Medical genetics in China

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In July 1978 a Royal Society delegation visited the People's Republic of China for about three weeks to discuss medicobiological matters with the Chinese Academy of Sciences, in particular the reason for the high incidence of cancer of the oesophagus in one county in the north and of nasopharyngeal carcinoma in the south. Dr Michael Stoker was the leader (the Chinese are insistent on this protocol) and the other scientific members were Professor Walter Bodmer, Sir Cyril Clarke, Sir Richard Doll, and Professor Avron Mitchison. We were accompanied by Miss Elizabeth Wright, Director of the Great Britain-China Centre. She spoke excellent Chinese and reported on the translation of our lectures and other discussions. This varied greatly but was never manipulated.

The authors of this paper thought that readers of the Journal might be interested to hear about our impressions of genetics in the Republic, genetics being interpreted in the liberal Lederberg sense of 'anything interesting.'

Medical statistics

We did not come across any organisation such as our own OPCS (Office of Population Censuses and Surveys) and it seems probable that the most reliable data are those relating to cancer, particularly in the high incidence areas; these are collected by the Oncology Institutes.

In each commune (essentially a group of villages with, on average, between 50 000 and 100 000 people) individual registration is required for rationing purposes. It is therefore possible to obtain basic information about the size of the population. This is then looked at in more detail for one of the 10 to 20 communes which make up each county, and by summing the total populations from each commune, a rough estimate of the population structure of the whole county can be made by extrapolation. The provinces, which are large regions,

are divided for administrative purposes into counties corresponding roughly to those in the UK.

As regards malignancy, data obtained from the Peking Institute of Oncology showed that cancer mortality had been determined by means of a retrospective study of death certificates in selected provinces over the 3-year period 1972, 1973, and 1974, and is now being determined for the whole country by a similar study in 1975. Information obtained in discussion suggested that a positive diagnosis of cancer on a death certificate was reasonably reliable. In Kiangsu Province (containing Shanghai and Nanking, and not a high incidence area) we were shown a detailed map of the cancer mortality in each commune and how the diagnosis had been arrived at. This was by microscopy in 16% of cases, by hospital investigation including x-ray in 65%, by clinical examination in 15%, and by history of barefoot doctor alone in 4%. Similar information is available from the high cancer incidence areas.

Data on congenital malformations seemed to be based only on personal experience and individual hospital records. For example, in discussing anencephaly, spina bifida, and hydrocephalus in Peking we were told that there was an extraordinarily high incidence: up to 1% of births in Peking itself, and up to 3% further north, but much lower in Shanghai. This seems highly improbable and it may be that there was some confusion and that the Chinese were talking about total malformations. In Taiwan the incidence of anencephaly is 'intermediate' around 1·17/1000 births (Emanuel *et al.*, 1972).

Visits to Genetics Institutes

ACADEMY INSTITUTE OF GENETICS, PEKING
The Institute was started in 1951, at first doing mainly plant genetics, but in 1959 animal work was started as well. There are now 250 research workers (the distribution between scientists, technicians, and others is not clear) in five departments. One of these dealt with human and animal genetics, and we paid it two visits. The first time, we heard a great deal about

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Fig. 1 Map of China indicating by crosses the places visited by the Royal Society Delegation. The area with a high incidence of NPC is just to the south of Kwangchow (Canton) in the Pearl River delta.

'genetic engineering' which seemed to equate with 'remote hybridisation', for example, barley $\times$ rice hybrids, though it was not clear how these were obtained. On the human side we were told about chromosomal studies done some years ago on 155 mentally retarded children. The studies seemed competent but did not involve banding techniques. We were also given a description of chromosomal abnormalities in a mouse leukaemia strain.

On the second occasion, the discussion was much more lively, there being three obstetricians present. We were told about a study on the offspring of 10 000 radiologists which had been done some 14 years ago. There was a claim for an increased incidence of stillbirths and abortions. We also had a long discussion about work on the H-Y antigen, directed at separating X and Y sperm, and we pointed out some of the difficulties of such studies. The most substantial discussion, however, was with the three women doctors from the obstetrics and gynaecology hospital. Of great interest was the occurrence of haemolytic disease of the newborn caused by ABO incompatibility. This, we were told, occurs with a frequency of 5 per 1000, 40% of the population in Peking being group O; the disease is

more frequent if the baby is group A than if it is group B, as in the European experience. We asked for details on immune anti-A and anti-B antibody levels during pregnancy and were told that these were about to be done. However, they also said that traditional medicines could lower the incidence of the disease, presumably by lowering the antibody titres. Rhesus haemolytic disease was not a problem, as the Rh negative frequency was given as 0.2 per 1000.

Genetic engineering came up again and we learnt about egg transfer experiments done in 1973 with rabbits, in 1975 with sheep, and in 1978 with cattle. The calf was due to be born in August.

Our overall impression was that though there was some good work being done, the Chinese often wanted to run before they could walk, a phenomenon also not unknown in the UK.

ACADEMY INSTITUTE OF ZOOLOGY

Among a variety of interesting work being done in this Institute, from imaginative studies on insect pheromones to human chorionic gonadotrophin characterisation and work on membrane bound mitochondrial ATPase, were the notorious studies on nuclear transplantation and mRNA 'transformation' in goldfish, bitterlings, and carp. We were told about these experiments in some detail, but, as apparently others have before us, found the results quite unconvincing.

FUTAN UNIVERSITY INSTITUTE OF GENETICS, SHANGHAI

Futan University was founded in the 1930s based on a French missionary school started in 1905. It has 14 departments in arts and sciences and three research institutes, of which one is the Genetics Institute founded in 1962. We were told that in the whole University there were about 2000 teaching staff and 3000 students, though it was not clear what was meant by the former. The University was to expand to a size of 10 000 by 1985, with relatively greater emphasis on postgraduate work and a ratio of one postgraduate to three undergraduate students.

The Institute of Genetics, whose director, Professor Tan, is Vice President of the University and is a well-known geneticist with experience and training in the United States and Great Britain, has 60 research and teaching staff, and 30 undergraduate and 10 postgraduate students per year. It is divided into four sections: microbial genetics, biochemical genetics, plant and evolutionary genetics, and human and medical genetics. In the last, work before the cultural revolution had been principally on radiation genetics in monkeys and on sex anomalies in man. At present, in microbial genetics they had started

Fig. 2 A group outside the Oncology Institute, Peking. From right to left; Dr Tsung T'ang (Head of Immunology), Sir Richard Doll, Professor Wu Huan-Sing (Director of the Institute), Dr M. G. P. Stoker, Dr Li Ping (Deputy Director of the Institute), and behind her Professor N. A. Mitchison.

work on temperature sensitive mutants of *B. subtilis* but apparently had not yet set up DNA transformation. In biochemical genetics they were working on the structure and function of genes using plasmids and were preparing to do DNA sequencing. This was all apparently directed at the development of 'genetic engineering' and they talked about work on DNA restriction mapping, but had obviously hardly started. In the plant and evolution section they had just begun work on somatic cell hybridisation and work with protoplasts.

In the human and medical genetics section we were told more in detail about their work, which was carried out mainly in a cell and tissue culture laboratory. Here they were growing amniotic cells and they said the criterion for amniocentesis was that the first birth had been abnormal. On further questioning, however, it seemed that the rationale for such sampling was not clear-cut and that they were mostly working with experimental samples taken from women who were to have an abortion anyway.

In relation to malignancy, we saw a picture of sister chromatid exchange in the Don hamster cell line, induced by NMNg at 1 μ g/ml, and were told of comparative work using the Ames test strains. They used 199 medium with newborn calf serum, but apparently were unaware of, or did not have access to, the use of CO₂. They were interested in work on cell fusion, but had obviously hardly started here. They had very complicated schemes for trying to cure chronic myeloid leukaemia by some sort of nuclear transfer, again an attempt at genetic engineering.

We talked about work on a form of mental retardation in consanguineous families in a mountainous region, and also heard about the work on the long term effects of the contraceptive pill, with a

suggestion of an increase in chromosome abnormalities in blood samples, a result which was obviously not yet by any means significant.

Perhaps the most interesting discussion concerned contraception. All the standard methods are being used, with abstinence under 25 years of age and the IUD the most favoured. Vasectomy, however, seems to be quite unpopular in China. An anti-fertility agent (gossypol), obtained from the pigment in cotton-seed oil, reduces the semen count by 99%. This had been discovered accidentally when men who chewed the seeds complained of infertility, and it was now being tried out experimentally on about 1000 men. The only side effect to have been detected, and that uncertainly, is hypokalaemia. The chemical formula of the agent is shown below.

There is, however, evidence that this agent may be quite toxic and we were told that studies on cancer incidence in men taking gossypol were in progress (National Co-ordinating Group on Male Antifertility Agents, 1978).

While the human genetics laboratory at Fudan was reasonably well equipped, our overall impression was that with one or two exceptions they were very much at the beginning of significant research in human genetics.

Meeting with HLA workers in Shanghai

One of us (WFB) lectured on HLA typing, and a discussion with workers from the 2nd Medical College and the Institute of Blood Products (roughly equivalent to a Blood Transfusion Laboratory) was held the following day.

It was clear that the group as a whole were familiar with published reports in the HLA field and with previous Histocompatibility Testing volumes. In answer to the question of whether they had started any B lymphocyte typing, they said that their work had been retarded by the Gang of Four (a very frequent comment throughout our visit) and was just beginning again. They had been screening some sera against peripheral blood lymphocytes and were just beginning the analysis, but they had had no antisera from outside China and so clearly were not yet in a position to do typing for defined antigens. However, they seemed to be well aware of the problems of the techniques and were using a standard micro-lymphocytotoxicity test with fresh lymphocytes and rabbit complement. Ways of collaboration with other laboratories outside China, through exchange of sera and cells, were discussed, and it was pointed out to the Chinese that there existed an Asian tissue typing group and they were urged to make contact with them. They seemed very keen to do this and to become established in the field, and their questions reflected a sound knowledge of what is going on. These included interpretations, for example, of some of the data presented on the structure of the Ia molecules, questions on advances in transplantation matching, and on approaches to screening for obtaining antisera.

It will be interesting to see whether contact can be maintained with the Shanghai workers.

Cancer of the oesophagus

In England, with a population of about 50 million, cancer of the oesophagus is responsible for about 3500 deaths a year, but in a particular area of north China in or near Linhsien (Lin County) the disease is 20 to 40 times as common, though the inhabitants drink very little alcohol and it is certain that there is no opium smoking. The disease has been common in the area for hundreds of years and the incidence rates have shown little change since 1941 (Kaplan and Tsuchitani, 1978).

The most striking fact is that the incidence is closely paralleled by that of hypopharyngeal carcinoma in chickens, which live largely off domestic scraps. When a section of the population was displaced from its homeland in a high incidence area (to allow the construction of a reservoir) and was resettled in a relatively low incidence area, the people maintained their accustomed diet and their new chickens, which were drawn from the stock in the low incidence area, were again fed on the scraps. These then began to develop the disease (Table 1).

Without knowledge of the numbers concerned, or of how the prevalence in chickens was determined, it is impossible to draw firm conclusions. We strongly urged the Chinese, however, to try and persuade their

Table 1 *Cancer of the oesophagus: human and chicken data*

	Annual mortality per 100 000 humans	Prevalence per 100 000 chickens	
High incidence	132	176	
Intermediate incidence	24	18	
Low incidence	1.8	21	
Migrants from high incidence area	83	228	} Same stock of chickens
Native population in area to which migrants moved	23	0

Fig. 3 *The Delegation with our host and interpreters at the Summer Palace outside Peking. From left to right; Professor N. A. Mitchison, Dr M. G. P. Stoker, Comrade Ma Hsu-jen, Professor Wu Huan-Sing, (Director of the Oncology Institute, Peking and our principle host there), Sir Cyril Clarke, Sir Richard Doll, and Comrade Ch'en Yung-Hsin.*

Fig. 4 Professor Wu Huan-Sing examines a patient at the Yao Commune Hospital in Linhsien.

Department of Agriculture to finance a large chicken farm stocked with low incidence birds and to investigate the factors which the Chinese suspect are relevant. These are (1) Pickled vegetables, which are stored in pots with the addition of salt and water. Samples of these have given positive results with the Ames test. (2) Fungi or their metabolites; mouldy bread fed to rats produced cancer of the oesophagus in 1% of the animals in about a year. (3) Nitrosamines, which may be produced by interaction between fungal metabolites and nitrites *in vivo*. (4) Molybdenum deficiency, which renders oesophageal epithelium unusually sensitive to cancer induction, possibly because it is required by the enzyme nitrate reductase. The main difficulty with such a study is the length of time the birds must be kept in order to assess the cancer incidence properly. Indeed, the varying ages to which birds are kept could be a factor in explaining the data shown in Table 1.

Preventive measures based on the above hypotheses have already been initiated, for example, the use of pickled vegetables is discouraged, efforts are made to improve the drying and dry storage of cereals, water supplies are being further cleaned to reduce the formation of nitrites, and ammonium molybdate is being used as a fertiliser. The last, we were told, has increased yields of wheat by 15%, maize by 20%, millet by 20%, and rice by 5 to 10%, while the nitrite content has been reduced by about 20%.

FAMILIAL AGGREGATIONS

With such a high incidence, familial aggregations of the disease are bound to occur, but some of the Chinese oncologists thought that there was a definite genetic factor present. Thus, in some areas 60% of cases had a positive family history, defined by more

than one case in the family. Chromosome studies appeared to support this view, for data on 5500 mitoses from 103 apparently high risk family members showed 1.6% of numerical chromosome

Fig. 5 The 24-hour baby crop at Hsiao Lan Commune Hospital.

changes and 3.25% structural abnormalities; the controls from 30 members and 1567 mitoses of low risk families were 0.5% and 0.7%, respectively. Detailed data on seven families were presented, showing examples where there were two branches, one with high and one with low incidence, but some husbands and wives were affected. The Chinese had found no association with the ABO blood groups.

One of us (CAC) was particularly interested in possible genetic factors because of the Liverpool families in which the presence of a 'dominant' skin marker (tylosis) gave a very high probability that the subjects would develop the disease (Howel-Evans *et al.*, 1958). None of the Chinese patients that we saw had this skin condition. Chromosome studies in the Liverpool cases are being carried out by Professor D. G. Harnden, who is unaware when he carries out the analysis whether the subject is a tylotic or an unaffected sib, and it seems likely that chromosome abnormalities found are not significantly different in the two classes. This rigidity of control was not carried out by the Chinese.

PREVENTION BY MASS SCREENING

In the absence of certain knowledge about prevention of the disease, great stress has been laid on its early detection and treatment. One important advance has been the development of a method for obtaining cytological smears of the oesophagus that can be used in the field. A plastic tube ending in a balloon is passed into the oesophagus and the balloon is inflated by injecting air from a 20 ml syringe. The balloon is then withdrawn and its surface is rubbed on to three slides which are stained and examined in two hours. The whole procedure, including the preliminary inspection of the smears, is carried out by barefoot doctors. The procedure has been used extensively in Linhsien for the diagnosis of patients who attend hospital for treatment, for the detection of cases in the community by seeking out people with symptoms, and for the detection of cases by screening whole populations over 30 years of age. The results in Table 2 were obtained over the period 1961 to 1976.

The screening raised many problems, for example, how to proceed when a positive test was obtained and the patient was symptomless, and how to assess the prognosis for the negatives. The population was resistant to repeated screening because the examination was followed by retrosternal soreness for a week. Nevertheless, repeat screening was being attempted periodically in selected 'production brigades' (villages).

The operative mortality associated with oesophagectomy was reported to have been 5% in 1308 resections carried out at Linhsien during the period

Table 2 *Exfoliative cytology of esophageal cancer**

Type survey	No examined	No of esophageal cancer	No of early cases	%
OPD survey† 1961-1976	35 172	11 452	976	8.52
Population survey‡ Survey of persons aged 30+ §	39 720 42 190	1504 568	622 359	41.36 63.22

*Studies conducted by the Co-ordinating Group for Research on the Etiology of Esophageal Cancer of North China.

†Office of Prevention and Detection Committee for Environmental Cancer, Linhsien County.

‡33% sample of a population in selected small areas over a 2-month interval.

§Survey of population over 30 years of age in one small area.

Based on our own information and on Kaplan and Jones Tsuchitani (1978).

1964 to 1976. At the Commune Hospital at Yao Tsun one operative death in 400 oesophagectomies carried out in the last 3 years was reported. Five-year survival rates were reported as 84% for stage O (carcinoma-in-situ), 52% for stages I and II, and 14% for stages III and IV.

There seemed one very useful line of approach. There was a category in the survey known as 'dysplasia', which the Chinese thought was a pre-malignant phase, and they report favourable results in converting the epithelium to normal using an American drug 'tilerone' and an additional preparation 'anti-cancer agent BIII'. Placebos were said to have been followed by a smaller regression rate, but a controlled trial with random allocation had not been attempted (see the Barefoot Doctor's Manual, 1978). This must be very difficult to assess because of the unpleasantness of the test, but it would be possible to try out the treatment on leukoplakia of the mouth, which occurs independently of oesophageal cancer, and where repeat observations would be easy to do. Conversely, tilerone and the anti-cancer BIII might be tried in the Liverpool families where the tylosis was often associated with leukoplakia from which viral-like organisms were cultured (see Tyldesley, 1974; Tyldesley and Kempson, 1975).

In spite of all these problems we felt that the Chinese had made a magnificent attempt at mass screening in extremely difficult circumstances.

Nasopharyngeal carcinoma

In the south China province of Kwangtung, containing Kwangchow (Canton), nasopharyngeal carcinoma is the commonest cancer, the incidence varying between about 3 and 15 per 100 000 persons per year (2 to 3 times commoner in men than in women) from county to county. The upper limit, recorded in Chung Shan County, is some 50% greater than that recorded for Chinese in Singapore

and the Bay area of California when standardised for age on the standard African population, which is perhaps the most appropriate for comparison. It is much higher than that recorded for all other populations, but is low in comparison with the figure of 120 per 100 000 per year recorded for oesophageal cancer in parts of Honan; this implies, since it is the commonest cancer, that the total incidence of cancer is low. Indeed, the figure of about 50 per 100 000 which was given as the annual mortality rate for all cancers must be one of the lowest rates recorded anywhere.

Serum antibodies to EB virus antigens have been found to be much higher in patients with nasopharyngeal cancer than in other patients or in healthy members of the population (as has been reported in many studies) and the link with EB virus was regarded as established. (The Chinese (Oncology Institute, Peking) do seem to have developed a rather simple, sensitive, and specific test for VC IgA.) Some other factor or factors must, however, also be involved, but apart from the suggested HLA association (Simons *et al.*, 1976) there is no evidence to suggest what they might be. The consumption of salted fish was reported to be a characteristic item of the diet in Kwangtung, but a retrospective study has not provided any support for believing that it might be related to the development of the tumour.

Examination of the hair of persons in high incidence areas had shown a relatively high content of nickel and a relatively low content of molybdenum, and similar differences were observed between affected patients and healthy controls.

In the Institute of Oncology in Canton we were shown chromosome studies in relation to nasopharyngeal carcinoma and here, for the first time, we saw Leitz microscopes from West Germany. Preparations were made from fresh biopsy material incubated for two hours in colchicine. Most karyotypes were polyploid, usually triploid or more, and included chromosome and chromatid breaks, as well as minutes. A marker chromosome, which was a translocation between 1 and 3, was described as being found in a high proportion of cases. It had been identified by banding done at the Medical College in Cheng Chow, and published in the Chinese Medical Journal of March 1978. This and other markers were found, however, in near normal cells and it seems likely that they could have been derived from EB virus transformed lymphocytes, rather than the NPC tumour cells, which would explain the observation that they were occasionally found in the peripheral blood of the NPC patients.

There was some evidence of familial concentration, one family of 52 members having 9 with NPC. Overall, we were told that of 244 patients, 10% had at least one other family member with a cancer, and

of these half were NPC, suggesting a total of about 10 to 15 families with more than one affected. This may well be a chance finding in such a high incidence area.

No inquiries had been made about the HLA status of patients with the disease nor of southern Chinese compared with northern Chinese, despite the reports of an association of nasopharyngeal cancer with a specific HLA allele in Singapore.

Two cases of nasal sinus cancer had been found in pigs in the province, but this disease is unlikely to have the same causes as cancer of the nasopharynx. No cases of nasal sinus cancer had been seen in people in the commune of Hsaio-Lan (a high incidence commune) in 10 years, compared with about 15 cases of NPC and one case each of cervical and corpus cancer a year.

The principal aim of the preventive campaign is for early diagnosis, and the barefoot doctors are encouraged to take smears and send anyone with a suspicious lesion to hospital for biopsy.

General impressions of science in China

It is clear that in many areas with which we had contact the Chinese are considerably behind the western world in their biomedical research, but they are keen to catch up, have all the contacts needed for this, and work extremely hard. Our contacts with the scientists we met were most open and friendly and our comments, though often frank and critical, seemed to be thoroughly appreciated.

Human genetics seems to have been particularly affected during the cultural revolution and the time of the notorious Gang of Four. This may be because they were, until recently, quite significantly affected by Lysenko from the time when they were on good terms with Russia. Again, it seems likely that human genetics was a particular target, for political reasons, during the cultural revolution and also the Chinese as a whole seem most reluctant to give blood samples.

Nevertheless, the efficiency of their preventive medicine shows what can be done in a disciplined country and there is no reason why genetic data should not follow the same lines. We have a lot to learn from each other.

We are grateful to the Royal Society for allowing us to draw freely from their report to Council, and particularly to Sir Richard Doll for epidemiological data.

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