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INFECTIVE HEPATITIS IN THE GARRISON OF MALTA*

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This paper is based on the clinical observation of 450 cases admitted to a general hospital during 1941, 1942, and early part of 1943. The siege conditions prevailing in Malta at the time facilitated this investigation.

Epidemiological Consideration.—The epidemic is practically confined to autumn and early winter, but sporadic cases are seen throughout the year. Over 65% of the cases occur in the peak months of October, November, and December, about 86% falling in the age group 20–29. Men over the age of 40 appear to be less susceptible to the disease. The majority of cases occur in the fourth week after exposure to infection, but there is considerable variation in the incubation period. Infectivity seems to be confined to the pre-icteric stage. There is a tendency for the cases to appear in series at intervals of about four weeks. The probable explanation is that the disease is infectious only for a short time, and the cases occur in series at intervals corresponding to the incubation period. It is probably airborne through infectious droplets, and overcrowding in barracks and quarters tends to its spread. About 6% of the cases occurred in the R.A.M.C., including medical orderlies of other units. This is a high figure considering the proportion of R.A.M.C. to the whole Army.

Clinical Types

Infective hepatitis may be described under four clinical types according to the mode of onset, signs and symptoms, and course of the disease: (i) gastro-intestinal; (ii) febrile; (iii) icteric; and (iv) the group without jaundice (hepatitis sine icterus).

(i) *Gastro-intestinal Type (52%).*—The onset is insidious. This type starts with malaise, nausea, anorexia, vomiting, constipation, or (rarely) mild diarrhoea. Epigastric pain or a feeling of discomfort or distension is present in most cases. After the lapse of three to five days the urine turns dark. Within an interval of 24 to 48 hours an icteric tinge appears in the conjunctivae. Frontal headache, retro-orbital pain, generalized muscular pain, pain in the loin, vague pain in the joints, and a feeling of chill and faintness have been noticed at the onset. Injection of conjunctival vessels, giving the appearance of radiating streaks from the corneal margin, was observed in a number of cases. Flushing of the face and a faint generalized erythematous rash were seen in a few very early cases. The signs, symptoms, and course of the disease in this type closely resemble the so-called catarrhal jaundice of civil life.

(ii) *Febrile Type (30%).*—All patients with marked pyrexia at the onset (100° F. or higher) are included in this group. The temperature may rise to 105° F. The onset is more rapid than in the previous type. Usually the patient notices a sensation

of cold or chill, not amounting to a rigor, accompanied by frontal headache, retro-orbital pain, and sometimes generalized muscular pain. Rarely it begins with a rigor. Injection of conjunctival vessels and mild erythematous rash have been noted in some cases of this type too. The temperature after three or four days usually drops by rapid lysis. Within a day or two after lysis bile appears in the urine, and 24 to 48 hours later there is an icteric tinge in the conjunctivae. Relative bradycardia is a noteworthy sign. Some typical cases were very closely observed, and four-hourly pulse and temperature charts were maintained. The charts revealed Faget's sign in a number of cases. Symptoms usually subside soon after the onset of jaundice. The subsequent course of the disease is similar to that of the previous type. Post-influenzal jaundice has been recorded, especially towards the end of the last war. It is extremely doubtful whether influenza is responsible for jaundice at all. The fever resembles influenza very closely, but by tracing the source of infection we have been able to establish the fact that the febrile type may be the source of infection to a case of the gastro-intestinal type, and vice versa. Besides, in barracks and billets both types occur side by side.

(iii) *The Icteric (Ambulatory) Type (10%).*—No definite prodromal symptoms are observed in this group. Occasionally there may be a feeling of general malaise for two or three days. These patients report sick only if the icteric tinge of conjunctivae is pointed out to them by some other person or is noticed in the looking-glass by themselves. Teetotallers, patients over the age of 35, and Maltese usually belong to this group. The great majority feel quite well subjectively. Jaundice is not deep. Bradycardia is as frequent as in the other types.

(iv) *The Group without Jaundice (Hepatitis sine Icterus).*—We came to know about the existence of this group under the following circumstances: Eight officers were staying together in a billet. In the last week of Oct., 1941, one of them developed jaundice and was admitted to hospital. About five weeks later four others developed the same symptoms—fever, headache, nausea, and slight epigastric pain—and were also removed to hospital, where three of them developed jaundice, but the fourth did not, though he had the same symptoms at the onset. On admission his liver was enlarged and tender. White cells, 5,200—polymorphs 44.5%, eosinophils *nil*, basophils 1.5%, lymphocytes 51.5%, monocytes 2.5%. Van den Bergh—direct and indirect, negative. The onset in this group is similar to that of the first two groups. One feature is the definite enlargement of the liver (often two fingerbreadths or more below the costal margin). The spleen may or may not be palpable. Relative lymphocytosis is more pronounced. The temperature settles down in less than a week; the liver returns to the normal size in a fortnight. Urine is normal throughout. Sometimes a trace of bile may be seen for a few hours only.

* Abridged specially for the *B.M.J.*

The main signs and symptoms are as follows:

Symptoms and Signs	Frequency %	Remarks
Anorexia, nausea, and general malaise	90	Usually appear at onset. Very mild in icteric type
Vomiting	46	Most marked in gastro-intestinal type. Not present in icteric type
Headache, retro-orbital pain, vague pain all over body	21	More severe in febrile type
Pruritus	10	May occur just before, during, or after appearance of jaundice
Fainting	2	At the onset
Bradycardia	75	Lowest pulse rate recorded 34. In febrile cases there is always a relative bradycardia
Icterus	All except group without jaundice	First appears in conjunctiva a day or two after urine turns dark; then spreads to trunk and limbs. Disappears in same order
Haemorrhagic signs:	Rare	The case with haematuria had <i>B. coli</i> infection of urinary tract complicating infective hepatitis
Epistaxis	One case	
Ecchymosis	" "	
Petechiae	" "	
Haematuria	" "	
Herpes labialis	" "	In one case herpes appeared on forehead
Erythematous rash ..	5	Very faint generalized macular rash all over trunk. Face escapes. Seen only in very early cases. Easily missed
Flushing of face ..	4	Seen only in very early cases
Conjunctival congestion	10	Blood vessels dilated to show red radial striation. Some of these cases complained of photophobia
Urine		Mild amber to deep dark; acid. Bile pigments plus. Bile salts present only in about 3%. Bile free in about 12 days. Extremes: few hours and three months
Bowels:		
Constipated at onset	51	Stools usually light in colour, but may vary from almost normal to definite clay colour. Stercobilin present even in palest stools
Diarrhoea	9	
Loose bowels	12	
Normal	28	
Liver:		
Lower edge below rt. costal margin	15	Area of hepatic dullness increased in many patients when examined early enough, but soon shrinks after onset of jaundice. When hepatomegaly marked, jaundice usually mild. Gall-bladder not palpable
Enlargement of spleen	15	Splenomegaly may exist independently of hepatomegaly
Distension of rt. lateral thoracic vein ..	15	This vein becomes distended in some cases late in the disease. The flow is upwards. Liver dullness diminishes at same time. It is probably a sequel to intrahepatic obstruction to blood flow
B.S.R. (Westergren) (studied in 25 cases)		Within normal limits in uncomplicated cases. Slightly raised during pyrexial period and also if there is any lung complication
Leucocyte count (taken in 50 cases)		Slight leucopenia in most cases at onset of jaundice. Total W.B.C. may be as low as 2,550. Relative or absolute lymphocytosis usual. Leucopenia may be followed by slight leucocytosis
Van den Bergh test (qualitative) (made in 25 cases)		Direct reaction is either prompt positive or biphasic; becomes negative soon after urine is bile-free. Indirect reaction is positive a little longer
Van den Bergh (quantitative) (done in 10 cases)		Bilirubin content varied from 0.4 to 28 mg./100 c.cm., according to intensity of jaundice

Prothrombin Content of Blood.—Estimation of prothrombin content of blood was carried out in a group of 18 patients and two controls by one of us (S. J. H.). Quick's method of estimation as modified by Kark and Lozner was employed, using the stable thromboplastin preparation described by Souter and Kark. In seven of these patients, in whom a low prothrombin level was found, the estimation was repeated in four weeks to ascertain the progress of the case. The prothrombin percentage varied from 35 to 100, depending upon the severity of the case. There was considerable improvement after an interval of four weeks, but in severe cases the prothrombin level was still low (about 60%). Assuming that the liver was the source of prothrombin, it was seen that the liver function was deranged, at least so far as it affected the manufacture and storage of prothrombin.

Complications

Acute Hepatic Necrosis (Icterus Gravis).—This is the most serious and fatal complication, and its possibility renders the disease potentially dangerous. Fortunately this complication is exceedingly rare. We have come across only one fatal case out of 450. A few days after the onset of jaundice, mental irritability, vomiting, and stupor occur. Cheyne-Stokes breathing, coma, and pyrexia supervene, and the patient usually dies in three days. Haemorrhagic manifestations such as haematemesis, epistaxis, or haematuria may occur. Urine contains bile, albumin, and casts. Either suppression of urine or incontinence may occur. A marked diminution in liver dullness can be made out on percussion, and the right lateral thoracic vein may be very much distended. The clinical picture is that of cholaemia

(icterus gravis), and the necropsy findings are those of acute necrosis of liver.

Subacute Hepatic Necrosis.—This is a more frequent but less fatal complication. It is met with in all grades of severity. At the onset there is nothing to distinguish it from an ordinary case of jaundice, but gradually jaundice becomes deeper. Liver is tender and slightly enlarged in the beginning, but shrinks later. Nausea, vomiting, and constipation are more pronounced than in an average case of jaundice. The stay in hospital and convalescence are prolonged, but these cases have a fair chance of ultimate recovery.

Other complications are not worth mentioning here.

Second Attacks of Jaundice; Relapse

Apart from icterus neonatorum and relapse due to alcohol, second attacks of jaundice occurred in two cases—two years and five years after the first attack, respectively. In both cases the second attack was milder than the previous one.

Relapse.—True relapse, though rare, is occasionally met with. It appears to be favoured with too early convalescence or too early discharge from hospital. Bile reappears in the urine. The patient may develop a mild pyrexia and feel sick. The icteric tinge of skin and conjunctivae deepens and stools turn pale. The signs and symptoms clear up quicker during this type of relapse than during the original attack.

Relapse due to Alcohol.—The following case first made us realize the part played by alcohol in bringing about relapse of jaundice.

A corporal aged 25 was first admitted on Sept. 8, 1941, with jaundice of moderate intensity. There was tenderness in the hepatic area, but liver and spleen were not palpable. Urine bile-free on Sept. 16. Jaundice had cleared up well on discharge to unit on Sept. 26. Took 5 or 6 bottles of beer a day since the beginning of Nov., 1941. Took 18 bottles of beer on Nov. 19, 1941. Felt pain in the hepatic area on the 22nd. Vomited once in the night. Next day jaundice obvious. Readmitted on Nov. 24 with jaundice of moderate intensity. Lower edge of liver just palpable and tender. Urine contained both bile salts and pigments. Bile-free on Nov. 30.

We have come across eight more similar cases of relapse due to alcohol. The amount of alcohol taken in each case is quite considerable, and is the maximum consumed on any single day since leaving hospital. Beer, whisky, gin, sherry, champagne, all appear to be capable of bringing about relapse. Urine turns dark within 24 to 48 hours after taking alcohol in such cases, and jaundice is quite obvious in 3 or 4 days. The following case illustrates the facts mentioned above.

An officer had his first attack of jaundice two months previously. Took 10 oz. of sherry, 10 oz. of champagne, and 4 oz. of liqueur one day. Within two days developed jaundice again. Urine bile plus; hepatic tenderness plus; liver not palpable; spleen palpable. Total W.B.C., 2,550. Blood bilirubin, 20 mg./100 c.cm. Prothrombin content of blood, 40%; a month later increased to 60%. Urine bile-free a month after onset. Ever since, similar attack of jaundice occurred within 24 hours of taking any alcohol. Finally boarded out to U.K.

Alcohol sometimes produces a hepatitis without jaundice:

An officer attended a party four weeks after hospital treatment for infective hepatitis. Took 12 oz. of whisky. Within about 12 hours developed a mild rigor. Temperature 102° F.; liver enlarged 1 in. below costal margin; urine N.A.D. Temperature normal next morning. Liver appeared normal five days later.

Effect of Liver Poisons on Infective Hepatitis

1. Alcohol.—The effect of alcohol on infective hepatitis was studied in over 300 cases. Relapse due to alcohol has been discussed above. Apart from relapse, alcohol appears to precipitate jaundice in persons who are incubating the disease. If an appreciable amount is taken any time between three and six weeks after infection jaundice is very likely to be precipitated within from a few hours to three days. We have about 100 cases to illustrate this fact. The following is a typical example.

A sapper aged 22 had been in contact with a case of jaundice five weeks previously. Did not take any alcohol for three months previous to Oct. 17, 1942. That night he took two cocktails, two bottles of stout, and three glasses of imbeet (crude Maltose wine—alcoholic content 15%). Next day he had a good amount of rum and imbeet. Noticed dark urine within 48 hours. Deep jaundice on admission to hospital on Oct. 23.

The intensity of jaundice increases if alcohol is taken during the course of the disease.

Two oz. of brandy, 3 oz. of gin, 3 oz. of whisky, 10 oz. of imbeet, and three bottles of beer appear to have a more or less equal precipitating effect on jaundice. In all probability the factor responsible for the toxic action on the liver is the alcoholic content of the liquor and not any flavouring agent in it. A bottle of beer or an

equivalent quantity of wine or spirit does not seem to have any effect. It is also doubtful whether two bottles of beer would precipitate jaundice. But if in addition to two bottles of beer some other alcoholic beverage is taken within 24 hours there is a possibility of some effect on the intensity and onset of jaundice. In several instances jaundice has become manifest 24 to 72 hours after taking three bottles of beer. A fortnight's ration of three bottles of beer is usually issued on a single day. Men usually empty the three bottles at the same time, and two or three days later develop jaundice. Alcohol of all kinds was severely restricted in Malta during the latter part of 1942. There was an appreciable fall in the incidence of jaundice, especially among officers, during that period as compared with the previous year.

2. *Arsenic*.—There has been no general agreement as to the causation of jaundice occurring during and subsequent to the treatment of syphilis by arsphenamine preparations. Though syphilis itself can cause jaundice, the fact that the latter often occurs after the serum reactions have been rendered negative proves that syphilis has very little to do with it. The incidence of jaundice due to arsphenamine therapy has increased in recent years *pari passu* with "catarrhal jaundice" in the areas affected. A seasonal prevalence has also been noticed. The signs and symptoms closely resemble those of catarrhal jaundice or infective hepatitis. There is considerable evidence to support the view that the majority of cases of jaundice met with during and subsequent to arsphenamine therapy are not due solely to arsenic, though that drug is a strong contributory factor. The incidence of jaundice is less in American clinics, where arsphenamine is administered by continuous I.V. drip or by frequent I.V. injections during a short period of intensive treatment varying from 1 to 5 days. We have some across 14 cases of jaundice in syphilitic patients. The majority occurred during the season when infective hepatitis was prevalent. All were sero-negative when jaundice was manifested. There was no definite relation between the total amount of arsenic given and the onset of jaundice. Jaundice occurred in the beginning, middle, or towards the end of a course of injections or, in some cases, even long after the last injection. If an injection was given after the urine turned dark jaundice was precipitated within 48 hours. In such cases the jaundice was deep and the course of the disease prolonged. Jaundice which occurred a considerable interval after a course of injections was very mild when compared with that occurring during the course of injections. In all these respects the effect of arsenic is similar to that of alcohol, already discussed, but is more pronounced. Nine out of 14 cases arose in naval personnel. Two main reasons for this preponderance seem to be the daily issue of the rum ration and the I.V. administration of arsenic.

3. *Gold*.—In reviewing 900 cases of arthritis (rheumatoid) treated with gold at an arthritis clinic in Leeds one of us (S. J. H.) noticed a high incidence of jaundice after gold treatment. Among the first 100 cases (1935) there was no jaundice. In the second series, of 300 cases (1936), 3.5% developed jaundice, and in the third series (900 cases) 9.4%. The clinical picture was indistinguishable from the classical catarrhal jaundice. The van den Bergh test gave biphasic reactions, and in severe cases a transient positive direct reaction. There was a sparse outbreak of infective hepatitis (sporadic) for about eighteen months during 1936 and 1937 in the area from which most of the cases came. The proportion of cases of toxic jaundice among patients on gold treatment was much greater than could be accounted for by chance infection. Presumably the cause of jaundice was the temporary toxic effect of the gold salts on the liver cells, inducing a hepatitis which in some cases progressed to subacute necrosis. Gold is therefore brought into line with arsenic in producing similar toxic effects upon the liver. All evidence favours the view that gold was not entirely responsible for the jaundice, but was only accentuating the effect of the attack of ordinary infective hepatitis.

Discussion

The clinical findings, already discussed, indicate that the jaundice is, at least partly, obstructive in nature. The gall-bladder was not palpable in any of our cases. Our post-mortem cases showed no evidence of obstruction in the bile ducts, cystic duct, and bile canaliculi, but there was diffuse hepatitis with necrosis. The obstruction lies in the liver parenchyma, resulting from the swelling and compression of liver cells consequent upon direct damage to them.

Relationship with Catarrhal Jaundice.—Virchow, in 1864, first put forward the view that catarrhal jaundice was due to catarrhal swelling of the opening of the common bile duct the result of an acute gastro-intestinal disturbance. Later it was believed that the inflammation extended into the smaller ducts. Eppinger described obstruction of the ostium of the common bile duct by a mucous plug in his much-quoted post-mortem report of a jaundice patient who died by accident. Later, however, after following up his cases for over 18 years, he supported

the view "that acute catarrhal jaundice is merely acute yellow atrophy in miniature." Schrupf, in 1932, secured a piece of liver removed on the eighth day at an operation undertaken for a mistaken diagnosis, and described the changes as those of "acute yellow atrophy in miniature." Gaskell, in 1933, described a case of jaundice which ended fatally at an earlier stage (third day) from another cause, and the condition found in the liver was an acute inflammation with degeneration of the liver cells. The bile ducts were intact with normal epithelium, and appeared to be in no way involved in the inflammatory process. A. M. Gilchrist recently published pathological reports upon material removed at operation from the liver of two patients with jaundice who were operated on "because of" mistaken diagnosis." The finding in both was a subacute hepatitis with swelling and albuminous degeneration of the liver cells, accompanied with necrosis of a few liver cells in the centre of the lobules. Findley, in 1941, reviewing catarrhal jaundice, quoted post-mortem records of eight published cases in which were found degenerative changes in the liver cells and round-cell infiltration in the portal tracts with no change in the bile ducts or duodenum.

Clinically, it is impossible to separate catarrhal jaundice from infective hepatitis—especially the gastro-intestinal and icteric forms: the symptoms and signs of the two conditions are identical. There is usually leucopenia, the total W.B.C. reaching a figure as low as 2,000. There is a relative lymphocytosis, and primitive forms sometimes occur. The monocytes are increased. It also sometimes occurs in sporadic outbreaks. In fact, there is nothing to distinguish widespread catarrhal jaundice from infective hepatitis. It breaks out in epidemic form when conditions are favourable for its spread. During the epidemic in Malta the few cases admitted to the civil hospitals were diagnosed and treated as ordinary catarrhal jaundice. In the light of these facts the theory of catarrhal pathogenesis of jaundice is not tenable.

Aetiology

The long incubation period, the seasonal prevalence, the appreciable immunity after the first attack, and the high infectivity during the pre-icteric stage favour the view that it is a virus disease. We know very little about the nature and paths of entry of the virus. The prodromal malaise, the occasional generalized rash, and the early splenomegaly rather suggest a generalized blood-borne infection. The mode of infection is probably droplet, after brief exposures as in "speech contact," with a possibility of transmission by fomites. Since the period of infectivity is very limited, conditions in civil life are less favourable for its spread. Overcrowding in barracks and billets is an important factor for its epidemicity in the Army.

Alcohol is another contributory factor. It seems that two hepatotoxic factors—virus plus gold, virus plus N.A.B.—increase the liability of the patient to develop hepatitis. We have no doubt that the same explanation holds in relation to virus and alcohol. During the incubation period alcohol is capable of precipitating jaundice, and after the onset of jaundice it is capable of intensifying it. It is quite probable that alcohol precipitates jaundice in the group of hepatitis without jaundice. In civil life it is impossible to identify this group. Teetotallers appear to be less susceptible to jaundice. During the last war Indians serving in the Middle East were found to be much less susceptible to infective hepatitis. The mortality due to jaundice among the Indian force was less than half that among the other forces. During the present war the number of infective hepatitis cases treated in Indian hospitals in the Middle East is negligible when compared with that treated in British hospitals. The vast majority of Indians are teetotallers. The Mauritians serving in the Middle East are more susceptible to infective hepatitis, though the majority of them are descendants of Indians originally settled in Mauritius. The Mauritians are addicted to alcohol as much as anybody else.

Prophylaxis

Under war conditions the temptation to indulge in alcohol is great, and it is difficult to avoid overcrowding. But the disease is most prevalent in September to January, and restrictions are needed only during these months. A possibly useful preventive measure would be the reduction of consumption of alcohol to one bottle, or perhaps two bottles, of beer or an

equivalent amount of other alcoholic beverage for periods of three days during these months. Measures should also be taken to prevent overcrowding, so far as is possible, from the middle of August to the end of December.

One might ask how soon after discharge from hospital can a patient take alcohol or resume arsenic or gold therapy? We have come across cases in which a considerable amount of alcohol was taken a few weeks after discharge without any untoward effect. We know at least one patient who received a complete course of arsenic injections after an interval of only five weeks from the date of discharge without any toxic manifestation. It should be remembered that the normal liver can withstand large doses of all these drugs. The capacity of a damaged liver depends upon the amount of damage already done. Recovery is complete in a short time in mild cases, whereas in severe cases it may be months before the liver is capable of withstanding even small doses of these drugs. In a case of moderate severity a period of six months is a reasonable interval, after which the administration of these drugs can be resumed with safety. Great caution and longer intervals are needed in relapse cases. Evidence is accumulating to support the view that a weak liver poison such as alcohol may have a stimulant action on the fibrous tissue stroma of the liver while exerting a degenerative effect on the liver parenchyma, and the prolonged stimulant action may lead to cirrhosis in course of time. In all probability these properties of the drug hold good only if the liver is already damaged by a previous attack of hepatitis, with or without jaundice. If the stroma is as much damaged as the parenchyma, stimulation can produce no proliferation, and cirrhosis is unlikely in cases of moderate or severe jaundice except as replacement fibrosis in multiple nodular hyperplasia. This is rather speculative, but it is hoped that future work will confirm it.

Summary

A review is given of 450 cases of infective hepatitis treated in a general hospital in Malta. The epidemiology, clinical types, signs, symptoms, diagnosis, complications, and cause of relapse are discussed. The effect of liver poisons—alcohol, arsenic, and gold—is described. The pathogenesis of catarrhal jaundice is reviewed critically.

The clinical findings suggest that the jaundice is partly obstructive in nature.

We wish to express our gratitude to Col. Morrison and Col. Whalley for permission to carry on this investigation and publish this paper. Our thanks are also due to Lieut.-Col. McPherson, Major Kidson, Major Wilson, Major Shucksmith, Major Light, Capt. Oakes, Sister Bevan, and Sister Nicholson.

HUMAN-MILK INTOXICATION DUE TO B₁ AVITAMINOSIS

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For the first few months after the birth of their infants the Chinese women in Hong Kong live in constant dread of losing them. This anxiety is comprehensible, taking into consideration the infantile mortality, which amounted to 345 per 1,000 live births in 1939 (Hong Kong Annual Medical Report)—i.e., more than one-third of all infants born alive died within their first year of life. A certain proportion of deaths occur suddenly in apparently healthy, well-fed, and well-cared-for babies, with a predilection for the male sex, thus giving rise to a belief among the Chinese that evil spirits, out of jealousy, snatch their infants, especially plump baby boys. Hence the rather pathetic efforts of the parents to protect their infants from such a fate: "joss" papers are pasted on the windows and "joss" sticks are burned before the entrance of their homes to prevent the incursion of evil spirits; the infants are disguised as animals by sewing fur ears on their caps; protective talismans are hung on their necks and chains on their ankles to fetter them, allegorically, to their homes. However, in spite of all these "precautions," a mother may find, to her

horror, that her infant has died, unobserved, during the night or while strapped to her back (the usual method of carrying infants in China). Sometimes the mothers observe that their infants suddenly become cyanotic and dyspnoeic and die, apparently of suffocation. In such cases women believe that suffocation is due to "wind" which drives mucus into the child's throat. Furthermore, they believe that this "wind" is transmitted to the infants through their own milk, which is considered to be "no good."

Aetiology

Actually the belief that their milk is not good has been scientifically proved. In 1888 Hirota, in Tokyo, was the first to observe a complex of symptoms in infants fed by beriberic women, and he called this complex "infantile beriberi"—thus connecting this disease with a condition later found to be B₁ avitaminosis. Since then a number of Japanese workers (Ito, 1911; Asakura, 1932; Takamatsu, 1934), and also I myself (Fehily, 1940), have suggested that the milk of B₁-avitaminotic women, besides being vitamin-deficient, contains some toxic substance or substances. We now know that in B₁ avitaminosis, owing to a reduction of certain co-enzymes, the intermediary products of incomplete carbohydrate oxidation accumulate in the tissues, organs, and body fluids, including human milk. These intermediary metabolites are believed to consist of lactic acid, aceto-acetic acid, glycuronic acid, glyceraldehyde, acetaldehyde, dihydroxy-acetone, methylglyoxal, and others. Most of these intermediary metabolites (lactic acid excluded) are estimated as "bisulphite binding substances" (B.B.S.), which are found to be increased threefold to fourfold over normal values in all body fluids in B₁-avitaminotic living beings. After the administration of vitamin B₁ the B.B.S. decrease almost immediately to the normal values. Although the correlation between the intermediary metabolites and B₁ avitaminosis has been definitely established, many workers (Haynes and Weiss, 1940, and others) have proved that these metabolites are not the causative factor in the development of the acute nervous and cardiac symptoms encountered in this condition.

One of these substances—methylglyoxal—has been shown to be actively toxic (Kermak, Lambie, and Slatyer, 1927; Vogt-Moller, 1931), and as it is never found in the milk of healthy women it has been suggested that this product is the toxic factor in the milk of B₁-avitaminotic women. However, various authors have stated (not in connexion with infantile beriberi) that other intermediary products, if in excess, are toxic, and this seems to have been demonstrated by many experiments, including the following (Haynes and Weiss, 1940):

The administration of large doses of pyruvic acid or sodium pyruvate to normal and deficient rats was followed by death of the rats, both normal and deficient. Pyruvic acid in sublethal doses was especially irritating to the throat and had an injurious effect on the digestive and respiratory systems, whereas sodium pyruvate in sublethal doses produced diarrhoea. In the case of B₁-avitaminotic rats, the lethal dose of sodium pyruvate is smaller than that for normal rats, and the animals developed neurological symptoms shortly before death.

It would seem that the amount of pyruvic acid and sodium pyruvate in the milk of B₁-avitaminotic women is beyond the infantile tolerance, as one encounters all the above-mentioned symptoms as well as similar modes of death in infants fed on such a milk. It would seem also that besides methylglyoxal and pyruvates, other intermediary metabolites, in the amounts encountered in the milk, may take part in the intoxication, and their action would appear to be synergic and also cumulative, as even a few feeds may be fatal to an infant. This action is especially evident in acute cases, in which the intermediary metabolites may possibly give rise to acidosis similar to that of diabetic coma—an acute intoxication caused by the products of disordered carbohydrate and fat metabolism. In addition, it seems that the accumulation of intermediary metabolites alters the taste of the milk, as obviously hungry infants, after sucking greedily for a few moments, avert their heads protestingly and spill the milk (while water or cow's milk is taken without trouble).

Thus infantile beriberi differs considerably from the adult type, being primarily and mainly an intoxication, with acute