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CHINESE RESEARCH RELATED TO
INFECTIOUS HEPATITIS IN THE PAST DECADE
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CHINESE RESEARCH RELATED TO
INFECTIOUS HEPATITIS IN THE PAST DECADE

[The following are translations of selected articles
from Chung-hua Nei-k'o Tsa-chih (Chinese Journal of Inter-
nal Medicine), Peiping, Volume III, No 11, 13 November 1959.]

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RESULTS OF CHINESE RESEARCH RELATED TO INFECTIOUS HEPATITIS IN THE PAST DECADE

[The following is a translation of an article written by Chia K'o-ming, in Chung-hua Nei-k'o Tsa-chih (Chinese Journal of Internal Medicine), Vol III, No 11, Peiping, 1959, pages 1044-1047.]

Before liberation very little had been written on the subject of the epidemic situation of infectious hepatitis. But, after liberation, under the guidance of the Communist Party and the People's Government, large-scale mass movements were initiated to investigate and study the various methods for the prevention and treatment of infectious hepatitis. Within the past decade much has been accomplished in the investigation of the epidemiology of infectious hepatitis by means of clinical and laboratory analyses of the facts.

A. Investigation of the Epidemiology of Infectious Hepatitis

There has been a steady increase in the incidence of infectious hepatitis during the past few years. This may have been due to the great advancements made in treating cases of infectious hepatitis within the organizational network of medical facilities, the widespread system of public medical treatment facilities, the advanced progress in the application of clinical techniques, and the universal investigation of all communicable disease, which is constantly undertaken wherever such diseases occur--in any region of the country.

Taking the total number of hospitalized patients suffering from various types of diseases in 1954 as 1.0, then the total number of hospitalized patients in 1955 would be 1.18, and 1.44 ^{1/} in 1956. Approximately 034-350 [sic] percent of the total number of hospitalized patients were found to have been afflicted with infectious hepatitis during these periods.^{2/}

However, within the past few years, large-scale patriotic health movements have been directed by the Central Committee

of the Communist Party to eradicate the four pests and to promote hygienic living conditions among the masses. Thus, many localities were able to strengthen their [program of] precautionary measures against infectious hepatitis. Consequently, the incidence rate of infectious hepatitis was reduced within a comparatively short time. The following illustrates how a certain locality greatly reduced the incidence of infectious hepatitis within a period of three years.^{3/} By taking the number 100 as the incidence rate of infectious hepatitis in 1956, then the incidence rate for the given area in 1957 would be 48.2, and for 1958 it would be 13.9. This indicates very clearly that even though there are still many unsolved theoretical problems concerning this disease, yet, under the guidance of the Communist Party, the masses were able to control completely the spread of this disease.

Much has been accomplished in China during the past decade in respect to research and investigation on the epidemiology of infectious hepatitis. The following are some of the important aspects of this subject which now confront research workers:

(1) Epidemic season of infectious hepatitis:

Reports which have been submitted by Ch'ien and other research workers^{4/} from Hunan, Chang and others^{5/} from Hunan, Ts'ung and others^{6/} from Peiping, have clearly indicated that there is a definite season for the appearance of infectious hepatitis epidemics. Although the disease occurs throughout the year, yet the peak incidence occurs during the late autumn and early winter months. The reason why infectious hepatitis epidemics occurs at this time is probably the long incubation period of the disease. For in such communicable disease of the gastro-intestinal tract as dysentery, typhoid fever, and infectious hepatitis the peak of the epidemic usually follows immediately after the incubation period, so that, if the incubation period has been gradually lengthened, then the proper sequence of the epidemic would be retarded and delayed. However, this does not necessarily explain why infectious hepatitis occurs during certain seasons of the year.

According to the data submitted by all areas, in the compilation of which all had participated at the All-China Conference on Acute Infectious Diseases in 1959, it was observed that infectious hepatitis generally occurs in late

autumn and early winter in the regions of Sinkiang Province, the northeastern provinces, and the northern provinces of China (it is to be noted that this material was not gathered during the period of universal investigation).

There does not seem to be a definite season for outbreaks of epidemics of infectious hepatitis in the provinces of Hunan, Hupeh, and Shantung; nevertheless there is a definite increase of the disease in spring in Kiangsu and Chekiang provinces. According to data submitted at the conference, it was ascertained that the peak of infectious hepatitis epidemics in Kiangsu and Chekiang generally occurs in the spring time.

A general observation can be derived from the above-mentioned data: In all epidemic regions, sporadic cases are usually observed throughout the year, so that there is usually a sudden flare-up of the disease in its epidemic form, which is localized in certain areas of these regions. Therefore, to prevent the further spread of the disease, it is necessary to eradicate the source of infection. Careful investigation of the close contacts of each patient should be reported at the patient's organizational unit, for this is one of the most effective means of controlling the spread of infectious hepatitis.

It has probably been difficult to detect the season during which epidemics of infectious hepatitis occur from statistics released from hospital records. Huang and other research workers^{8/} in Shanghai were unable to detect the season for infectious hepatitis epidemics during their research on the disease.

(2) Transmission of infectious hepatitis:

The modes of transmitting infectious hepatitis have been investigated by Chang and other research workers in Hunan Province, and by Ts'ung and others in Peiping. Reports and information on the means of transmitting infectious hepatitis were submitted to the All-China Conference on Acute Infectious Diseases in 1959 by Harbin, T'ung-hua, Fukien, Kunming, Sinkiang, and other areas.^{9/} Each of these [areas] submitted reports which also mentioned that the chief sources of infection were found to be eating utensils, water, and other oral-intestinal methods of transmission. Contradictory reports on the respiratory means of transmission were also included in some of the reports.

Over 1,900 epidemic cases were carefully investigated by Ts'ung and his co-workers. They discovered, at the emergency shelters erected for the accommodation of epidemic victims, that not one of the 239 residents in that area had contracted the disease, even though they had been living together with 300 infectious hepatitis patients for a period of 15-40 days. This was because these people had used separate eating utensils and had been separated from the patients at meals.

Besides this, Ts'ung and his co-workers were also able to prove that, when precautionary methods for gastrointestinal infections were conscientiously carried out during a four-month long epidemic of infectious hepatitis, they were able to end the epidemic a month earlier, although no precautions had been undertaken or observed for the respiratory transmission of the disease.

Very few investigative reports on the epidemiology of infectious hepatitis stated that it is an infectious disease transmitted through the respiratory system.

Many problems confront investigative work in epidemiology. China does not apply the "volunteer" system for recruiting people for experimental work; therefore, [the study of] all problems in epidemiology must undergo a carefully detailed procedure of epidemiological research, before such problems may be considered correctly solved or verified. For instance in research determining the possibility of transmission of the disease through the air or by means of vector transmission, close cooperation between epidemiologists and clinicians is necessary, so that other research work on the disease can be carried out.

Such research work should include the solution of questions pertaining to the length of time, during which the disease remains infectious, the cause and course of the non-icteric type of the disease in all regions of the country, preventive and treatment methods, the cause of relapse, and a comparison of precautionary measures for infectious hepatitis with other types of precautionary measures. From now on, this rather difficult and monumental duty should be undertaken by all research workers.

B. Clinical Manifestation of Infectious Hepatitis in China

Hardly any data on infectious hepatitis were published in China before liberation, except for the 623 cases of infectious hepatitis observed in Mukden in 1947 and reported by Chang ^{10/}. Nevertheless, with the exclusion of sporadic infectious hepatitis cases, many reports were published during the decade following liberation: Ch'ien and others from Kiangsu, ^{4/} Wu and others from Hunan, ^{11/} Wu ^{12/} from Anhwei, Tan ^{13/} from Harbin, Chang and others ^{5/} from Hunan, Ch'iu and others ^{14/} from Peiping, Ma ^{15/}, Huang and others ^{8/} from Shanghai, Hsuan ^{16/} from Chekiang, Chia and others ^{26/}, Chang and others ^{17/} from Peiping. In pediatrics, infectious hepatitis was also mentioned in the reports by Hu and others ^{18/} from Shanghai, Huang ^{19/} from Hangchow, the Pediatric Department of Shanghai People's Hospital No 1 ^{20/}, Chen and others ^{21/} from Kunming, Lo and others, ^{22/} P'an and others, ^{23/} and Wang and others, ^{24/} from Peiping.

All these studies analyzed clinical reports received from all over the country and have greatly contributed to clinical data on infectious hepatitis in China. At the All-China Conference of Acute Infectious Diseases in 1959, facts and figures were submitted from each province, municipality, and autonomous district. This increased and gradually helped to complete, the amount of clinical data relating to infectious hepatitis in China.

In adult cases of infectious hepatitis, jaundice is less frequently observed in China than in foreign countries, according to data cited in articles on this subject in foreign literature. During epidemics of infectious hepatitis there are 2-24 times as many cases without jaundice as there are cases with jaundice. Rarely do reports show a greater difference in this non-icteric type when compared to the icteric-type of the disease.

For instance, during the 1957-1958 epidemic, a certain district had 40 times as many cases of non-icteric infectious hepatitis as the icteric type. In another district, during the epidemic of 1958-1959, there were 100 times more cases without jaundice than cases with jaundices; ^{25/}, ^{26/} this fact created many doubts and suspicions in the minds of the people. This was also one of the more important subjects discussed at the All-China Conference on Acute Infectious Diseases.

As a preliminary step towards a unified system of observation, the following procedures, which were based on an analysis of the material submitted to the Conference by research workers from all over the nation, were adopted with the consideration that the non-icteric type of infectious hepatitis could possibly have been caused by the natural immunity of certain human beings towards this disease, or that it depends upon the amount of immunity acquired by the individual, or by the attenuation of the virus through environmental changes. A wrong diagnosis could also have been possible because of the difficult diagnostic procedures involved, and because infectious hepatitis is so often seen without the presence of jaundice.

The following are some of the reasons why non-icteric infectious hepatitis is considered to be a comparatively mild disease:

(a) According to past and recent observations, non-icteric infectious hepatitis is comparatively easy to treat. For instance, a study of 1,335 infectious hepatitis patients showed that, on an average, each jaundiced patient was hospitalized for 64.4 days before being considered well enough for discharge, while patients without jaundice could be discharged within 48.6 days, a difference of more than 18 days.¹⁷ However, a year after discharge [of the patients], the ratios of cases with residual symptoms of the disease in both icteric and non-icteric types of infectious hepatitis were equal.²⁷

(b) In laboratory diagnostic tests more than 90.9 percent of jaundice cases were observed to react positively to the cephalin flocculation test and were usually above (++) , for most of these cases have (+++) and (++++) reactions. In non-icteric types of infectious hepatitis, only 40-54 percent, and sometimes even less, react positively in the thymol turbidity and thymol flocculation tests.

(c) Pathological changes are comparatively slight, since very few mild infectious hepatitis cases have necrosis of the liver cells. Generally death occurs when the disease develops into acute cases of severe jaundice or in acute yellow atrophy of the liver. All this merely explains that infectious hepatitis cases which do not have any symptoms of jaundice are comparatively mild forms of the disease.

Since the non-icteric type of infectious hepatitis is a comparatively mild illness, there is no need to be too apprehensive in regard to it; quarantine facilities should not be enlarged without careful thought, nor should a patient's [period of] hospitalization be prolonged unnecessarily. However, the effects of illness on the broad masses cannot be overlooked. For, even though the hospitalization period is much shorter than for the icteric type of infectious hepatitis, yet, because the non-icteric type is more prevalent than the icteric type of infectious hepatitis, absenteeism is quite high. This affects production to a great extent.

Although the non-icteric type of infectious hepatitis may not be so communicable as the icteric type, since such large numbers of people are usually afflicted with the disease, the source of the contagion cannot be wholly disregarded. Unfortunately this disease cannot be detected and treated during its early stages; therefore, it is important not to overlook the source of contagion.

In respect to the total number of infectious hepatitis cases in China, more men contract infectious hepatitis than women. For instance, Chien and other research workers report that the incidence ratio between men and women is 5:1, but this could be due to the fact that most of the material on this subject was compiled from hospital cases. In general, it was found that males under 30 were most susceptible.

Huang and other research workers ^{8/} listed the following occupations in order of the degree of contagion in which infectious hepatitis was found: workers, staff employees, students, and medical personnel. According to Wu, ^{12/} infectious hepatitis is found in the below-listed order in the following occupations: staff employees, military personnel, students, medical personnel, and housewives.

Thus it can be seen that the disease strikes at the majority of those people who live and work in collective groups, such as workers, students, military personnel, etc., or else at those who have intimate contact with infectious hepatitis patients, for 7-14 percent of these cases consist of medical personnel. This fact supports the data cited in reports published in foreign literature.

In analyzing all these hospital cases from each district in China, it was discovered that the mortality rate in China was much higher in comparison to other countries. It was approximately 0-10.4 percent higher, and averaged 6.6 percent [higher]. However, according to statistics compiled during infectious hepatitis epidemics, the mortality rate was 0.19-1.0 percent and closely approximates the figures given by other nations.

Reports from Shanghai have stated that there is a "malignant" form of infectious hepatitis, but since only a few scattered cases were reported, the situation was not considered to be as serious as the epidemics of eastern Europe where very severe cases of infectious hepatitis occur.

China has contributed only a comparatively small amount of information on the long-range treatment policy for patients suffering from the after-effects of infectious hepatitis. To fully clarify the entire problem of preventing infectious hepatitis after-effects, it may be better to carry out a complete investigation of various forms of the disease manifested during an epidemic, so that the causes of chronic hepatitis and cirrhosis of the liver can be evaluated; this would help in estimating the incidence ratio of the different forms of this disease.

A year after the epidemic of 1956-1957, a follow-up of 1,071 recovery cases was made in a certain North China district, following the patients' discharge from the hospital. A total of 1.9 percent of these cases was not considered fully recovered. This was also the clinical viewpoint after liver function tests had been taken, and after the condition and symptoms manifested in the patient's body testified to the development of chronic hepatitis. 27/25/

The percentage of chronic cases developing after an attack of infectious hepatitis was observed to coincide with the data provided by Capps (three percent of his infectious hepatitis patients develop chronic hepatitis a year after an attack of infectious hepatitis). However, since the time prior to the follow-up of these patients was rather short, there is a possibility that these "chronic cases" would eventually have recovered anyway and would have recovered from the effects of infectious hepatitis after a year or so.

The question of whether patients with infectious hepatitis could develop cirrhosis of the liver and how many of these cases would develop into cirrhosis of the liver was one of the most important topics under discussion at the All-China Conference on Acute Infectious Diseases in 1959. There is evidence, based on the material submitted at the Conference by Peiping, Sian, and Mukden that in certain special cases of non-icteric infectious hepatitis, a tendency towards developing cirrhosis of the liver is possible.

At present, however, no final clarification of this question can be made in China. For there is no way to verify the statements made by Cullman in 1958 and by Smetana in 1955, in which they had affirmed that cases of infectious hepatitis would not develop into cirrhosis of the liver. Further observations will have to be made in China before a definite verification can be made on this subject.

Of 2,500 autopsy cases observed by Liang and other research workers ³⁰ in Canton in 1956, during the six-year period after liberation, 80 cases, or 3.2 percent of the deaths, were found to have been caused by cirrhosis of the liver. In 19 of these cases, cirrhosis of the liver developed--after necrotic changes in the liver had set in--following an attack of infectious hepatitis.

Liang believed that Laennec's cirrhosis of the liver and the necrotic changes observed in the liver--which later develop into cirrhosis of the liver--are essentially the same thing, since these are simply different manifestations of the same disease at different stages of the disease. This point is worth looking into, for the question whether or not some infectious hepatitis cases could later develop into cirrhosis of the liver is debatable according to Laennec and should be studied further.

The relation between physical activity and relapse has not been fully clarified. China cannot presently verify the fact that an early resumption of physical activity would directly lead to the relapse of a patient, as has been suggested in certain foreign literature, e.g., Chalmers in 1955 and Nelsen in 1954.

During the All-China Conference on Acute Infectious Diseases in 1959, Hunan and Peiping presented papers which attempted to establish a relation between physical activity and the deterioration of the patient's physical condition.

The report stated that physical activity did not lead to any severe after-effects in patients who had had mild attacks of infectious hepatitis. There even were reports of patients who had already returned to heavy physical labor, such as farming and other laboring work, and these people did not show any harmful after-effects from such activities. Most of these patients however, had not shown any clear-out symptoms of the disease in the first place, and their only indication of having had the disease was the palpability of the liver below the costal region. It might have been possible that some of these cases could have been mistakenly diagnosed as infectious hepatitis.

Based on the material which Peiping had submitted at the Conference, there was evidence that in 3-10 percent of infectious hepatitis cases an early resumption of physical activity may possibly have delayed recovery 3/28/. Yet, at the same time, it is necessary to prevent the patient from feeling any anxiety--especially in mild cases and in cases of questionable diagnosis. It is useless to frighten both the patient and his community at this juncture, for, until enough evidence can be offered to support the detrimental effect of the early assumption of physical activity, it would be wise, at this time, to proceed with caution.

C. Laboratory Diagnosis of Infectious Hepatitis

At the present time there is still a lack of specific laboratory methods for diagnosing infectious hepatitis. The diagnostic methods generally employed in other countries already are, for the most part, widespread use in China.

Flocculation reaction tests have been reported by Wang, 31/ and Wang 32/ and Chen, 33/ In 1955, Huang and other research workers in Shanghai, 34/ and, in 1957 Shih and other research workers in Peiping 35/ had successively analyzed the specific significance of each of the various flocculation tests which have been used to diagnose infectious hepatitis clinically. Surveys were carried out by Shih and his co-workers on 100 normal individuals to estimate their reactions towards the cephalin flocculation and thymol flocculation tests. It was discovered that the normal reactions of these persons were registered at O-(+) but that the normal reaction of these people to thymol turbidity tests was less than nine Ma units (from the above, Wang has estimated it to be equivalent to 0-5 units, and Chen--to 0-4 units).

Huang pointed out that cephalin flocculation tests would react positively five days after the manifestation of the disease, and that thymol flocculation tests would be positive after seven to eight days had elapsed. These results generally conform to reports submitted by research workers of foreign countries. But Shih, however, had already reported earlier on this kind of reaction from thymol turbidity tests.

During convalescence, reactions from cephalin flocculation tests disappeared much earlier than from thymol turbidity and thymol flocculation tests. This corresponds with Neefe's results and the results made by other research workers in foreign countries.

In compiling these reports of laboratory tests made in China, it was discovered that a unanimity was reached in estimating the diagnostic value of the thymol turbidity and the thymol flocculation tests on infectious hepatitis patients who have been ill for some time, but that no agreement could be reached on evaluating the best type of flocculation test to be used as a specific diagnostic means to detect early cases of infectious hepatitis.

Reports made in relation to S-GOT and S-GPT, concerning the reactions of aldehydes in reducing enzymes to test the enzyme function of the liver, have been submitted by Hsu,^{36/} Wang,^{37/} Chiang,^{38/} Ku,^{39/} Li,^{40/} and by the regions of Peiping, Fukien and Mukden. All these reports have stated that S-GOT is comparatively more valuable in diagnosing early cases of non-icteric infectious hepatitis. S-GOT often reaches a high level of several thousand units, and it has been hard to interpret its meaning when the units were registered in tens and hundreds. More experience should be accumulated from now on, so that the clinical value of these tests can be judged.

In 1957, Li and other research workers ^{41/} reported on the marked increase of iron in the blood serum of infectious hepatitis patients. Most of these patients registered an iron content in the serum above 200 micrograms, while patients who were afflicted with other types of hepatic diseases usually registered in iron content below 200 micrograms.

In 1958 ^{42/} Kuó and other research workers estimated, in Wuhan, that the normal iron content in the serum of an

average Chinese would be 118 micrograms percent, that the iron content of infectious hepatitis patients would average 225.1 micrograms percent, and that in chronic hepatitis cases it would be 218.4 micrograms percent. The iron content in the blood serum of other types of hepatic diseases was about 100 micrograms. Kuo and his associates felt that his method of estimating the iron content in the blood serum was at least of some diagnostic value in the determination of infectious hepatitis, and that it was just as diagnostically valuable as the thymol turbidity test.

In 1958, K'uang and other research workers ^{43/} in Shanghai reported that the amount of 17-ketone bodies was markedly reduced below normal in the urine of infectious hepatitis patients, and that the phenolphthalein count was higher than normal. It was also pointed out that patients who had other types of hepatic diseases suffered diminished sexual powers, and that this is especially true for those patients whose urine showed a reduction in 17-ketone bodies. However, the relationship between the enlargement of breasts and the increase of phenolphthalein in the urine of male patients has not been clarified.

D. Pathology of Infectious Hepatitis

Since the majority of infectious hepatitis patients succeed in recovering their health, any information on the pathological aspects of the disease had to be obtained from biopsies of infectious hepatitis patients. According to incomplete current data, such biopsy specimens have been procured from at least 4,000 infectious hepatitis cases. This does not take into account the number of unreported biopsies which were performed in all regions of China. Therefore, the total number of biopsy specimens obtained should surpass the number used for comparative purposes. A certain Nanking hospital supplied the majority of the biopsy specimens used for research, in comparison with all other regions where biopsies were reported. This Nanking hospital was able to obtain 1,796 biopsy specimens from a total of 1,685 patients.

Since, frequently, many of these patients do not show any marked changes in liver function tests, biopsy specimens of the liver tissue have been our sole means, in recent years, for research study on the liver of infectious hepatitis patients. Even so, it has always been rather difficult to

differentiate histological changes in a normal liver and in the liver of a patient suffering from a mild case of infectious hepatitis.

Up to the present time very little has been reported in organized research work on the normal type of liver in a healthy human being. The majority of "normal" livers have occurred in those cases where liver ailments had been suspected clinically but were found to have had no histological changes after biopsies of the liver were made. Or else the livers could have been basically normal in the first place. Future research work on this subject, if carried out, would greatly aid in the pathological diagnosis of mild non-icteric infectious hepatitis cases.

Typical cases of infectious hepatitis, and cases of the icteric type of infectious hepatitis, show that pathological changes in the liver basically consisted of necroses of the liver cells. Thus, even in the mild non-icteric type of infectious hepatitis, pathological changes in the liver would accompany any change in the liver cells.

For instance, during an infectious hepatitis epidemic in a certain North China region, some of the cases were found to have been due to interstitial hepatitis. At the same time, there was also a possibility that these changes in the liver could have been due to a mild form of infectious hepatitis, and, therefore, it was difficult to differentiate the liver tissue of this form of infectious hepatitis from the tissues of a normal liver.^{22/}

It was observed that in the process of comparing the more serious cases with the mild cases of infectious hepatitis, necrosis of the liver cells was generally found to be present in the former. Different degrees of pathological changes can be present in the liver cells, a circumstance which is related to the degree of toxicity to which the liver was subjected. Thus, in a few cases, a mild type of toxic necrosis could manifest itself, while in some other cases, even if necrosis is not evident, yet, proliferation of liver cells and the formation of double nucleated liver cells would occur very often; or else, an infiltration of large and small liver cells would take place (In general, newly developed liver cells are comparatively larger than others). If all these changes are found in the liver tissue, then it indicates that the liver-- at some time or other--had undergone a necrotic process.

Valuable degeneration and flabbiness or reticularization of the liver cells are some of the most common pathological changes in this type of hepatitis. The hyaline appearance of the hepatic cells show that slight hydropic degeneration has occurred. The deep pigmentation of the cellular fluid and the hyaline appearance of the liver cells state clearly the development of toxic regressive changes in the liver cells. Deep pigmentation of the nucleus in the liver cell and the appearance of vacuole cells could be the precursor of necrosis of the liver. Where red areas appear in the lobules, the cells within these red areas become immersed in exudate, and this clearly denotes a possible parenchymatous infection of the liver.

Hsu and other research workers ^{45/} have generally made similar observations.

The Data submitted by the city of Sian demonstrated that the liver in the non-icteric type of infectious hepatitis undergoes pathological changes which may extend through a period of many years, without developing any signs of cirrhosis of the liver. Reports from other countries state that similar changes in the liver have been observed in some cases for more than three years, without developing any signs of cirrhosis of the liver (Smetana, 1954). Therefore from observations of these pathological changes in the non-icteric form of infectious hepatitis in China, no special feature could be observed to differentiate it from infectious hepatitis elsewhere.

During this prolonged period where no changes could be observed, it might have been possible that only a few necrotic liver cells were centered in the lobules of the liver and had not as yet spread to the periphery of these lobules. Thus, no interstitial proliferation of fibrinous tissue would occur, and cirrhosis of the liver would not develop.

Ch'in and other research workers in Canton reported that death from acute infectious hepatitis do not usually show a necrotic process in the liver cells, for death may have been caused by liver dysfunction.^{9/} This is quite similar to some of the cases found in other countries, reported as "necrotic precursor types" of mortality.

E. Research on the Etiology of Infectious Hepatitis

Research on the etiology of infectious hepatitis was attempted quite late, but Chinese research workers have, within a very short time, carried out research work on virus infectious diseases on a large scale. Several places in the nation are conducting investigations on the virus which causes infectious hepatitis. Almost all of the methods cited on this subject throughout the world have been duplicated. Preliminary steps in this type of research work have already been attempted, and a few leads towards solving the mystery have been uncovered.

For instance, in each of the regions where chicken embryo grafts were attempted, uniform pathological changes in the embryos were noted. Next, domestic animals, unusually insensitive to the infectious hepatitis virus, were subjected to various experimental tests to increase their sensitivity to the virus. For example, since pregnancy would cause an exacerbation of the disease, gravid mice accordingly were used in these experiments, so that they would be repeatedly sensitized to the infectious hepatitis virus. The results achieved from these experiments thus were far superior to any other results previously reported in any literature on this subject.

Tissues from a monkey's kidney, testicle, epididymis, and pure tissue cells from one of the body's systems, Hela cells, Detroit-6 cells and neurofibrosarcoma cells were cultured with the virus. Although the experiments were not quite so successful as expected, yet, preliminary results have offered hope.

There currently is great hope that methods to prolong the time of tissue culture can be found, so that an ideal tissue cell for this kind of culture will be found to aid in the further research of the infectious hepatitis virus.

At present it is necessary to carry out further experimentation under strict laboratory conditions in different laboratories, where the same materials will be used in identical experiments, to make comparisons and also to observe whether these experiments could possibly be duplicated. Decisive conclusions could then be drawn from these and from previous experiments, so as to form a firm basis for any future experimental work.

Summary

During the past decade, under the leadership of the Communist Party, rapid advances have been accomplished in epidemiology, clinical research, laboratory tests, pathology and etiology of epidemic infectious hepatitis. Improved preventive measures have been instituted and much knowledge has been accumulated from experiences derived from several infectious hepatitis epidemics.

As yet, it has not been possible to isolate the virus causing infectious hepatitis, for, at present, no specific diagnostic method has been found. Nor can there be any clarification of the after-effects of infectious hepatitis and the future health of the patient. The effects of preventive inoculation, relapse, and the question whether or not the protraction of this disease was due to constitutional differences within each patient, cannot be decided at the present time. Effective treatment of infectious hepatitis is definitely lacking; therefore, greater efforts should be made to reach the following goals:

1. To continue to develop research work on the epidemiology of infectious hepatitis, so that an early isolation of the virus causing the disease can be made and an early production of the vaccine carried out;
2. Large-scale research work should be carried out in a search for non-specific diagnostic methods, so that early diagnosis of atypical and mild cases of infectious hepatitis can be made;
3. Research work on relapsing cases of infectious hepatitis, the cause of protracted courses of the disease, and the failure of patients to respond to treatment should be studied, so as to prevent any untoward effects of the disease upon the patient;
4. Traditional Chinese and Western-style physicians should cooperate in their search for definite and specific methods to treat infectious hepatitis, so that the menace of epidemic infectious hepatitis can be eradicated.

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BREAK THROUGH THE OBSTACLES TO INFECTIOUS
HEPATITIS RESEARCH

[This is a translation of an editorial in Chung-hua Nei-k'o Tsa-chih (Chinese Journal of Internal Medicine), Vol VII, No 11, Peiping, 1959, page 1013.]

Infectious hepatitis is a highly contagious disease, and since widespread epidemics have resulted, it is therefore very dangerous. The course of the disease and the time required for the complete recovery of the patient is quite a lengthy process. A prolonged period of convalescence is necessary to prevent any possibility of the disease becoming chronic, or of the disease developing into cirrhosis of the liver.

Of the more frequently observed acute infectious diseases, this is the one which is least understood, and, because of this fact, preventive measures against this disease have been inadequate.

Infectious hepatitis is an oral-intestinal infection. At present, no satisfactory explanation has been given for the disease in its epidemic form, nor what special characteristics of this disease would contribute to the development of the disease in its epidemic form. In cases where long incubation periods occur, and in cases of atypical non-icteric forms of infectious hepatitis, the incidence rate has been much higher than in any other forms of the disease.

Such infectious hepatitis cases increase the difficulties of epidemiological investigation. Thus, it is practically impossible to concede that the disease is definitely transmitted through the oral-intestinal tract or by means of the inoculation of infected serum. There is the further possibility that the disease is transmitted through the respiratory tract, and this has been claimed by some research workers.

The contagious period of the disease definitely occurs during the latter part of the incubation period. There is no proof that this may be due to a protracted period of contagion, nor can anything be definitely said concerning the length of this contagious period. These circumstances have

made preventive work rather difficult, for there is the question of the time required to isolate acute cases of infectious hepatitis, and [also the question] whether patients suffering from chronic infectious hepatitis should be isolated.

No standard clinical diagnostic measures have been established for diagnosing the non-icteric type of infectious hepatitis, and it is difficult to diagnose this type of infectious hepatitis, for there are no specific characteristics to differentiate this type of infectious hepatitis from any other types. Such cases are often scattered among many other types of hepatic diseases, and it has always been rather difficult to extract any information on the patient's contacts, since many of these patients have had long incubation periods before the disease was manifested, and too long a time has elapsed for patients to recall such details.

A more objective method for the diagnosis of this disease is through the palpation of an enlarged liver. However, the significance of this diagnostic method is difficult to estimate, since, in children and a few adults, the liver can be palpated only in the upper right quadrant of the abdomen.

Present clinical diagnostic methods of infectious hepatitis have been made by examination of histological sections obtained through biopsy, and in accordance with the following laboratory diagnostic methods:

(1) Various laboratory tests which determine the amount of bile pigmentation.

(2) Tests to determine the quantity of albumin in the blood serum, as well as the changes in the quality of the albumin causing the various flocculation reactions observed in these tests.

(3) The determination of enzyme function (aldehydes for enzyme reduction, which change into aminopeptidase), for estimating necrosis of liver cells and checking the increase of iron in the liver cells.

The first laboratory diagnostic test is obviously of no use in determining the non-icteric forms of infectious hepatitis. The last two types of tests show a relation

between the severity of the disease and the type of positive reactions produced by these tests, or a direct ratio can be found between these tests and the amount of damage incurred by the liver cells. However, when these tests have been considered to be negative, it does not mean that a diagnosis of mild infectious hepatitis can be dismissed.

Non-icteric infectious hepatitis is not only found in the majority of the cases, but it is of the utmost significance from the standpoint of epidemiology. Since this is a mild form of infectious hepatitis, immediate treatment is not provided very often, so that there is a great possibility for untreated cases to develop into chronic cases.

For the past ten or more years, nothing new in the way of treatment has been developed, except for the administration of broad-spectrum antibiotics, adrenocortical steroids, or Ku amino acids, for comparatively severe cases before coma sets in or in cases of liver dysfunction, but some good results were produced. Patients are generally advised to increase the nutritional value of their diets, and rest in bed is indicated.

There is a lack of effective measures of treatment, especially in chronic cases-- and especially so in cases which have a combination of so-called liver symptoms resulting from an attack of hepatitis. Symptoms of protracted discomfort in the upper right quadrant, anorexia and mental depression, etc., often persist and prevent the complete recovery of the patient as well as his ability to work.

Immediate action is necessary to further the study, research, extension, and the summarization of all effective Chinese traditional medicines and methods for the treatment of acute and chronic infectious hepatitis. There is a dearth of material on effective measures to aid the recovery of the patient and prevent after-effects of an attack of infectious hepatitis.

It has been generally assumed that the ratio of infectious hepatitis cases developing into cirrhosis of the liver was not very high, but this does not offer a definite response to the question of how many of these cases do eventually develop into cirrhosis of the liver and what factors would encourage this development. At present, exact information on this subject cannot be supplied from the data on hand.

The question of the kind of immunity a patient would receive after an attack of infectious hepatitis, as well as whether there would be a possibility of reinfection, has not as yet been answered.

The mode of infection is now known, as well as the fact that differences in the type of immunity and in the length of the incubation period could be used to divide the disease into A and B types. However, it still cannot be determined whether there are any other types of infectious hepatitis.

From each of the above-mentioned points, it can be clearly observed that, during the past decade or so, no important progress has been made in solving the many problems relating to this disease. The most important problem which must now be solved is the isolation of the virus of infectious hepatitis.

Common laboratory animals and a few rarely seen animals were used in laboratory tests to isolate the infectious hepatitis virus from specimens obtained from patients. The results were all negative. Even though [articles in] foreign literature had already discussed the isolation of the causative virus of infectious hepatitis in certain laboratory animals such as white mice, guinea pigs, and large white rats, nevertheless, these results have not been completely verified.

A certain amount of difficulty is involved when animals were used in isolating the virus. For instance:

- (1) There is a possibility that the animal itself has a latent viral infection of the disease;
- (2) The isolated "infectious hepatitis virus" cannot propagate itself in succeeding generations, nor can it generally produce a change in the liver;
- (3) Convalescent serum was not established as being of value in the treatment of infectious hepatitis, according to the results of laboratory tests.

Thus, even though success has been reported along this line of research by research workers from many other places, yet, their results have not been publicly recognized. Many of these research workers have reported isolating the virus in an embryonated hen's egg. But no special characteristics

were developed in the inoculated chicken embryo, which would denote the development of the disease, or of any variations or transformations. Therefore, it cannot be determined at this time whether the infectious hepatitis virus is capable of propagation within a chick embryo.

In general, laboratory research workers usually test for the reactions by means of complement-fixation tests or blood cell agglutination tests to establish the presence of the infectious hepatitis virus. It is strongly urged that frequent adjustments should be made in the application of these tests, because the complement-fixation tests are not always reliable. This is because the results have not been sufficient to provide a final and definite conclusion, the reasons for this are as follows:

(1) The serum of infectious hepatitis patients often reacts readily and non-specifically to the various antigens used in the complement-fixation test:

(2) Necrosis of liver tissues of infectious hepatitis patients will cause another type of non-specific reaction: the production of anti-bodies in the albumin of the liver tissue. This phenomenon was observed as early as 1933, when serum reaction tests of yellow fever victims were being verified in laboratory tests. The same kind of non-specific results were observed in the agglutination reaction of the red blood cells in infectious hepatitis patients.

Due to the development of research in the culture of the infectious hepatitis virus within the past four or five years, many research workers have been optimistic about the application of this method in isolating the virus of infectious hepatitis. However, up to the present moment, no article has cited any definite results along this line of research.

At present, it would be more feasible if one or more research organizations would collect the already isolated virus from material produced as a result of preliminary laboratory steps, and then would compare the neutralization reactions of convalescent serum, taken from a patient having a positive diagnosis of infectious hepatitis, with [reactions of] other types of serum. Control serum should be provided from patients suffering from other types of hepatic diseases, but not from infectious hepatitis. In this way this important scientific problem, which has been so baffling to research workers, can be speedily solved.

This suggestion on the part of the Communist Party was specifically aimed at rooting out superstition, providing freedom of thought, and promoting a technical revolution on a large scale. By means of the combined efforts of all medical workers in China, the problem of isolating the infectious hepatitis virus could then be solved at an early date. After the infectious hepatitis virus had been definitely isolated, the problems involving epidemiology, prophylaxis, clinical diagnosis, and treatment for various related forms of the disease could be easily solved with a single stroke of the sword.

Above all it is very important not to be too conservative, for this would impede progress in the isolation of the infectious hepatitis virus, nor should those methods and procedures, which have been mentioned in literature as being unsuccessful, be duplicated.

The following methods are not being fully utilized at the present time:

(1) Various methods to administrate or inoculate medication in laboratory animals to create physiological changes in the animals, so that they would become sensitive to the infectious hepatitis virus by virtue of a reduction of their immunity to the disease, have not been carried out;

(2) In addition to applying the usual methods in selecting specimens from infectious hepatitis patients for inoculation of laboratory animals, other methods--which would closely approximate the natural epidemic environment--should be attempted;

(3) Methods should be employed to prolong the life of liver cells or of carcinomatous liver cells under conditions specifically provided for tissue culture, and studies should be undertaken [to devise] different methods by which specimens can be inoculated into different cells for culture and for the propagation of the viral specimen;

(4) Biochemicals which have already been selected for experimentation should be studied for their reactions, so that they can be used to examine specific forms and be of special significance in detecting the presence of the infectious hepatitis virus, after infection by the virus has occurred in the body.

RESEARCH ON THE ETIOLOGY OF INFECTIOUS HEPATITIS*
[from the article]

CHINA'S ACHIEVEMENTS IN THE STUDY OF LIVER DISEASES
IN THE TEN YEARS SINCE THE FOUNDING OF THE STATE

[This is a translation of an excerpt from an article written by P'an Ch'i-ying, and others, in Chung-hua Nei-k'o Tsa-chih (Chinese Journal of Internal Medicine), Vol VII, No 11, Peiping, 1959, page 1028.]

At the beginning of the fourth quarter of 1958, many of the laboratories included in the regions of Ch'ang-ch'un, Mukden, Peiping, Nanking, Shanghai, Ch'ang-sha, Canton, etc., had started investigative work on the etiology of infectious hepatitis.

Ten kinds of animals (monkeys, white mice, guinea pigs, large white rats, dogs, cats, suckling pigs, goats, rabbits and moles (ti-shu) and seven kinds of birds and fowl (chickens, pigeons, serinus canarea, gray thrush, parrot, "hsiang-ssu niao" and quail) were used in the experiments--performed in all the laboratories--to isolate the infectious hepatitis virus. Many procedures and inoculations were selected to be carried out on certain laboratory animals for this experiment.

It was discovered that monkeys (the Rhesus monkey; weight, three kilograms) seemed more susceptible to infectious hepatitis, for positive symptoms of the disease were observed in the monkey from the various physiological changes in its body and from the reactions of biochemical tests.

A total of five monkeys were infected with the infectious hepatitis virus, and all were found to have enlarged livers (before the monkeys were infected with the disease, their livers were not palpable, but afterwards the largest liver could be felt two millimeters below the costal region); two of the monkeys had markedly elevated temperatures; bile was found in the urine of two others, and punch-biopsies of

* This research material on the etiology of infectious hepatitis was contributed by Dr Wu An-jan.

the liver in all five showed only slight changes in the liver tissue.

No indication of any appreciable change as a result of these experiments was demonstrated in the other animals, even after X-ray radiation and resections had been performed on the spleen and adrenals to decrease the animals' resistance to the virus. No increase was detected in the sensitivity of any animal to the viral infection of infectious hepatitis.

Experimentation with chick embryos showed a few changes, after specimens of the virus had been injected into the chick embryo. During the period of infection, and after the chick embryo had been inoculated with the primary viral specimen or with viral descendants from the primary viral specimen, characteristic changes were noted in the liver of the chick embryo, which followed a definite course of change which was directly related to the degree of pathological change in the liver. For instance, pathological changes in the liver cells, such as necrosis, shrinkage or flabbiness of the liver, were quite evident.

Antigens developed in the chick embryos, and the reactions to the convalescent serum in the complement-fixation tests were positive. However, this reaction is of an unusual nature, and therefore it is difficult to define exactly the significance of these results.

The four types of embryonic liver tissue used in the culture of the infectious hepatitis virus included human tissues and those of the chicken, duck, and quail. Tissue cells from the human amniotic-sac, monkey kidney, and human embryonic musculocutaneous tissue, as well as Hela cells, neurofibroma cells, and Detroit-6 cells were used to isolate the infectious hepatitis virus. No viral specimen has been discovered which would cause pathological changes in the tissue cells, and at present this type of research work is still being carried out.

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