

THE ROLE OF CHINA NATIONAL CENTER FOR PREVENTIVE MEDICINE IN DISEASE CONTROL

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The China National Center for Preventive Medicine was organized in 1983 with the objective to strengthen the link between research and practice in preventive medicine in China. It is primarily a research center with the following main tasks:

- 1) to carry out fundamental and applied research on preventive medicine and to coordinate such research programs throughout the country;
- 2) to provide technical assistance to the provincial health institutions and to train health professionals for the provinces;
- 3) to engage in surveillance, monitoring and supervision on matters relating to health, disease prevention and quarantine;
- 4) to develop the scientific basis for the formulation of health regulations, standards and policies;
- 5) to collect, study and exchange informations in the field of preventive medicine.

At present, the Center is composed of seven institutes. Four of these, namely, Institute of Health, Institute of Parasitic Diseases, Institute of Epidemiology and Microbiology and Institute of Virology, were originally parts of the Chinese Academy of Medical Sciences. The Laboratory of Industrial Hygiene was originally under the Ministry of Health. The other two, namely, National Institute of Food Hygiene Supervision and Inspection and National Station of Environmental Monitoring, were newly founded.

Although the Center was only established in 1983, most of its constituent institutes existed since the 1950's. In this paper, I shall review some of the scientific achievements of these institutes and describe how they have contributed to the cause of disease control in China. Due to the limitation of time, I have purposely left out the role these institutes played in health promotion.

Etiological and epidemiological research

Knowledge on the etiology and epidemiology of diseases is often an essential prerequisite to accurate diagnosis and effective control. Consequently, etiological and epidemiological studies on infectious, occupational and nutritional diseases have always been on the forefront of our research activities. As examples, the results of our studies on leptospirosis, epidemic hemorrhagic fever and allyl chloride poisoning will be described.

Leptospirosis exists in 26 of 29 provinces (excluding Taiwan province) and in 67.1% of counties in China. Epidemics are of two types: those occurring after heavy rainfall and flood, and those occurring along the ricefield. 14 serological groups and 59 serotypes of leptospira have been identified, including a new group, the "Manhao" group consisting of 5 serotypes. Only one serotype, *L. pomona* has been found in North China, with pig as the main reservoir host. Multiple types of different composition are found in different provinces of South China where rodents are the main reservoir hosts. These studies have provided the scientific basis for practical preventive action. Thus, rat control or enforcement of proper swine breeding practice, together with application of vaccine prepared from locally prevalent serotypes, have been effective in reducing the incidence of this disease.

Epidemic hemorrhagic fever (EHF) or hemorrhagic fever with renal syndrome is a rodent-borne disease characterized by fever, hemorrhage and renal damage. The case mortality may be as high as 20%. Presently, cases have been notified from 26 provinces. The virus of EHF was first isolated in 1981. Since then, infection has been detected in 13 species of rodents. Three types of EHF have been recognized in China, namely, the classical type mainly transmitted from *Apodemus agrarius*, the mild type mainly transmitted from *Rattus norvegicus*, and the laboratory type transmitted from albino rats. One of our notable contributions has been the recognition

in 1981 of epidemics of a mild type and the identification of *Rattus norvegicus* as the reservoir. Subsequently, vigorous rat control measures have controlled this disease in the affected areas. The viruses isolated from *Apodemus* and *Rattus* were indistinguishable by immunofluorescence but showed distinct difference in neutralization and blocking tests, a point of importance for vaccine development.

Previous reports on chronic toxicity from allyl chloride described only liver and kidney damage. After the finding of a number of cases of peripheral polyneuropathy among workers in factories manufacturing sodium allyl sulfonate, epidemiological, clinical and electroneuromyographic studies showed that polyneuropathy is the main clinical manifestation of chronic allyl chloride poisoning and electroneuromyography is valuable for early diagnosis and monitoring. Neuropathological studies in experimental animals confirmed that chronic allyl chloride poisoning resulted mainly in central-peripheral distal axonopathy. Based on these results, diagnostic criteria and principles of management have been prescribed.

Disease control via control of vectors or reservoir hosts

Control of vectors or reservoir hosts, where feasible, represents a more radical approach to the control of arthropod-borne or animal-borne diseases. Two outstandingly successful examples are illustrated by the eradication of enzootic plague in Tongliao district of Inner Mongolia and the control of schistosomiasis in many parts of South China. In both cases, our scientific research has made significant contributions.

Tongliao is located in the north-east part of Inner Mongolia and was a famous plague area where 30 human epidemics were reported from 1918 to 1949. After liberation, vigorous measures have reduced human plague to a few cases per year, but enzootic plague among rodents remained active. From 1950 to 1959, we concentrated our effort on studies aiming at understanding the basic pattern of enzootic plague in this area and came to the important conclusion that *Citellus dauricus* is the primary reservoir responsible for maintaining enzootic plague, whereas *Rattus norvegicus* responsible for transmission to man is only secondarily infected. From 1959 to 1963 when massive campaigns were organized over the whole area of 5,390 km² aiming at the extermination of the target reservoir animal, *Citellus dauricus*, we laid down the scientific principles of deratting in accordance to the results of ecological studies, such as the proper timing and priority places for deratting, method for spotting *Citellus* holes etc. Methods were also developed for the evaluation of the effectiveness of eradication campaigns. After 5 successive years of effort, it was determined that the density of *Citellus* population had been reduced from

5.29 to less than 0.2 per hectare and no plague-infected animal could be found after 1960. Since then, in the last 24 years, not a single case of human or rodent plague has been discovered in spite of extensive surveillance. We conclude that enzootic plague in this area has been eradicated.

Schistosomiasis (due to *Schistosoma japonicum*) was widespread in the rural areas of 12 provinces and municipalities in the early 1950's, with about 11 million patients and a total area of 12 billion m² infested by the intermediate host *Oncomelania*. After 30 years of vigorous control effort, chiefly consisting of snail killing by physical and chemical means, clearing up of snail breeding places and treatment of patients, both the number of patients and snail-infested area has been reduced to 1/3 of the original and the disease has practically disappeared in many regions. What is left at present mainly involves shoals and marshlands along the big rivers and lakes and hilly regions where large scale control of snails is difficult. Recently, a new molluscicide, bromoacetamide was developed, which is highly active, of relatively low toxicity to fishes, highly soluble in water and easily handled. This drug is over 10 times more active than NaPcP or chloroacetamide and is especially effective against the snail eggs. Satisfactory results have been obtained in the field by immersion at a concentration of 1 ppm or spraying at a dosage of 1 g/m². At 6 ppm, it was not harmful to several common species of fish tested. It did not affect the growth of rice seedlings at 10 ppm concentration. Thus, this molluscicide may be widely applicable to rice fields and fishraising water and may help to eliminate snails in places difficult to reach by other means.

Development and evaluation of vaccines

In collaboration with other laboratories, several bacterial and viral vaccines have been developed and evaluated in the field. A live oral poliovaccine was first prepared from Sabin's strains in 1960. The safety and efficacy of the vaccine were demonstrated in the following years. As a result of widespread use of oral poliovaccine, the annual incidence of the disease has been reduced to less than 0.50 per 100,000 in 18 provinces in 1979. A meningococcus vaccine consisting of Group A polysaccharide was developed between 1973 to 1980. The rate of protection was 93% and immunity appeared to last for at least 3 years. Its use in epidemic areas has been effective in controlling outbreaks or leveling off the seasonal peak incidence.

China is a country with a high prevalence of hepatitis B infection. The overall positive rate for hepatitis B surface antigen (HBsAg) by reverse passive hemagglutination is 8.75%. A remarkable feature is the family aggregation of hepatitis B virus infection, primarily due to transmission from

HBsAg-positive mothers to their infants. Several studies have been undertaken to test the possibility of interrupting perinatal transmission by administration of hepatitis B vaccine to the newborns. The results of one such study is illustrated here. Ninety percent seroconversion was obtained after two of three doses given at 24 hours, 1 month and 6 months after birth. At the end of 6 months, 6.5% of vaccinated group and 53.1% of the placebo group became HBsAg-positive, yielding a protection rate of 88%. The results of such studies have thus provided the scientific basis for prevention of perinatal infection of hepatitis B virus by vaccination.

Development and evaluation of drugs

Development of drugs which are highly active, low in side-effect and convenient to administer has been the goal of several constituent institutes of the Center. Only two outstanding examples will be described here.

The first example is the treatment of silicosis with Tetrandine (TT). It is well known that silicosis, once established, does not yield readily to medical treatment. In recent years, we found in screening tests that TT had a definite effect in inhibiting silicosis in rats. TT is an alkaloid of the dibenzylisoquinoline group isolated from a plant, *Stephanin tetrandia* S. Moore. Since 1979, we have carried out extensive laboratory and clinical studies on this drug in collaboration with many other institutes and hospitals. When given to rats immediately after injection of silica dust, the dry weight and total collagen of the lungs of treated rats were both lower than those of untreated controls 30 days after dusting. Histologically, no silicotic nodule was found in treated rats. When given to rats with established silicosis, degeneration and loosening of collagen fibers in silicotic nodules were noted. These results indicate that TT not only inhibits the progress of silicosis, but also induces the degeneration of collagen fibers which have already been formed. 240 cases of silicosis of different categories have been treated with TT. About 50% of patients in the 200mg and 300mg groups showed clinical improvement; 24.8–32.6% of patients showed definite improvement by chest X-ray films 3–6 months after starting treatment. The nodules became smaller and the shadows became lighter. The main side-effects were pruritus and pigmentation of skin. Some cases showed impairment of appetite and abdominal distension and a few showed changes in liver function or electrocardiogram. These side-effects were not severe and disappeared after cessation of treatment. Research into the mechanism of action suggests that TT probably acts through inhibition of the excretion of procollagen and glycoaminoglycan from the cells. It may also inhibit the cross-linking of collagen by chelating with Cu^{++} .

A second example is the treatment of chloroquine-resistant malaria. The appearance of chloroquine-resistant *Plasmodium falciparum* has been a serious obstacle for attempts to eradicate malaria. Up to 1982, chloroquine-resistant *falciparum* malaria has been found in 28 counties of 4 provinces in China. A new antimalaria compound, pyronaridine was developed. This drug is highly active against blood schizont and shows no cross-resistance with chloroquine. It may be administered orally, intramuscularly or by intravenous drip. In laboratory tests, it is more active and less toxic than chloroquine. Clinical trials have been carried out since 1971 and over 1,000 patients with *falciparum* or *vivax* malaria have been treated, including cases infected with chloroquine-resistant *P. falciparum* and cerebral malaria. All patients responded to treatment. The recrudescence rate within 30 days was 14% in the group treated with 4 mg/kg, but no recrudescence occurred in the 6 mg/kg group. In addition, 9 patients either highly resistant to chloroquine or concurrently resistant to other antimalaria drugs were treated and cured. This new compound thus appears to be very promising in the control of chloroquine-resistant disease.

Control of diseases of unknown etiology

Our experiences have demonstrated that reduction of morbidity and mortality of certain diseases may be achieved even before their etiology is established. In fact, under certain circumstances, control measures found to be effective in the field may even help to establish the etiology of these diseases. Our studies on the prophylaxis of Keshan disease with selenium salt and on the early detection and treatment of nasopharyngeal cancer may well illustrate these points.

Keshan disease is an endemic cardiomyopathy of unknown etiology prevalent in many hilly regions of 14 provinces in China. Ever since its discovery, there has been no effective method for its prevention. In 1968, the prophylactic effect of orally administered sodium selenite (1 mg per week) was first tested in heavily affected areas of Heilongjiang and Sichuan provinces. Observations on treated groups and non-treated control groups were continued for 5 years. The results indicate that morbidity in the treated group was decreased by 84–89% and mortality decreased by more than 88%. Analysis of samples of grains as well as blood, hair and urine from residents in the affected areas showed definite deficiency in selenium as compared with data from control areas. After oral selenite, the selenium content of affected areas was raised to the level of control areas. Blood glutathione peroxidase activity was increased to normal level after oral selenite intake. Long-term intake at the scheduled dosage caused no obvious side-effects. Since 1974, selenite prophylaxis has been accepted in the affected areas

of 69 counties of 10 provinces and its effectiveness has been confirmed. Selenium deficiency is currently believed to be an important factor in the etiology of Keshan disease.

Nasopharyngeal cancer (NPC) is an important cancer in south-east China. It may reach an incidence of 15.8 per 100,000 per annum in the high risk area of Guangdong and represents 10–15% of all tumor death. Ever since 1966, the association of EB virus with NPC has been suspected, but an etiological relationship still remains unproven. Our efforts have been directed primarily to the study of serological methods for the early detection of NPC which may save the life of many patients through early radiotherapy and which in turn may throw light on its etiology. An immunoenzymatic test for IgA antibody against the virus capsid antigen (IgA/VCA) of EB virus was developed which is positive in 92.5–95% of NPC patients and in <6% of normal persons or patients with other malignant tumors. Two mass screening surveys in high risk areas have been organized. In one survey covering 148,029 persons, 87 NPC cases, of which about 60% were in early stages, were detected. In another, 13 cases of early NPC were detected amongst 12,932 persons screened. More recently, an even more specific test for IgA antibody against EB virus early antigen (IgA/EA) has been developed. Since EB virus infection is almost universal, specific positive tests for IgA/VCA or IgA/EA must mean activation of EB virus in NPC cases by some unknown factors. In fact, some locally abundant plants such as tung oil trees and 15 medicinal herbs have already been found to activate EB virus infection and to act as co-carcinogens in laboratory tests. Genetic factors such as the HLA types of patients are also being studied. This example of NPC study argues strongly for EB virus as one factor in the causation of NPC and indicates that reduction of mortality from this cancer may be achieved even before the etiology of the disease is fully elucidated.

Development of diagnostic reagents and procedures

Sensitive and specific diagnostic reagents and procedures are often essential for clinical diagnosis and

epidemiological surveillance. In this regard, the rapid development of immunological technics is particularly relevant. In recent years, ELISA tests have been developed and improved for the immunodiagnosis of malaria, schistosomiasis, viral hepatitis, epidemic hemorrhagic fever, meningococcus infections etc. Monoclonal antibodies have been developed for Japanese encephalitis, dengue and epidemic hemorrhagic fever etc. As examples, the application of an IgM test by indirect fluorescent antibody technic (IFAT) for the early diagnosis of epidemic hemorrhagic fever and the use of monoclonal antibody against the EHF virus for surveillance in rodents may be cited. Parallel assay of IgM and IgG antibodies by IFAT were performed on serum specimens from 40 cases of EHF collected on day 3–11 after the onset of disease. IgM antibody was detected in 95% cases and was positive as early as day 3. This method is now being used for the early diagnosis of EHF by a number of institutions in epidemic areas. Again, for detection of EHF antigen in rodents, we have replaced human or animal immune sera with a broadly reactive monoclonal antibody and obtained comparable results. This type of antibody is high titered, specific, easy to prepare and may be used in direct immunofluorescent test.

Recently, drug-coated microplates and freeze-dried medium for the *in vitro* quantitative testing of chloroquine resistance of *P. falciparum* were developed. Only 0.1 ml of patient's blood is required for the test. The freeze-dried medium may be stored at 4°C for one year without affecting its capacity to support the growth of malaria parasites, while the drug-coated microplates may be preserved at room temperature for at least one year. These qualities have rendered the test especially suitable for field use. Field investigations in several malarial endemic areas have demonstrated that these home-made plates are equally effective as those provided by WHO and this technic may become an important tool in the surveillance of chloroquine-resistant malaria.

These examples illustrate that the application of newer diagnostic methods may be of great assistance in disease control.