealed that alpha esterase, an estrolytic enzyme, is present in the bladder urothelium, in higher concentration in leukoplakia and other urinary schistosomal manifestations, and in still greater [illegible] bladder cancer .[1] This finding has raised hopes of early [illegible] of new or recurrent cases of bladder cancer through the use of an easier reproducible biochemical test depending on urine analysis.

Certain biological markers were studied to test their values in detecting bladder cancer. It was found that urinary alpha esterase enzyme activity was consistently increased in all cases with bladder cancer.

A study of the enzyme activity in serum and urine was conducted at the Cancer Chemistry Department. As shown in Table 1 the level in serum cannot be used as an indicator, and the variation in serum/urine ratio is mainly the function of the activity in the urine. So it was decided to take an arbitrary level of 150 units in urine as the demarcation line (Table 2).

Table 1 (6)

Group	Enzyme Activity + S.D. Serum (Units/ml)	Urine (Units/L)	Serum/Urine Ratio X10^3
1. Healthy controls (22)	6.22 + 2.24	46.63+3.59	17
2. Schistosomal bladder cancer (35)	8.84 + 2.31	219.86+30.25	39
3. Schistosomiasis patients with other urologic diseases (92)	8.97 + 2.52	79.12+35.88	107

Table 2 (6)

Enzyme Activity (Units/L)	Schistosomal Bladder cancer	Schistosomal Non-Bladder cancer	
150	33	3	
150	2	89	
Total	35	92	

a- False Positive = 3.37 % p 0.001
b- False Negative = 5.71 %

From this we can deduce that the sensitivity of the test is approximately 94 per cent while the specificity is about 96 per cent, which is very satisfactory as will be shown in the following paragraphs.

2. Sensitivity and specificity of the test

A screening test is a tool to divide a population into two groups, one contains most if not all individuals who are likely to have disease. The other includes most if not all individuals unlikely to have disease. The degree of ability of the test to detect the diseased group is called its "sensitivity" and is higher the less its false negatives. "Specificity" on the other hand is defined as the ability of the test to exclude the non-diseased group and is higher the less its false positive cases. In practice, the level of sensitivity and/or specificity for a screening programme is selected according to the severity of the disease, the opportunities that will exist for rescreening and the inconvenience and dangers of diagnostic investigations (8). Attention should be given to demands placed on services necessary for follow-up of screening procedures, thus high sensitivity and specificity are essential qualities for any test.

It may be argued that false positives are more tolerable than false negatives, so long as the former cases are to be subjected to confirmatory diagnostic procedures. This may be true if we use the test (e.g. urine cytology) as a diagnostic procedure on individual bases. For a screening test, however, the specificity must be much higher if we are to husband diagnostic procedures and avoid [illegible] tional and biological costs to healthy participants.

A theoretical illustration is outlined to explain this point. Suppose we want to screen a population of 100 000 persons for a single tumour whose rate is 1:1 000 or less, using a test with a sensitivity and specificity of 90 per cent each. Out of the 100 000, a hundred persons will be missed, but may be identified during rescreening or eventually present with symptoms. On the other hand, 99 900 cases will be non-diseased and with a specificity of 90 per cent nearly ten thousand persons will be falsely labelled as diseased (false positive) and will thus be subjected to unnecessary diagnostic procedures which may be expensive in terms of manpower and facilities, apart from the inconvenience and emotional stress to healthy participants.

If the test is applied to millions, as it should be, such costs may be prohibitive. Thus it is agreed that tests with sensitivity in the order of 70-80 per cent are generally acceptable, but specificity should be much higher (8).

3. Defining the high risk groups (screened and control)

Whatever the relationship between schistosomiasis and bladder cancer, every schistosomiasis patient runs a real risk of developing bladder cancer at some stage of his disease. In a case control study (5) 98 per cent of cancer bladder cases at the Medical Research Institute had a history of treatment for schistosomiasis as compared to 17 per cent in the control group.

It was found in the same study that only 2 per cent of cases were born in Alexandria; the rest, 98 per cent, were born in the rural areas mostly in the nearby Beheira Province, which is well known for the high prevalence of schistosomiasis. Thus it was decided to choose both the screened and control groups form this province and to define the high risk groups as those affected with schistosomiasis as evidenced by history of schistosomiasis treatment.

The age group of the screened population and of the control group needs further discussion. It is observed that cancer may develop at a younger age in developing countries, especially for cancers of environmental origin. This is indeed the case with schistosomal bladder cancer. A typical age distribution is illustrated in Figure 1. This observation may be partly apparent - a shift towards earlier decades would be expected in any population of younger composition - but it is also real.

The earlier inception may be attributed to the exposure to a highly potent carcinogen at a very young age. (4) It may be observed from the figure that schistosomal bladder cancer becomes prominent at the fourth decade, but about 6 per cent of cases appeared before.

There may be a tendency to start screening early enough to cover nearly all the persons at risk. Moreover, for younger people, lives saved would yield more years of life than for corresponding numbers

of older patients. On the other hand, the pick-up of cancer cases is likely to be low, and the number of people screened may be too enormous to handle. So we attempted to define the optimum starting point beyond which we can detect the maximum number of cancer cases by screening the least number of people.

Figure 1 shows two curves : one shows the age distribution of bladder cancer cases in the Medical Research Institute and the other shows the age distribution of the population in Beheira Province. The point of intersection of these two curves (age 32) was taken as the starting point. Table 3 further illustrates this point. If we screen the group at risk beyond 30 years, we pick up 93.9 per cent of cases by screening only 27.8 per cent of the high risk group, but if we take 40 years as a starting point, we detect 76.7 per cent of cases by screening only 14.1 per cent. It may be advisable to start screening above the age of 40, and as facilities and experience are developed, to lower the age to 30.

Table 3

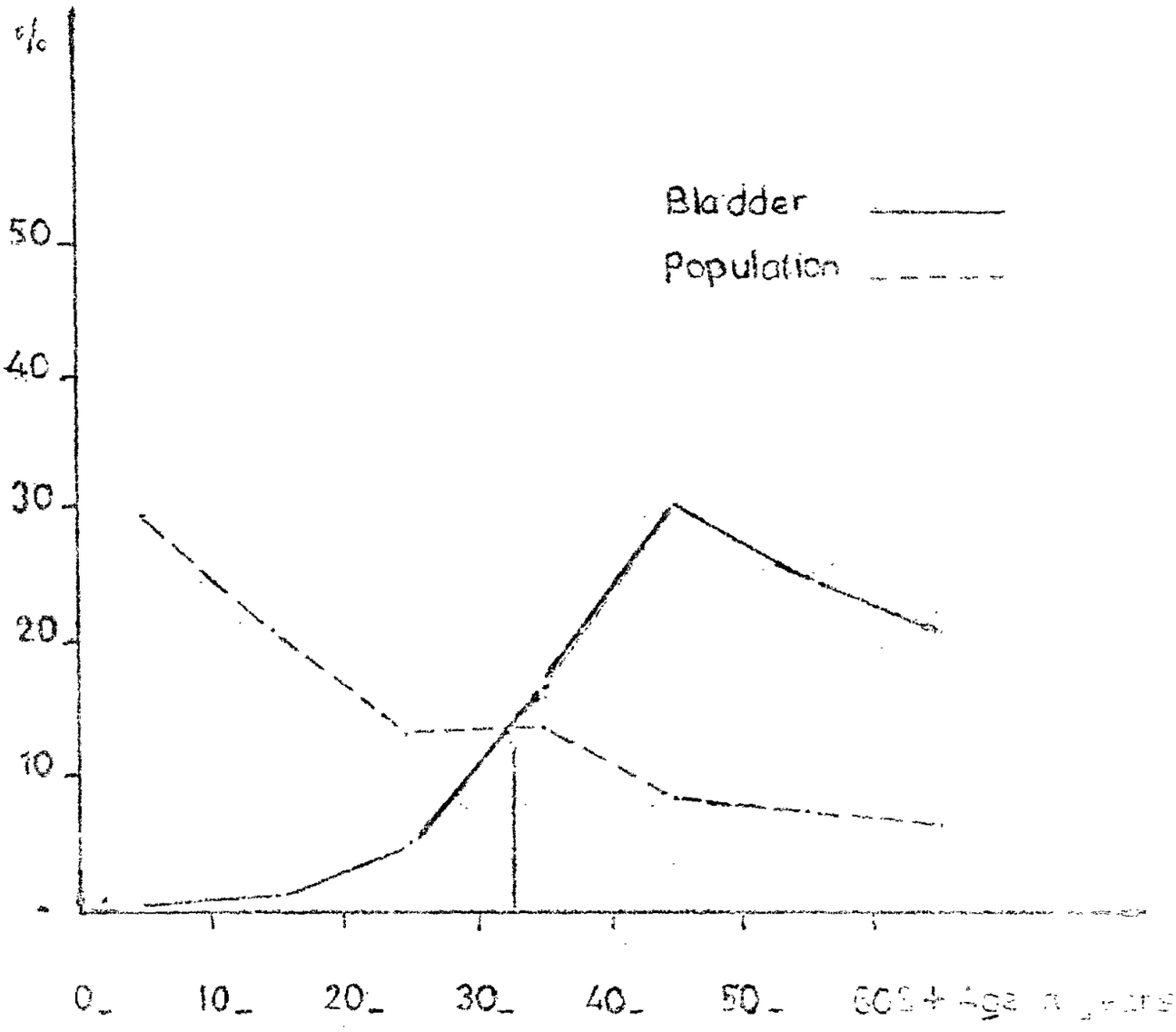
Bladder Cases, Medical Research Institute, and Average Beheira Population/Year 1960-1976

Age in years	Cancer Bladder	%	Beheira Population	
Below 30	71	6.1	835 73[illegible]	[illegible].2
Above 30	1 101	93.9	321 72[illegible]	27.8
Total	1 172	100.0	1157 45[illegible]	100.0
Below 40	272	23.3	994 91[illegible]	85.9
Above 40	900	76.7	163 03[illegible]	14.1
Total	1 172	100.0	1157 45[illegible]	100.0

Importance of rescreening

It should be recognized that a screening test will detect incident and prevalent cases at a certain point of time. Thus it is necessary that individuals with both positive and negative screening results should be followed up until all cases of disease become manifest, the first group

Figure 1.



Age Distribution, Cancer Bladder, A.C.R & Average Population
Behiera Governorate 1960 - 1976

(the positives) by appropriate diagnostic procedures, and the latter by periodic rescreening . This is very important, as a negative result may impart a sense of false security and thus a tendency to delay if cancer symptoms appear.

Problems of implementation

The problems of such a survey cannot be overestimated, even with limitation of the screened population by age or by area. Apart from the demands placed on the services necessary for follow-up of screening procedures when even highly sensitive tests are used, attention should be given to the relative merits of using manpower and other resources for new procedures in the light of competing medical needs of the community. Inorder to economize in personnel and facilities, the cancer detection campaign should be integrated into the already existing services, namely the schistomiasis dispensaries which are widely distributed in all rural areas. It was decided to start in one such dispensary, as a pilot study, and to extend the operation as experience is developed, enough personnel trained, and the problems of implementation solved. The control group is chosen from the same region. As there is an ethical problem in denying persons in the same group a method which may be beneficial, but certainly harmless, and to avoid sampling difficulties, it was decided to choose the control group from separate dispensaries, not necessarily the same number, but serving an equal size of population. Assuming that the prevalence of schistosomiasis is the same, the total risk of developing bladder cancer would be equal.

Evaluation

Although a very long time may elapse before there is any demonstrable impact on the screened population, it is not premature to discuss the important point of evaluation. Any medical procedure has to be evaluated in order to decide whether or not it is worthwhile in cost and effort. In this, two different criteria are used :

1. Cost/benefit ratio. Here the benefit gained is compared to the cost in terms of manpower and facilities.

2. Risk/benefit ratio. This should be considered in such procedures, where a potentially harmful procedure is contemplated. A clear example is mammography, where the possible benefit of screening to find early cancer is evaluated against the risk of inducing breast cancer by radiation exposure. It is clear that this does not apply to our procedures as there is no introduction of chemicals or drugs or exposure to radiation.

In evaluation an important cause of misinterpretation is the lead time . Increased survival after diagnosis may mean that the time of diagnosis has been advanced without necessarily meaning that the time of death has been delayed. The lead time is defined as the interval between diagnosis with the screening programme and when the disease is diagnosed under current medical practice. If this is known, it can be subtracted from the observed survival time, and the residual time. However, estimation of the "lead time" may be difficult if not impossible, although many formulae have been worked out. (9) The difficulty is that these formulae require a knowledge of variance of the duration of the pre-clinical phase. This formation has not been available for any of the diseases so far studied. (7)

It is recognized that there are many other pitfalls, [illegible] the time being the only reliable method is the comparison of [illegible] mortality or age specific survival rates in the entire screened population with those of the control group. This comparison should take place in the same period of time to avoid any temporal variations such as the falling rates of incidence of some types of cancers (e.g. stomach or cervix). This is especially important in environmental cancers, where it may be difficult to know whether the benefit is due to the screening programme or to schistosomiasis control measures, or whether it is due to the combination of both methods, i.e. primary and secondary prevention.

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Annex II

THE BIOCHEMICAL DETERMINATION OF SERUM AND URINARY ALPHA ESTERASE

By

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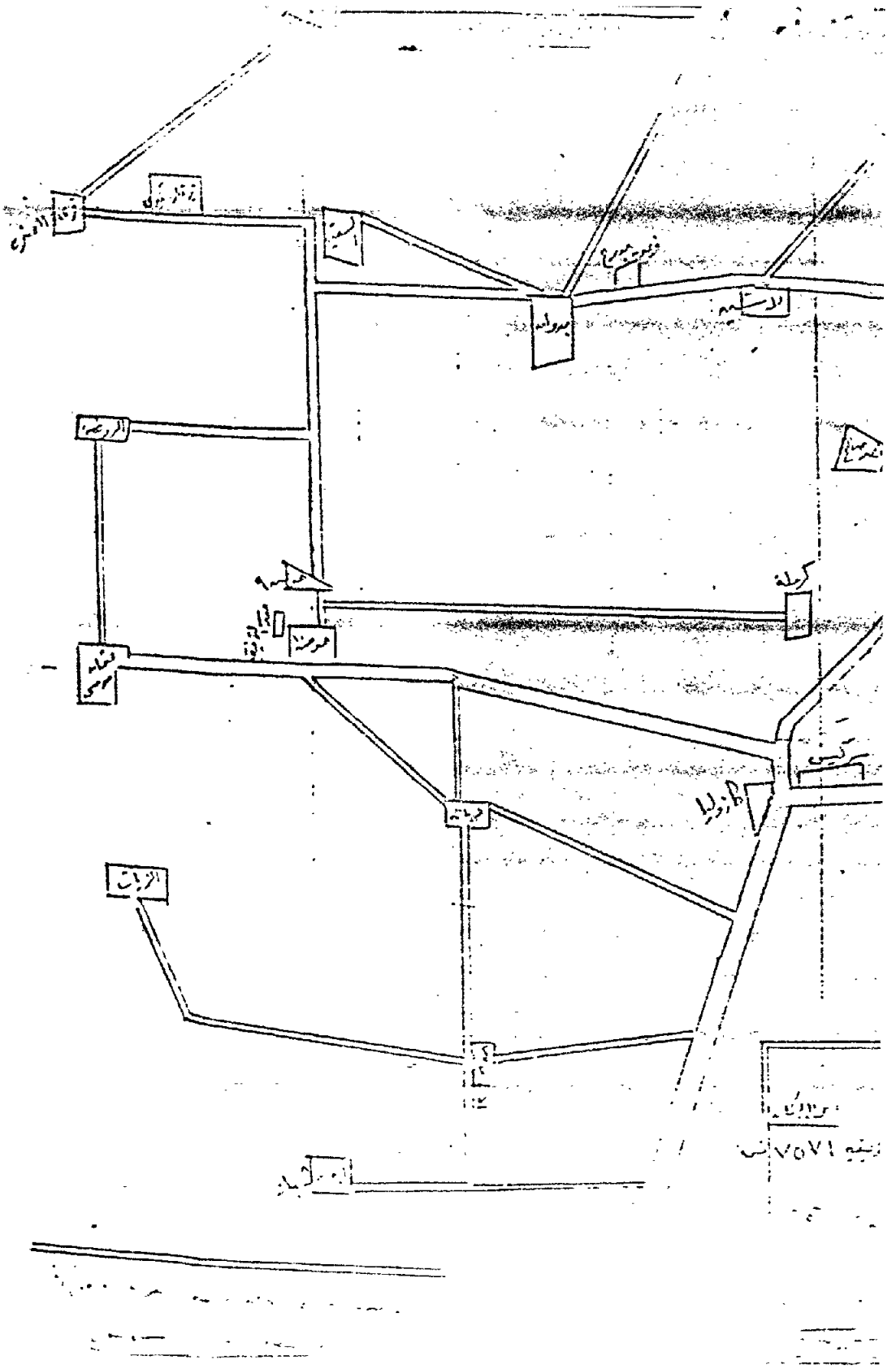
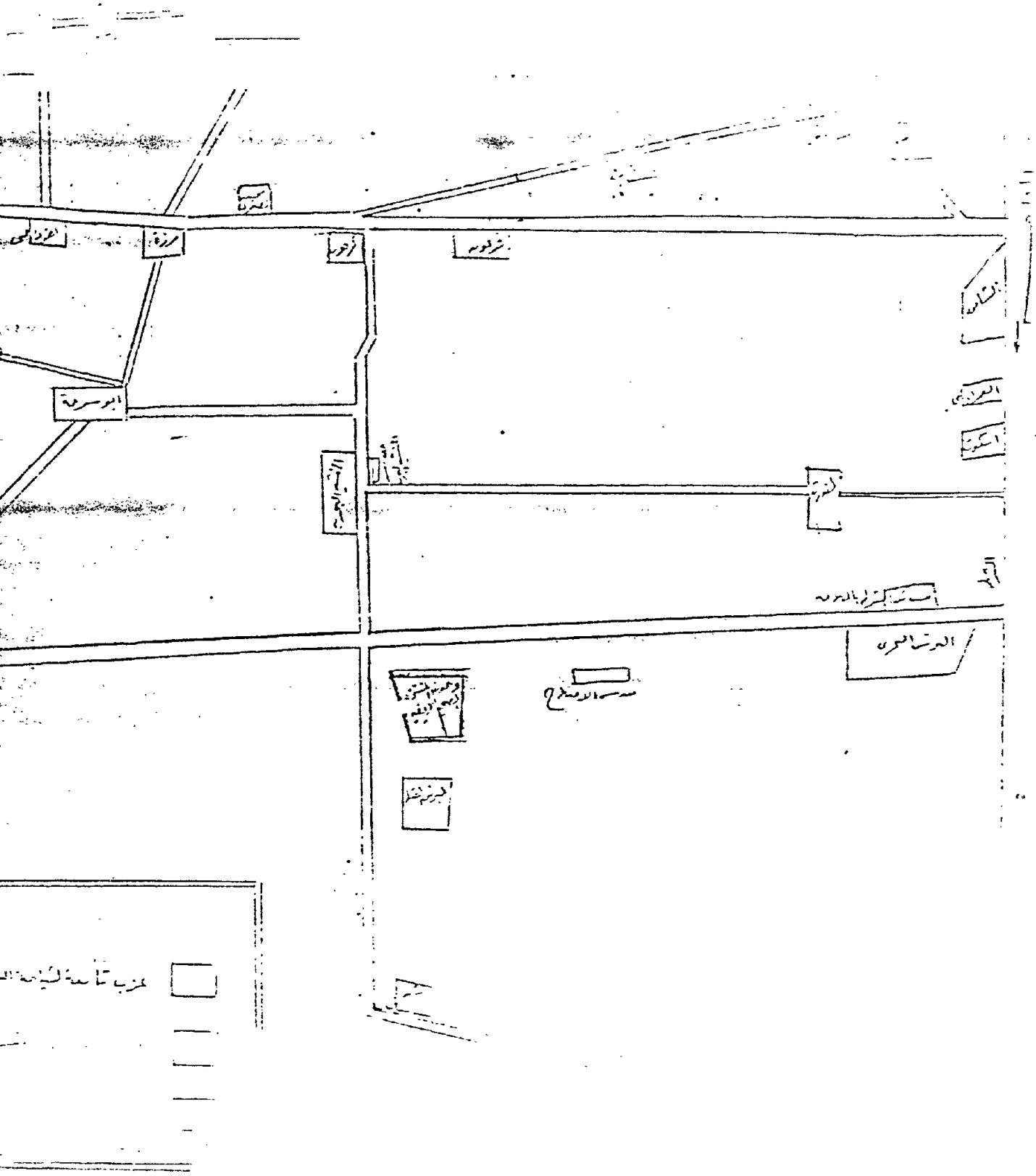
Submitted for Publication in the Royal Society
of Tropical Medicine & Hygiene

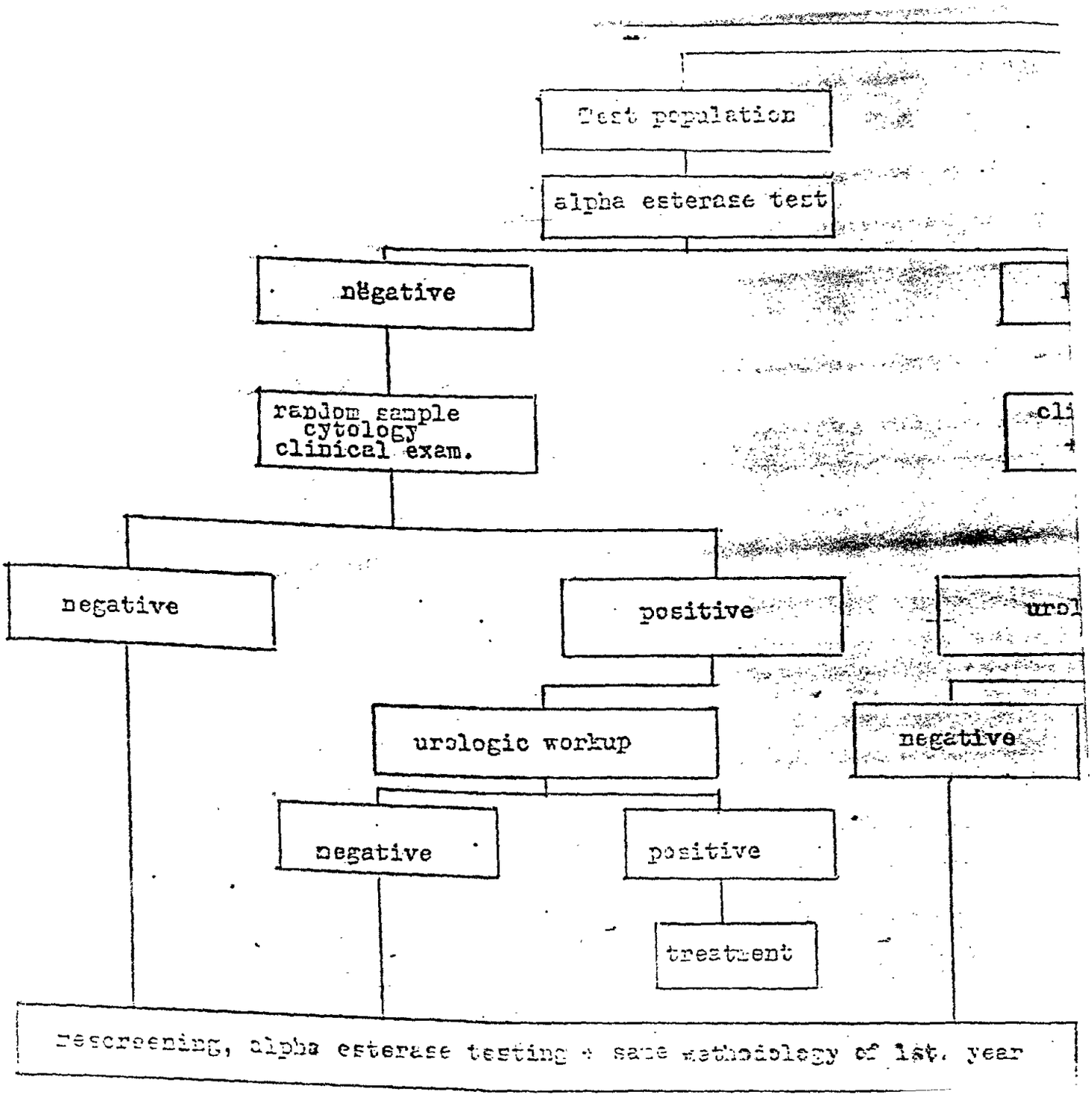
The activity of serum and urinary alpha esterases was determined as follows:

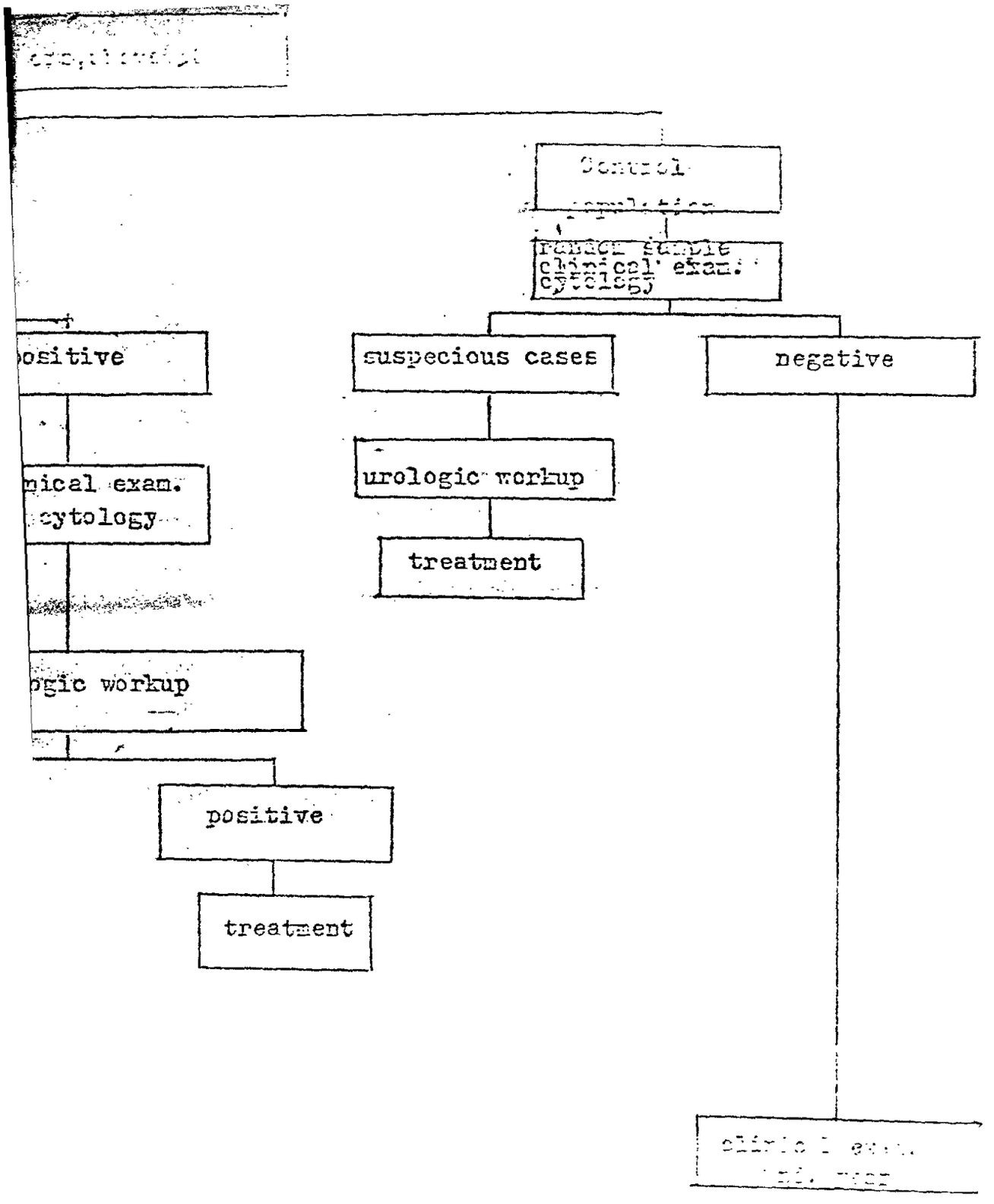
1 ml of fresh urine or 0.1 ml of fresh serum was incubated at 37°C in phosphate buffer containing alpha naphthyl acetate. After incubation, the clear supernatant was separated by centrifugation. The reaction product of hydrolysis was determined colourimetrically by coupling Fast Garnet reagent with the supernatant. The absorption was determined colourimetrically at 555 nm.

The enzyme activity was expressed in units. One enzyme unit is equivalent to 1 u mole alpha naphthol produced per unit time.






Test population
alpha esterase test
negative
random sample
cytology
clinical exam.
negative
positive
urologic workup
negative
positive
treatment
negative
rescreening, alpha esterase testing + same methodology of 1st. year


positive
suspecious cases
negative
urologic workup
treatment
positive
treatment

IMMUNOHISTOCHEMICAL LOCALIZATION OF CARCINOEMBRYONIC ANTIGEN (CEA) IN CANCER BLADDER USING IMMUNOPEROXIDASE TECHNIQUE

Our work includes the investigation and possibility to localise the CEA by immmnoperoxidase (PAP) method, in cancer bladder cases and in different bilharzial metaplastic and proliferative lesions that are known to be associated in bladder schistosomiasis.

36 bladder tissue specimens were examined, 5 normal specimens, 14 specimens with bilharzial proliferative, and metaplastic lesions, in addition 17 cancer bladder specimens were examined.

All normal urothelium was negative for CEA. The Bilharzial proliferative & metaplastic lesions, except squamous metaplastic lesions, did not demonstrate CEA with the squamous metaplastic lesions (6 cases) demonstrated CEA positive reaction. Thus this lesion could be considered as precancerous or squamous cell carcinoma in situ.

The differentiated cancer bladder cases (bilharzial and non-bilharzial) including squamous cell carcinoma (7 cases) transitional cell carcinoma (5 cases), and adenocarcinoma (one case) were positive for CEA with varying degree of positivity not only between different specimens but also in the same specimen. The undifferentiated cancer bladder cases (4 cases), bilharzial and non-bilharzial, were negative for CEA. These obtainable data prove that, CEA staining by PAP method can be used with other histological methods, for determination of the degree of differentiation of a tumour and this helps in evaluating the patient's prognosis.

However, this method should be used alone as a routine procedure for tumour identification, in screening purposes, because as it does not identify the anaplastic tumours, the percentage of false negative results will be high.

In addition some studies were done to identify the CEA synthesis, and it was able to prove that, CEA is synthesized in the cytoplasm of the cells and secreted through the cell membrane, and it is not a constituent of the cell membrane.

RADIOIMMUNOASSAY OF CARCINOEMBRONIC ANTIGEN (CEA) IN PATIENTS WITH CARCINOMA OF THE BLADDER IN EGYPT

CEA is measured using radioimmunoassay in the following groups to give the subsequent results :

1. 15 normal healthy volunteers, showed CEA plasma values between 0.70 and 2.70 ng/ml.
2. Nine cases of chronic bilharzial cystitis, showed CEA plasma values between 1.2 and 4.4 ng/ml.
   There is no statistically significant difference between group 1 and group 2.
3. 35 cases with carcinoma of the bladder, CEA plasma values before treatment are between 0.20 and 11.30 ng/ml, and CEA plasma values after treatment are between 0.0 and 6.3 ng/ml.
   There is a statistically significant difference between group 3 and group 1 and 2.
4. Five patients evaluated immediately after radical radiotherapy show CEA plasma values before treatment between 5.26 and 8.30 ng/ml and CEA plasma values after treatment between 2.50 and 5.40 ng/ml.
   There is a statistically significant difference between patients before and after radiotherapy.
5. 13 patients evaluated six weeks after radical radiotherapy show CEA plasma values before treatment between 0.20 and 5.90 ng/ml and CEA plasma values after radiotherapy between 0.00 and 4.30 ng/ml.

There is a statistically significant difference between patients before and after radiotherapy.

6. 14 patients are submitted to surgical treatment. CEA plasma values before treatment are between 1.20 and 11.30 ng/ml and CEA plasma values after surgery are between 0.20 and 6.30 ng/ml.

A consistent drop is showed in CEA plasma values after surgery with reduction in tumour tissue.

Significance is:

a) The test when used in conjunction with other investigation and clinical assessment, helps to diagnose carcinoma of the bilharzial bladder.

b) The test can be used prognostically and to evaluate disease progress.

Three cases of carcinoma of the bladder were assayed for plasma and urine CEA evaluation. The plasma CEA values are between 4.9 and 8.7 ng/ml. The urine CEA values are between 10.2 and > 25 ng/ml. It was observed that the presence of heavy infection and pus cells in the urine may mask the accurate result. Further studies to clarify this point in Egyptian patients should be done.

CANCER PREVENTION AND CONTROL (PROGRAMME PROFILE)

1. Policy Basis

To promote cancer prevention and control, including coordinated cancer research . WHO will continue its efforts to:

- formulate and review standardized nomenclature, methodologies, etc. and encourage their widest possible use;
- disseminate information on the latest advances in prevention, detection, diagnosis, treatment and rehabilitation for common forms of cancer;
- mobilize resources for setting up national cancer control programmes within the general health services based on the above-mentioned standards and methods of detection, diagnosis, treatment and rehabilitation;
- concentrate on programmes for educating the population about known preventive measures (Sixth General Programme of Work 1978-83, Geneva, 1976 pp. 97). Resolutions: EB17.R40; WHA10.18; WHA26.61; WHA27.63 .

2. Objectives and targets

Pertinent to the general policy statement the Eastern Mediterranean Programme and Budget 1976-77 states: Cancer control, while further advanced than the control of mental disorders, receives considerable attention during 1976-77 programmes and assistance will be devoted to laying the "ground work for effective cancer control services, aiming to expand these in future years". And the RO statement for the Programme and Budget 1978-79 adds: in close cooperation with the Regional Cancer Panel and Regional Reference Centres a special trust will be made to produce better data on cancer of the sites with special importance in the Region, as well as to improve cancer detection, staging, classification, treatment and prevention.

2.1 Long-term objectives: to establish comprehensive cancer programmes in Eastern Mediterranean countries within the framework of national health services - developing adequate infrastructure for cancer prevention, detection, diagnosis, treatment and patient's rehabilitation.

2.2 Short-term objectives:

(a) to develop Hospital-based cancer registries in order to improve data collected on cancer and establish a real basis for the comprehensive cancer programme;

(b) to improve gradually detection, diagnosis and the practical use of international classification and nomenclature in order to have a uniformity in terms of data obtained throughout the Region.

3. Description

3.1 Problem

Cancer is the third cause of death in Eastern Mediterranean Region (Fifth Report on the World Health Situation 1969-72, WHO, Geneva 1975, pp.10). No figures on cancer incidence are available except for Israel where the incidence has reached more than 200 cases x 10^{-5} in 1965-69. For Baghdad an incomplete

cancer registration has produced figures of more than 120-140 cases x 10^{-5} inhab. in 1975. Some particular cancers have a very high incidence or frequency in various areas of the Region. Oesophageal cancer reaches figures as 93 to 110 cases x 10^{-5} inhab. in the area of Northern Iran, bladder cancer represents in Egypt more than 20 per cent of all malignant tumours and skin cancer is quite common in all Region being in most countries where data are available between the first few sites.

The impact of cancer on health economics and general economics of the EM countries is not clearly measured but an important number of hospital beds is used by cancer patients diagnosed in late stages and therefore in incurable status. Also taking an important toll of adult population cancer deprives EM countries of the most skilled and the most productive members of their total population.

3.2 Approaches

In order to meet the objectives and targets mentioned above the following approaches have been considered:

1. A Regional Cancer Panel was established in 1975 with the following terms of reference:

(a) To assess the cancer situation of the Region and advise the Regional Director on the best way to use WHO technical and financial support to obtain higher cost/benefit results.

(b) To elaborate a Regional Programme for cancer and to evaluate the development of such a programme making the required corrections from time to time in order to adapt the programme to meet cancer realities of the Region.

(c) To evaluate experience collected by Regional Reference Centres on various cancer sites and types and decide upon the best methods to be disseminated widely throughout the Region for Cancer prevention, detection, diagnosis, treatment, rehabilitation, etc.

(d) To assess the need to develop scientific and practical cancer activities in areas where a particular cancer epidemiological situation is evident throughout the Region.

2. Regional Reference Centres (RRC) - various sites on Cancer have been established for lymphoma and oesophageal cancer at the Cancer Institute, Teheran; bladder, head and neck cancers at Medical Research Institute, Alexandria and Cancer Institute, Cairo; and for breast and uterine cancer at Salah Azaiz Cancer Institute, Tunis. Future RRCs will be established for other sites if needed. The terms of reference of the RRCs are:

(a) Research in the field of epidemiology, aetiology and pathogenesis of the cancers which constituted the specific field of each RRC.

(b) Elaboration of adequate preventive measures.

(c) Development of early detection methods.

(d) Standardization and recommendation of methods for diagnosis, treatment, rehabilitation as appropriate for the Region.

(e) Training of cancer personnel at the regional and inter-country level.

3. Country projects have been redesigned in order to reach the idea of implementing National Cancer Programme instead of having limited impact in a specific area of cancer control.

4. Seminars, symposia and other similar activities are held with the aim to disseminate information about nomenclature and classification, adequate methods of detection, diagnosis, treatment, prevention and registration of cancer in EM countries.

5. Epidemiological studies are promoted with the aim to gather the necessary information about cancer patterns in EM countries which can lead to an adequate planning of Cancer Programme.

3.3 Past activities

Activities in the field of cancer have been conducted by this Regional Office since early 1960. Projects in various countries: (Egypt, Iraq, Iran, Israel, Jordan) have started in 1965-68. Courses on cytotechnology and cytopathology were organized since 1968. A Group Meeting on Cancer Control held in 1971 in Baghdad has reviewed the situation of cancer in EM countries and emphasized the need for a bigger effort in this direction (see EM/CAN/33). A Symposium on Lymphomas (Hammamet, Tunisia 1974) has defined the main approach in the field of a very common type of tumour for EM countries. (see EM/CAN/43). The First Meeting of the Regional Advisory Panel on Cancer has outlined the Regional Cancer Programme and recommended the establishment of Regional Reference Centres for various sites of cancer (see EM/CAN/44).

3.4 List of present projects and activities within the programme - for projects see attached table.

Other activities within this Programme were:

1. First Meeting of the Regional Advisory Panel on Cancer, Alexandria, 19 - 21 February 1975.

2. Courses on Cytotechnology and Cytopathology, Teheran, August 1975 - February 1976.

3. Symposium on Breast Cancer organized by the Cancer Institute, Teheran and co-sponsored by WHO/EMRO, Teheran, 14 - 16 April 1975.

4. Multidisciplinary Meeting on Lymphomas and Alpha Heavy Chain Disease, Teheran, 19 - 21 April 1975.

5. National Seminar on International Histological Classification of Tumours, Karachi, 27 - 30 October 1975.

6. National Seminar on Bone Tumours, Karachi, 15 - 18 March 1976 .

7. Group Meeting on Cancer of the Cervix Uteri, Tunis, 15 - 17 November 1976.

8. Second Meeting of the Regional Advisory Panel on Cancer, Tunis, November 18,1976

9. Regional Seminar on International Classification of Tumours with the participation of pathologists from: Egypt, Iran, Iraq, Libya, Saudi Arabia, Syria, Sudan and Tunisia, Baghdad, 28 November - 2 December 1976.

10. Course on Epidemiology of Chronic Diseases with special emphasis on Cancer, Karachi, 22 October - 3 November 1977.

11. First Middle East Cancer Conference organized by the Federation of Middle East Cancer Organization, November 1977.

12. Third International Symposium on Oncology, organized by the Cancer Institute, Teheran University and co-sponsored by WHO/EMRO 4 - 8 March 1978.

13. Third Meeting of the Regional Advisory Panel on Cancer, Teheran, 9 March 1978

14. Slide Seminar on Cancer Pathology (WHO co-sponsoring with National Cancer Institute, Cairo), Cairo, 1 - 5 December 1978

15. Seminar on Bladder Cancer, National Cancer Institute, Cairo 11 - 14 December 1978.

16. Fourth Meeting of the Regional Advisory Panel on Cancer, Karachi, 14 - 15 March 1979.

4. Monitoring and control information

4.1 Programme milestones - see attached table 4.1

4.2 Programme staff - see attached table 4.2

4.3 Fellowships - see attached table 4.3

4.4 Supplies and equipment - see attached table 4.4

4.5 Other activities - see attached table 4.5

4.6 Budget and finance information - see attached table 4.6

5. Participants persons, groups and institutions

5.1 WHO Staff - all WHO long-term field staff in this Programme was discontinued gradually during 1975 and 1976. Only the Regional Adviser and one secretary covering two other programmes (Biomedical aspects of Radiation and Maintenance and repair of medical equipment) are left at the Regional Office level.

5.2 Other participants

A- Regional Advisory Panel on Cancer

1. Dr M.E.A. El Kharadly, Professor of Oncology, Medical Research Institute, Alexandria, Egypt.

2. Dr Youssef T. Omar, Chief Radiotherapist, Al Sabah Hospital, Kuwait

3. Dr N. Mourali, Director, Salah Azaiz Cancer Institute, Tunis, Tunisia.

4. Dr Kh. Al Qassab, Professor of Surgery, Medical College, Baghdad, Iraq

5. Dr El Sheikh Abdel Rahman, Director, Radiation and Isotope Centre, Khartoum, Sudan.

6. Dr S. Shahbender, Dean, National Cancer Institute, Cairo, Egypt
7. Dr I. El Sebai, Professor of Surgery, National Cancer Institute, Cairo, Egypt
8. Dr S.H.M. Zaidi, Professor & Head, Radiotherapy Dept., Jinnah Postgraduate Medical Centre, Karachi, Pakistan.

B- Regional Reference Centres (RRC)

1. RRC on Bladder, Head and Neck Cancer, Medical Research Institute, Alexandria - Dr M.E.A. El Kharadly, Professor of Oncology.

RRC on Bladder, Head and Neck Cancer, Cancer Institute, Cairo - Dr S. Shahbender, Dean.

2. RRC on Lymphoma and Oesophageal Cancer, Taj Pahlavi Cancer Institute, Teheran -

3. RRC on Breast and Uterine Cancer, Salah Azaiz Cancer Institute, Tunis - Dr N. Mourali, Director.

5.3 Potential participants

1. Dr Y.T. Omar, Chief Radiotherapist, Al-Sabah Hospital, Kuwait (Kuwait)
2. Dr S.M. Masood, Professor of Radiotherapy, Mayo Hospital, Lahore (Pakistan)
3. Dr Gul Rahman, Director, Institute of Radiotherapy & Nuclear Medicine, Peshawar, (Pakistan)
4. Dr A. Toussi, Radiotherapist, Nemazee Hospital, Shiraz (Iran)
5. Dr T.H. Minwer, Radiotherapist, Ashrafiah Hospital, Amman (Jordan)
6. Dr Philip Salem, Medical Oncologist, American University Hospital, Beirut (Lebanon)
7. Dr M. Sakka Amini, Director, Radiotherapy & Nuclear Medicine Centre, Damascus (Syria)
8. Dr D. Souliotis, Radiotherapist Consultant, Nicosia General Hospital, Nicosia (Cyprus)

6. Essential reports, documents and publications

6.1 Assignment Report "The Cancer Institute, Cairo", 9-31 December 1970 by Y. Cachin, WHO Consultant (EM/CAN/30)

- Assignment Report "Cancer Control in Iran, Iraq, Sudan and Tunisia" by Professor M.E.A. El Kharadly, WHO Consultant (September - October 1971) (EM/CAN/31)
- Group Meeting on Cancer Control, Baghdad, 27 November to 1 December 1971 (EM/CAN/33)
- Assignment Report "The National Cancer Institute, Cairo", 12-24 December 1971, by Professor M. Tubiana, WHO Consultant (EM/CAN/34)
- Rapport de fin de Mission "Lutte contre le cancer", 19-23 mars 1972 by Professor G. Riotton, WHO Consultant (EM/CAN/35)
- Report on a visit "Establishment of a Cancer Registry, University of Isfahan, Iran, 12-22 February 1972 by Miss E.H. Brolly, Regional Medical Records Officer (EM/CAN/36)
- Assignment Report "Cancer Institute, Cairo, 2-22 December 1971 by Professor G. Cardinali, WHO Consultant
- Rapport de fin de Mission "Lutte contre le cancer en Tunisie", 19 - 24 novembre 1972 by Prof. G. Riotton, WHO Consultant (EM/CAN/37)
- Rapport de fin de Mission "Registre des tumeurs eu Liban (Lutte contre le cancer)", 21-24 January 1973 by Prof. G. Riotton, WHO Consultant
- Report on a visit to the Sudan, 16 February - 2 March 1974 by Dr N.T. Racoveanu, Regional Adviser on Radiation Health & Cancer (EM/CAN/38)
- Assignment Report "Practice of Cytology in Israel", 6-16 November 1972 by Dr John K. Frost (EM/CAN/39)
- Assignment Report "Improvement of Radiotherapy, Iran", January - May 1974 by Professor Harold Ham, WHO Consultant (EM/CAN/40)
- Rapport sur une visite en Tunisie, 19-30 March 1974 by Dr N.T. Racoveanu, Regional Adviser on Radiation Health & Cancer (EM/CAN/41).

- Report on a visit to Democratic Yemen, 11-25 October 1974 by Dr N.T. Racoveanu, Regional Adviser on Radiation Health & Cancer (EM/CAN/42)
- Report on a visit to Pakistan, 9-21 March 1975 by Dr N.T. Racoveanu, Regional Adviser on Radiation Health & Cancer (EM/CAN/45)
- Report on a visit to Iraq, 3 - 7 March 1974 by Dr N.T. Racoveanu, Regional Adviser on Radiation Health & Cancer (EM/CAN/47)
- Assignment Report "Advanced Course in Cytotechnology, School of Cytotechnology, Israel, 5 March - 9 April 1975 by Mrs J.H. Rodner, WHO Consultant (EM/CAN/48)
- Assignment Report "Cancer Control, Libyan Arab Republic, September 1973 - September 1975 by Dr W.K. Jasinski, WHO Radiotherapist (EM/CAN/49)
- Assignment Report "Seminar on Tumours of the Bone, Karachi, Pakistan 15 - 18 March 1976 by Mr J. Chalmers, Prof. H.A. Sissons and Dr D.J. Stoker, WHO Consultants (EM/CAN/50)
- Report of the Group Meeting on Cancer of the Cervix Uteri, Tunis 15 - 17 November 1976 (EM/CAN/51)
- Report of the Second Meeting of the Regional Advisory Panel on Cancer, Tunis, 18 November 1976 (EM/CAN/52)
- Report on a visit to Bahrain, 27 March - 5 April 1977 by Dr N.T. Racoveanu, RA/Radiation Health & Cancer (EM/CAN/53)
- Assignment Report - Cancer Control in Saudi Arabia - 15 February to 14 March 1977 by Prof. M.E.A. El Kharadly, WHO Consultant (EM/CAN/54)
- Report on a WHO Seminar on Tumours of the Female Genital Tract, Karachi, 21-24 March 1977 by Drs R.M. Feroze & M.C. Anderson, WHO Consultants (EM/CAN/55)
- Report on a visit to Kuwait, 25 September - 1 October 1977 by Dr N.T. Racoveanu, RA/Radiation Health & Cancer (EM/CAN/56)
- Report on a visit to Isfahan, 8 October 1977 by Dr N.T. Racoveanu, Regional Adviser on Radiation Health & Cancer (EM/CAN/57)
- Assignment Report - Cancer Registration in Iran, 6-27 December 1977 by Dr Ruth Steinitz, WHO Consultant (EM/CAN/58)
- Report on Strengthening Cancer Control Activities at country level EMR (Kuwait, Iraq, Sudan) (EM/CAN/59 A/B/C)
- Report on a visit to Jordan, 20-25 September 1978 by Dr N.T. Racoveanu, Regional Adviser on Radiation Health & Cancer (EM/CAN/60)
- Report on the Third Meeting of the Regional Advisory Panel on Cancer, Teheran, 9 March 1978 (EM/CAN/61)
- Assignment Report, Project for Training of Cytology Personnel and the Establishment of two Gynaecological Cytology Laboratories in Alexandria, Egypt, 24 January - 22 September 1978 by S.L. Bradford, WHO Cytology Consultant (EM/CAN/62)
- Report on a visit to Cairo, 1-5 December 1967 by Dr G.Gomez-Crespo, Regional Adviser on Radiation Health & Cancer (EM/CAN/63)
- Report on the Fourth Meeting of the Regional Advisory Panel on Cancer, Karachi, 14-15 March 1979 (EM/CAN/64)

6.2 WHO Publications on Cancer - Expert Committee Reports

1. Cancer Control - Technical Report Series (TRS) 251, 1963
2. Cancer Treatment - TRS 322, 1966
3. Chemotherapy of Cancer - TRS 232, 1962
4. Early Detection of Cancer - TRS 422, 1969
5. Prevention of Cancer - TRS 276, 1964

6.3 Study Groups

1. Epidemiology of Cancer of the Lung - TRS 192, 1961

7. Related programmes and activities

7.1 WHO programmes and activities - no clear working relations are now established between this programme and all other WHO programmes which are really related,with two exceptions, Biomedical Aspects of Radiation which has some common areas - Radiotherapy mainly, and Family Health (Maternal and Child Health) with which cytology laboratories were developed in a joint effort.

Other WHO programmes have a real impact on the cancer programme and common activities should be developed in the future; these are:

1. Health of Working Population - the major activity being in the field of occupational carcinogenesis.

2. Control of Environmental Pollution and Hazards in related with the control of environmental carcinogens.

3. Food safety - in controlling carcinogens in food products.

4. Drug policies and management- in monitoring potential carcinogenic effect of drugs.

5. Malaria and other parasitic diseases - is particularly in this Region related with control of schistosoma-induced bladder cancer.

6. Bacterial and virus disease is related with viral etiology of cancer.

7. Oral health has relation with oral cancer programme very common in some areas of this Region.

8. Health Education has a very important role to play in comprehensive cancer programmes.

Unfortunately due to the inneficient system of co-ordination which exists inside of WHO and to the fact that cancer is not regarded by those in charge with the above-mentioned programmes as a real health problem for EM countries, the cancer programme has not been able to establish relations with the above activities.

8. Analysis and evaluation

8.1 Criteria - Cancer programme has specific indicators which could be applied to various activities as: detection, diagnosis, treatment, etc. Unfortunately with the actual lack of data in EM countries such indicators cannot be largely applied on a Regional basis. For small delimited areas information has been produced regarding cancer incidence - general or for a particular site, stage at diagnosis, efficacy of treatment measured by five years survival, etc.

The actual principal aim of the cancer programme is to improve cancer data throughout EM countries introducing hospital-based cancer registries. It is envisaged as a second step to define the population covered by the cancer registry and derive cancer incidence - as mentioned in Baghdad the relative incidence during 1975 has been already more than 100 cases x 10^5 inhabit.

Cancer incidence is a scientific measure of the magnitude of cancer as a public health problem and a basic indicator for all planning activities in the field of cancer.

Another step will be to improve the follow-up of cancer patients from 20 - 30 per cent to 90 - 50 per cent in order to be able to produce the survival rates. This is a scientific measure of the ffectiveness of detection, diagnosis, staging and treatment activities.

This is the rational approach for indicators able to measure both the efficiency and effectiveness of cancer programme which is followed.

3.5 Present projects in operation

Project Code	Project title	Project Profile location: WR - RO - HQ
IRA/CAN/001	Cancer control	RO
IRQ/CAN/001	Cancer control	WR
PAK/CAN/001	Cancer control	WR
TUN/CAN/001	Cancer control	WR

4.1 PROGRAMME MILESTONES

Milestone	Expected completion time	Status: date and description
1. Starting cancer control project IRQ/CAN/001	1965	January 1977: 23 Radiotherapy and Nuclear Medicine technicians were trained. A WHO Radiotherapy technical post has been discontinued since end 1975. The Government has been encouraged to start a Comprehensive Cancer Programme. Cancer Registry established in 1974 has been able to reach during 1975 an incidence figure of approx. 120-130 cases/10^{-5} inhab. for Baghdad area. Registration was continued during 1976.
2. Starting cancer control project IRA/CAN/001	1966	January 1977: This project has not been defined as target, consultant services, supplies and fellowships have been provided at the country's request. In 1975 after the First Meeting of the Regional Advisory Panel on Cancer and the establishment of the Regional Reference Centre on Lymphomas and Oesophageal Cancer at Taj Pahlavi Cancer Institute (TPCI) in Teheran, the aims of the project were reconsidered. Now a Cancer Registry is under preparation at TPCI. A study on IPSID has been started, TPCI acting as reference for all pathological material. A pilot project envisaging the utilization of cytology in early detection of oesophageal cancer is under trial.
3. Cancer control project SUD/CAN/001	1967 ended 1970	January 1977: The project has been successful in helping Sudan to establish a Radiotherapy and Radioisotope Centre in Khartoum which is now functioning. Attempts are now made to utilize this Centre as a focal point for a comprehensive cancer programme. A Pathology based Cancer Registry is functioning in Khartoum since 1967. WHO assistance to the project has been ended in 1970.

Milestone	Expected completion time	Status: date and description
4. Starting cancer control project TUN/CAN/001	1967	January 1977: The aim of the project has not been defined - a pilot study for early detection of accessible female cancers (cervix uteri, breast, thyroid) has been started in Djebel Lahmar (near Tunis). but has not been followed up. A hospital-based cancer registry has been organized with WHO assistance at Salah Azaiz Cancer Institute (SACI - Tunis). A WHO Technical Officer post has been terminated in 1975 and with the development of the Regional Reference Centre for Cancer of the Breast and Uterus the project has been reoriented. A consultation was organized in May 1976 concerning the epidemiological patterns of the inflammatory type of breast cancer and a Group Meeting on Cancer Cervix Uteri was held in November 1976. This Group Meeting was preceeded by an epidemiological study which has been successful in collecting data in regard with Cancer Cervix Uteri in 10 EM countries.
5. Cancer control project EGY/CAN/001	1968 ended 1971	January 1977: Not well defined as target the project has provided consultants, supplies and equipment and fellowships to the Cancer Institute in Cairo. WHO assistance has been terminated in 1971. At present an attempt is made to start again the activity as WHO Regional Reference Centre for Cancer of the Bladder and Head and Neck. No progress has been made since June 1975 when the RRC was designated.

Milestone	Expected completion time	Status: date and description
6. Starting project Courses on Cytopathology, Cytotechnology ICP/CAN/001	1969	January 1977: 3 Courses on Cytopathology and courses on cytotechnology were held at Taj Pahlavi Cancer Institute, Teheran. 28 cytopathologists and 8 cytotechnologists from various EM countries have graduated. Laboratories for cytology are now active only in few places in the Region (Teheran, Baghdad, Cairo, Kuwait, Tripoli, Tunis).
7. Cancer control project LEB/CAN/001	1971 ended 1972	January 1977: The aim and the achievements of this project are not clear.
8. Course on cytopathology ISR/CAN/001	1972	January 1977: The training organized has been successful. Israel has now a network of Cytology laboratories.
9. Group Meeting on Cancer Control Baghdad	1971	January 1977: The Meeting has reviewed the problem of cancer in EM countries and established some priorities.
10. Symposium on Lymphomas, Tunis	1974	January 1977: Recommendations have emphasized the importance of lymphoma in EM countries and particularly of IPSID and have proposed a rational approach for diagnosis, treatment and further studies particularly in the field of epidemiology.
11. First Meeting of the Regional Advisory Panel on Cancer, Alexandria	1975	January 1977: Regional Cancer Programme was approved. This programme could be used as a model for preparation of National Cancer Programmes. Regional Reference Centres for cancer of the oesophagus, lymphoma, bladder, head and neck, breast and uterus were recommended.
12. Designation of three Regional Reference Centres for Cancers of the: oesophagus, lymphomas, bladder, head and neck, breast and uterus.	1975	January 1977: The RRCs have been involved in developing epidemiological research in order to improve the actual data for the specific cancer site. Also some clinical protocols are under study in view of a larger application of the pilot study will end successfully.

Milestone	Expected completion time	Status: date and description
13. Multidisciplinary meetings concerning lymphomas and immunoproliferative small intestinal disease (IPSID)	1975	January 1977: A standard approach in studying IPSID has been discussed together with a protocol which will enable a correct multidisciplinary study aimed at clarifying the etiological mechanisms of this disease which represents the transition between chronic inflammation and malignancy.
14. National Seminar on International Histological Classification of tumours (IHCT) in Karachi (Pakistan)	1976	January 1977: This seminar has succeeded to brief the 40 Pakistani pathologists how to use the IHCT in their activity. It is hoped that the Cancer Registration in Pakistan will be improved and the pathological diagnosis will be better standardized.
15. Bone tumours Seminar, Karachi (Pakistan)	1976	January 1977: The participants have reached a better understanding of the way for diagnosis, treatment as well as epidemiology of bone tumours which have a higher incidence in some areas in Pakistan.
16. Group Meeting on Cancer of the Cervix Uteri (CCU), Tunis (Tunisia)	1976	January 1977: An epidemiological study has collected figures on actual situation of CCU in 10 EM countries. Stage at diagnosis, treatment methods and some epidemiological data are now available. In Tunisia also data on 3 and 5 years survival have been produced. The Group Meeting has reached an agreement on staging diagnosis and treatment methods as well as on a clinical and epidemiologic protocol for the use in EM countries.
17. Second Meeting of the Regional Advisory Panel on Cancer, Tunis	1976	January 1977: The following subjects have been examined and appropriate recommendations were made. (a) review of activities of RRC during 1976 and the programmes of RRC for 1977-78. (b) cancer priorities in EM countries: (i) how to improve the actual data on cancer incidence and prevalence; (ii) how to improve cancer prevention and detection

	Milestone	Expected completion time	Status: date and description
18.	Regional Seminar on International Classification of Tumours, Baghdad	1976	January 1977: 18 pathologists from 8 EM countries have examindd the ways to improve the use of IHCT during their activity and to reach a standardized way for classification and coding of tumours. The ICD-O coding was stressed.
19.	Meeting of pathologists investigating IPSID, Teheran	1977	January 1978 An epidemiological, immunological, pathological and clinical aspect of immunoproliferative small intestinal disease was reviewed and different proposals for research, in immunoproliferative small intestinal disease was studied.
20.	National Meeting on Female Genital Tract Tumours, Karachi	1977	January 1978:
21.	Regional Course on Epidemiology of Chronic Diseases with emphasis on Cancer, Karachi	1977	January 1978:
22.	Third Meeting of the Regional Advisory Panel on Cancer, Teheran	1978	January 1978: members of the panel have participated in the third meeting and the following subjects have been examined and appropriate recommendations were made: (a) evaluation of the activities of the RRCs on cancer during 1977. (b) review of cancer activities in EMR during 1977. (c) suggestions for cooperation in improving cancer infrastructure and cancer activities. (d) how to strengthen cancer activities in EM countries.

	Milestone	Expected completion time	Status: date and description
23.	Fourth Meeting of the Regional Advisory Panel on Cancer, Karachi	1979	January 1979: members of the panel participated in the fourth meeting and the following subjects have been examined and appropriate recommendations were made: a) report on the activities of the RRCs during 1978. b) new developments in cancer activities in EM Region during 1978. c) new activities proposed.

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTÉ

FIFTH MEETING OF THE REGIONAL ADVISORY PANEL ON CANCER

Nicosia, 8 - 9 September 1980

29 August 1980

Agenda item 6

RESEARCH IN THE REGIONAL CANCER PROGRAMME

INTRODUCTION

The promotion and development of research activities in relation to various WHO programmes at the regional level, have received an impetus since 1975, when the decision was made to establish Regional Advisory Committees on Biomedical Research, and to involve the Regional Offices to a much greater extent in the Organization's research activities.

However, in EMRO, interest in research activities in the field of Cancer dates back to the Group Meeting convened in November 1971 in Baghdad, when experts from within and outside the Region gathered to discuss and review the problems of cancer control and research in the Region.

In early 1975 the Regional Advisory Panel on Cancer was established with the following terms of reference:

1. To assess the cancer situation in the Region and advise the Regional Director on the best way to use WHO technical and financial support to obtain higher cost/benefit results.

2. To elaborate a Regional Programme for cancer and to evaluate the development of such a programme, making the required corrections from time to time in order to adapt the programme to meet cancer realities of the Region.

3. To evaluate experience collected by Regional Reference Centres on various cancer sites and types, and to decide upon the best methods to be disseminated widely throughout the Region for cancer prevention, detection, diagnosis, treatment, rehabilitation, etc.

4. To assess the need to develop scientific and practical cancer activities in areas where a particular type of cancer situation is evident throughout the Region.

The Panel, since its inception, has continued to meet annually in different countries of the Region.

Following the recommendations of the first meeting of the Advisory Panel, the following Institutes were designated as Regional Collaborating Centres:

1. Medical Research Institute, Alexandria
   Regional Collaborating Centre for Cancer of the bladder, hypopharynx and head and neck

2. National Cancer Institute, Cairo
   Regional Collaborating Centre for Cancer of the bladder, hypopharynx and head and neck

3. Salah Azaiz Institute, Tunis
   Regional Collaborating Centre for breast and uterine cervix cancers

4. Cancer Institute, Teheran
   Regional Collaborating Centre for lymphomas and oesophageal cancer

The terms of reference of these Collaborating Centres are:

1. Research in the field of epidemiology, aetiology and pathogenesis of cancer which constituted the specific field of each RCC.

2. Elaboration of adequate preventive measures.

3. Development of early detection methods.

4. Standardization and recommendation of methods for diagnosis, treatment, rehabilitation as appropriate for the Region.

5. Training of cancer personnel at regional and inter-country level.

The activities of the Collaborating Centres are reviewed during the annual meetings of the Regional Advisory Panel.

CANCER SITUATION IN THE REGION

In order that the proposed regional research activities in the field of Cancer can be reviewed in the correct perspective, a resumé of the Cancer situation in the Region and of the existing resources for Cancer Control and research, is given below.

Most of the available data on Cancer in this Region is based on relative frequencies obtained from hospital-based cancer registries. There are only three population-based cancer registries (Iran, Iraq and Israel), of which only one is able to produce true cancer incidence data.

Some of the common cancers in the countries of this Region are:

Skin Cancer

Skin cancer in most of the Middle East countries was found to represent between 10 and 28 per cent of all cancers. It is common not only in males, but the relative frequency in females is also high in Afghanistan, Iran, Iraq, Israel, Lebanon and the Sudan.

Until now no reliable information concerning the dose/effect relationship for ultraviolet exposure and skin cancer exists and the area of Middle East countries offers the best possibilities for such research. It is predictable that an increase in skin cancer will be observed in all countries of the area, if proper data become available in the future.

Lymphomas

These constitute another type of malignent tumour prevalent in Middle East countries. Under this term are included Hodgkins as well as non-Hodgkins lymphomas (lymphosarcoma, reticulosarcome, etc.) and abdominal lymphoma.

Lymphomas are the second commonest type of cancer in males in Afghanistan, Iran and Lebanon and the first in Iraq. Even in those countries where lymphomas are not among the first two types, they occupy the third to fifth place (Egypt, Israel, Sudan and Tunisia). Roughly it could be said that 8-12 per cent of all malignant tumours in Middle East countries are lymphomas.

Data obtained from the Israeli Cancer Registry about those who immigrated to Israel from various parts of the world show clearly that lymphomas are more frequent in immigrants from the North African coast (Morocco, Algeria, Tunisia, Libya, Egypt) and Asia (Iran, Iraq, Yemen, Democratic Yemen) than in those coming from Europe. Except for some African countries, in no other area of the world are lymphomas so frequent as in the Middle East countries.

A particular type of gastro-intestinal lymphoma with production of an abnormal immunoglobulin has been described. This type of lymphoma was later found in other countries around the Mediterranean as well as in South Africa, the Far East, etc., and was called Mediterranean lymphoma or immunoproliferative small intestinal lymphoma (IPSID).

Bladder Cancer

This is another frequently seen cancer in the Middle East, where schistosomiasis is widespread - the Nile Valley as well as the Tigris and Euphrates valleys seem to be the main areas involved, although schistosomiasis is known in some parts of the Middle East (Saudi Arabia, Democratic Yemen, Yemen, Iraq, Iran, etc.). Bladder cancer is a very interesting subject for the Middle East countries, being until now the only human cancer in which a parasite has an aetiological role.

In countries outside this Region bladder cancer does not constitute more than 7 per cent of all malignant tumours, while data from Cancer Registries in Cairo and Alexandria show that it accounts for 15 to 38 per cent of cancer in males and 4 - 11 per cent in females. In Iraq, where at least 1 million schistosomiasis cases must exist, there is also a high frequency of bladder cancer in males and females of up to 14 per cent. In the Sudan this observation is not seen due to misleading reporting (all urinary cancers which are perhaps mainly bladder). In Isral and Lebanon bladder cancer is also within the first ten most frequent cancers. Data obtained from the Israeli Cancer Registry show that immigrants from Morocco, Algeria, Tunisia, Libya and Egypt have twice the frequency for bladder cancer as that encountered in Israeli-born with Asian-born immigrants (Iraq, Iran, Yemen) being situated between the two above-quoted categories.

Oesophageal cancer

This is another type of cancer particularly widespread in Eastern Mediterranean countries. It constitutes 14 - 15 per cent of all malignancies in males and 6 - 9 in females in Iran. Although no proper data have been published, oesophageal cancer is also encountered in Saudi Arabia, the two Yemens and Afghanistan. In high incidence areas, the age-adjusted figures reach 140 for males and 130 for females per 100 000 population. The high frequency of oesophageal cancer is noted in North East of Iran with an incidence rate of 210 per 100 000 population in males and 185 per 100 000 population in females. The factors which may play a role in the aetiology of this disease in Iran may be due to the following: tobacco, Nass, alcohol, opium, sukhteh (burnt residue of opium), tea, riboflavin deficiency, Epstein-Ban virus or histo-compatibility antigen.

In the high risk area, an asymptomatic chronic oesophagitis was noted and is probably a preneoplastic lesion.

Oral Cancer

It has a high incidence especially in Pakistan; in the Karachi area more than 21 per cent of cancers in males and 18 per cent in females consist of cancer of the oral cavity. In terms of incidence this represents approximately 25 cases per 100 000 inhabitants. Premalignant oral lesions such as leukoplakia, severe dysplasia, etc. were found in 705 per 100 000 inhabitants. Apart from Karachi, oral cancer was reported also in Jamshoro, Multan and Lahore with a frequency between 10 and 20 per cent in males as well as in females. Other countries from the Middle East where oral cancer is reported are: Sudan (5.7 per cent in males; 3.2 per cent in females) and Egypt, Afghanistan, Iran, Lebanon and Tunisia.

The main explanation of the high frequency of oral carcinoma in Middle East countries could be related to chewing and smoking habits.

In the Sudan the use of Trombac (local tobacco) mixed with Atroon (mixture of sodium carbonate and bicarbonate and other chemiclas) placed under the tongue or lip has also been incriminated.

No epidemiological data are available concerning the effect of chewing bethel, khat or other similar vegetable products which are common in other Eastern Mediterranean countries.

Nasopharyngeal carcinoma

This has a higher frequency in Tunisia (11.5 per cent in males; 5.0 per cent in females) but is also found in Egypt, Iraq, Lebanon, Pakistan and the Sudan. As with this disease in the Chinese population, the hypothesis of EB virus is now under verification, together with the idea of a special susceptibility of local populations to this type of tumour.

Bone tumours

Mainly osteosarcoma - have a high frequency in Pakistan (5.2 per cent in males; 3.4 per cent in females) reaching in some provinces even a higher percentage (Peshawar 8.9 per cent in males; 5.6 per cent in females - Multan: 6.7 per cent in males; 5.5 per cent in females, etc.). Similar figures are found in Afghanistan. No explanation could at present be offered for this observation.

The most common tumours in other parts of the world which have a peculiar distribution in some Middle East countries:

1. Breast cancer - comments are based only on available figures on relative frequency and therefore could be subject to some bias. Eastern Mediterranean countries could be divided into three main categories in respect to breast cancer frequency in females:

(a) High frequency: Breast cancer is the first cancer site in females in Egypt, Israel, Pakistan, Sudan and Tunisia, accounting for 20 per cent and more of all cancers. A similar situation is found in many other countries such as Canada (22.5 per cent); New York State (23.4 per cent); England (23.7 per cent); Sweden (23.8 per cent); Denmark (19.8 per cent). Mention should be made of a particular form of inflammatory breast cancer which seems to be very common in Tunisia.

(b) Medium frequency: Breast cancer being the first or second most frequent malignant tumour in females with 15 to 19 per cent, as in Afghanistan, Iraq and Lebanon. A similar situation is found in Iceland, Finland, Nigeria, etc.

(c) Low frequency: Less than 14 per cent, breast cancer being in the third position - Iran (situation similar to Yugoslavia, Japan, etc.).

2. Cervical uterine cancer - three tendencies could be seen:

(a) High frequency: 20 per cent and over - cervical cancer being the first localization in females as in Lebanon (38 per cent) and Iran (21.1). Ethiopia has also a high frequency of cervical cancer; Uganda (26.2 per cent); South Africa (41.9 per cent); Chile (30.3 per cent); Colombia (35.0 per cent); Singapore (26.8 per cent). In Tunisia its frequency is 18.4 per cent and is in the second place.

(b) Relatively low frequency: Cervical cancer being between 6-12 per cent and having a position lower than the third localization among malignant tumours. Such a situation is encountered in Egypt, Iraq and Pakistan. Similar data were obtained from Canada, New York State, England, Finland, Iceland and Sweden.

(c) Very low frequency: Less than 3 per cent as in Israel and Afghanistan. Such a situation was not found in the group of countries which were investigated in this respect.

3. Lung cancer - is not very common in Middle East countries. Frequencies between 4.0 and 10.5 per cent were recorded in Iran, Tunisia, Pakistan and Israel; and its place being from third to seventh in the countries. In other Middle East countries, lung cancer does not appear among the first two localizations of malignant tumours.

Since smoking habits are increasing very rapidly, a rapid change in lung cancer trends in the future is expected.

4. Liver cancer - this has a relatively high frequency in Pakistan, Sudan and Iran. Aetiologically it is related to hepatitis B. Virus in Pakistan and to contamination with aflatoxin in the Sudan.

RESOURCES FOR CANCER CONTROL AND RESEARCH ACTIVITIES

National Cancer Institutes providing comprehensive services and some research facilities exist only in three countries of the Region. Departments of Radiotherapy are present in twelve countries where they carry the main burden of looking after cancer patients. Medical Oncology departments, outside comprehensive Cance Institutes are present in only 5-6 countries in the Region.

In the remaining eight countries of the Region, where there are no departments of Radiotherapy or special Cancer units/centres, cancer patients are being treated by surgery and/or chemotherapy, prescribed by a physician without any special training.

Cancer research is mostly clinical and based on accumulation and analysis of records of cancer cases. Some epidemiological studies of descriptive nature have been carried out in the recent years. Cancer epidemiologists and experts in other fields of cancer research are hardly available in this Region.

It is worth noting that national cancer control plans have not been formulated in most countries of the Region. This undoubtedly reflects the inappropriate attention being given to Cancer as a health problem.

No estimates can be made, however crude, of funds available for Cancer Research in the various countries of the Region. However, in view of the limited resources available for medical research in general, the funds allocated for research in Cancer would appear to be negligible.

PROPOSED RESEARCH ACTIVITIES

Objectives

The research component of the Regional Cancer Programme should have the following objectives:

a) to improve the existing knowledge and understanding of theCancer problem and of the associated causal factors in the Member States of the Region;

b) to assist in the formulation of National Cancer Control Programmes for prevention detection and treatment of common cancers;

c) to facilitate and improve the teaching and practice of Oncology.

PLAN OF ACTION

The research activities can be dealt below under four main topics:

1. Cancer causation
2. Cancer prevention and detection
3. Cancer management
4. Fundamental cancer research

1. Cancer causation

1.1 Cancer epidemiology

Considering the paucity of valid data on the cancer situation in the Region, and the meagre resources available for research in Cancer, it is proposed that planning and implementation of well designed epidemiological studies should receive considerabl emphasis.

Such studies will provide data on cancer incidence, mortality, morbidity, distribution according to age, sex, geographical areas, race, associated causative and other relevant factors. In addition, this data will be of great use in the planning of National Cancer Control Programmes.

WHO, with the help and cooperation of Regional Collaborating Centres, Cancer Institutes and Cancer Departments, can help in planning and implementing epidemiological studies on the most common cancers in the Region.

It is suggested that during the coming 3-4 years the following epidemiological studies be sponsored:

- Epidemiological aspects of uterine cervix carcinoma in Tunisia and the Sudan;
- Epidemiological aspects of inflammatory breast cancer in Tunisia;
- Epidemiological aspects of human lymphomas in Iran;
- Epidemiological aspects of oral and liver cancers in Pakistan.

If required WHO would be prepared to provide technical collaboration through consultant services for preparing protocols for these studies.

1.2 Cancer registries

Cancer registried yield valuable data. Some countries in the Region in recent years have established hospital-based cancer registries. The Organization will be collaborating with national authorities and cancer experts to extend the coverage of existing Cancer Registries and to establish them in those Cancer Centres where they do not exist.

It is also proposed to promote the development of population-based Registries in selected countries, preferably in conjunction with an ongoing population-based health related programme (in order to optimize resources).

To facilitate the implementation of the above proposals, it is planned to organize a Course in Cancer Registry, a meeting on Cancer Statistics, and to sponsor 2-3 National Training Courses on Cancer Registries, during the next 3-4 years.

2. Cancer prevention and detection

To reduce the mortality and morbidity in some types of cancer, promotion and development of research in the prevention and early detection are required.

The following research studies are proposed:

- early detection of breast cancer in general population in Tunisia and Sudan (a comparative study);
- early detection of uterine cervix in Tunisia, Pakistan;

- screening for the presymptomatic detection of bronchogenic carcinoma of the lungs in cigarette smokers in Egypt and Kuwait;
- study of premalignant condition of the oral cavity cancer in chewing and smoking tobacco in Pakistan by cytology;
- early detection of bladder carcinoma by cytology and biochemistry in Egypt (a comparative study).

2.3 Environmental carcinogenesis

To alleviate the danger of occupational cancer in industrial and petroleum export countries, WHO is essentially involved in promoting research in occupational cancer with the help of the health authorities of the country concerned, e.g.: cancer of the bladder in Egypt is due to chemical compounds; skin and lung cancer in Kuwait is due to sunlight and asbestosis; colon and lung cancer among carpet-makers in Iran and oral carcinoma in Pakistan, due to chewing tobacco or smoking.

The following subjects are proposed for consideration:

a. Occupational nasal cancers: nasal cancer morbidity and mortality in hardwood workers.

b. Occupational cutaneous cancers: carcinogenic mineral oil effects in metal machine industry (spinocellular epithelioma, particularly in the scrotal region).

c. Liver cancers: comparison between aflatoxin consuming and non-consuming workers exposed to similar levels of potential occupational liver carcinogens.

d. Environmental lung cancer: relationship between lung cancer mortality and morbidity vs smoke or total polynuclear hydrocarbons or 3.4 benzpyrene in the atmosphere.

3. Cancer management

Suitable protocols should be developed for diagnostic staging, treatment and rehabilitation of the most common cancer in the Region.

As the aim of the cancer control programme is to reduce the mortality and morbidity of cancer and to assure the best treatment for cancer patients, it is propose that in the countries where a special cancer is prevalent, a national coordinating body be organized for the coordination of a unique method of treatment throughout the country.

WHO can provide consultants to the health authorities of such countries for cooperation with the coordinating body. The cancers prevalent in the following countries are proposed to be included in this project:

- Egypt: bladder cancer
- Pakistan: oral and liver cancers
- Tunisia and Iran: carcinoma of uterine cervix
- Sudan: breast and bladder cancers

One of the major problems encountered in the management of cancer patients is a high rate of drop-outs, and where attempts have been made to ensure follow-up at required intervals, they have not been very successful.

Sociological studies are needed to determine factors which deter follow-up, and for formulating and testing of innovative measures for overcoming these factors and ensuring compliance for follow-up.

4. Fundamental cancer research

Research under this heading and covering subjects such as environmental carcinogenesis, experimental oncology, immunogenetics, cell biology, etc., is not considered as priority for WHO's collaboration with Member States during the near foreseeable future.