and received was the predominant factor in the issue of the case, no doubt by fostering those inherent powers of resistance and of somatic response which together constitute the *vis medicatrix naturæ* of the old-time physicians.

It remains for me to record my indebtedness to my Resident Medical Officer, Assistant-Surgeon E. A. Eates, I.M.D., and to my matron Miss J. Coulter, and the nursing staff, for their loyal co-operation in a difficult case, made no less difficult by the inability of the patient to speak or understand any language but Italian.

In conclusion I should like to add that the heavy cost of specific treatment in this case was met from a fund generously placed at my disposal recently by my friend Sir Prabhashankar Pattani, K.C.I.E., of Bhavnagar.

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SOME OBSERVATIONS ON TWO CASES OF DISORDER OF THE LIVER IN INFANCY AND CHILDHOOD*

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THE frequency of cirrhosis of the liver in infancy and childhood in India has been long recognized, but cases of disorder of the liver following a course simulating that of acute necrosis have not been reported very often in this country. Furthermore, the subject of cirrhosis has by no means been exhaustively studied, and a satisfactory explanation of many a feature of this illness is lacking.

Recently we came across two cases—one of acute necrosis in a child aged seven and a half years and the other of cirrhosis of the liver in an infant aged one year—in the Carmichael Hospital for Tropical Diseases. Certain observations were made on these cases, which are the subject-matter of this communication.

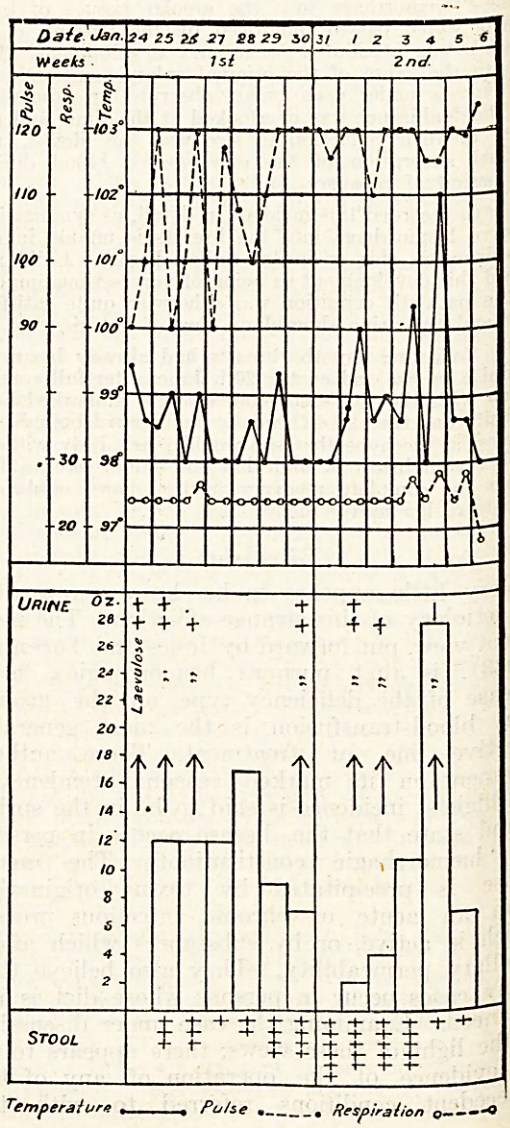
Case 1.—N. R. B., a boy, aged 7½ years, was born of healthy parents at full time. He was a resident of Rampurhat in Bengal. There was no history of any previous serious illness, neither was there any history of drug or alcohol administration. He took the usual Bengali diet consisting of rice, vegetables, fish, eggs and milk. His parents, brothers and sisters are healthy. No member of the family has had any disorder of the liver, neither was there any history of syphilis.

He had frequent, watery motions on the 10th December, 1932; this condition continued for about 10 days, and is reported to have been relieved by the administration of castor-oil emulsion. But he caught a chill and had a swelling of the right auricular region soon after. Following this he had a slow rise of temperature, enlargement of the liver, and jaundice. His condition improved considerably on a restricted diet containing very little fat, and on receiving three injections of emetine hydrochloride, grains 1/3 each, and a mixture containing salicylates. He was put back on to normal diet as he had no symptoms for about a week. On 5th January, 1933, his condition became suddenly very much worse, as evidenced by the appearance of deep jaundice, swelling of the legs, and rapidly-developing ascites. He was admitted to the hospital in this condition on the 24th January, 1933.

On admission to the hospital the patient was found to be a well-developed boy for his age. There was deep jaundice of the skin and sclera, and œdema of the lower extremities and eyelids. He looked markedly anæmic. The abdomen was protuberant with a considerable amount of ascites. The liver was palpable, hard and smooth, but not tender. The spleen was not palpable. The tongue was clean and moist. There was neither caries of the teeth, nor pyorrhœa alveolaris. The tonsils were septic. The apex of the heart was in the fifth intercostal space at the left mammary line and the precordial dullness extended to this line on the left. There was a thrill and a presystolic murmur at the apex. There was no evidence of disease of respiratory, nervous, or any other system.

Figure 1

Case No. 1.....*N.R.B.*.....*Age* 7½ *years.*



*Being a paper read at the British Medical Association (Calcutta branch) on the 21st April, 1933.

Investigations.—Van den Bergh's test gave both 'direct' and 'indirect' positive reactions. Blood examination on the 26th January revealed 45 per cent hæmoglobin, 3,070,000 erythrocytes, and 7,800 leucocytes per cubic millimetre, of which 88 per cent were polymorphonuclears, and 12 per cent lymphocytes. Fasting blood-sugar was estimated to be 0.065 milligramme per cent. The Wassermann reaction was negative and the blood was also negative for filaria. Microscopical examination of the stool showed no parasites or ova. Culture of the stool showed *B. pseudo-carolinus*. An examination of the urine done outside on the 16th January showed a trace of sugar. After the administration of 10 grammes of lævulose and 15 grammes of glucose the urine showed lævulose and bile pigment in fair quantities but no glucose; there was a trace of albumin but no casts.

The patient was given no lævulose and was put on a diet consisting of two pints of milk, four ounces of sugar, two ounces of butter, one egg, two oranges and eight ounces of bread daily. Urine examination showed the reaction acid, no glucose, leucin or tyrosin, and no leptospiræ. The other findings are shown in table I below. For the temperature, pulse rate, respiration and urine reports *vide* figure 1.

TABLE I

Date	Albumin	Lævulose	Bile-pigment	Casts
24-1-33	*Nil*	++	*Nil*	*Nil*
26-1-33	*Nil*	*Nil*	*Nil*	*Nil*
1-2-33	Trace	++	++	*Nil*
2-2-33	Trace	+	++	Hyaline granular
4-2-33	..	*Nil*	++	Do.

Lævulose was tested by polarimeter.

The lævulose-tolerance test was done to determine the efficiency of the liver; the results are tabulated in table II and in figure 1, compared with a control case.

TABLE II (*vide* FIGURE 2)

(Ten grammes of lævulose by mouth)

	Blood sugar, milligramme per cent.
Fasting ..	0.065
After 45 minutes	0.080
After 90 minutes	0.090
After 135 minutes	0.095

The blood sugar was estimated by the calorimetric method by Dr. J. P. Bose.

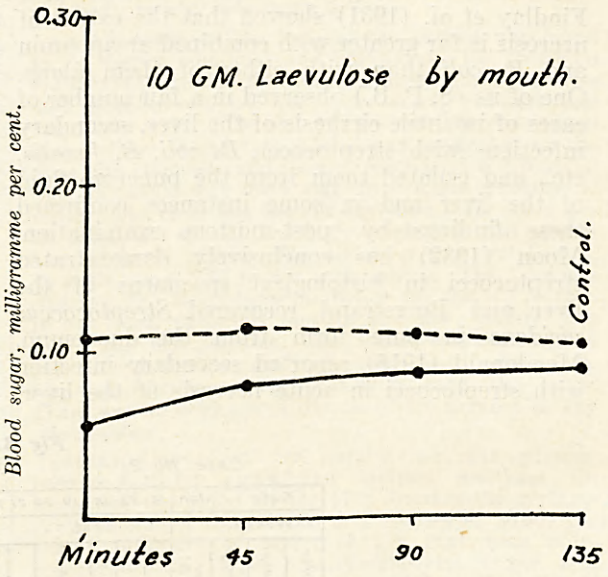
Progress.—The condition of the patient remained steady during the first few days. His appetite improved slightly on being given hypodermic injections of 5 units of insulin coupled with 4 drachms of glucose by mouth, but he did not improve very much. He was then given a fat-free diet consisting of 16 ounces of skimmed milk, 4 ounces of sugar, 3 oranges, one and a half pints of cocoanut water. The total output of urine diminished very much and on 1st and 3rd of February he was given two intramuscular injections of 0.25 and 0.50 cubic centimetre of novasurol, which increased the output from 6 ounces to as much as 28 ounces in a day, as will be seen from figure 2. His condition gradually became worse and on the 4th February he developed symptoms of loss of vision and hearing, and then passed on to a semi-conscious state. He died on the 6th February. No autopsy was permitted.

Comment

The clinical character of this case resembles very much those described by Wallgren (1930),

Figure 2.

Case No. 1.....N.R.B.....Age 7½ years.



Bergstrand (1930), Williams (1923), Roman (1927) and Morgan and Brown (1927), in which the onset was like that of a benign catarrhal jaundice, then there was slight temporary improvement, followed by the sudden appearance of symptoms pointing to an acute insufficiency of the liver. These authors attempted to establish the relationship between epidemic catarrhal jaundice and toxic necrosis. Many chemicals, such as organic arsenicals, trinotoluene, phosphorus and chincophen, which are known to produce acute necrosis, could be excluded in this case. Both epidemic and sporadic forms of Weil's disease being scattered throughout the country, leptospira infection should be considered as a possible ætiological factor. But the clinical history and course of the disease, and also the absence of leptospira in the centrifugalized deposit of the urine of the patient from the 10th day onwards, provide strong presumptive evidence against its being due to leptospira icterohæmorrhagiæ, although the negative findings might be of questionable value in some instances. Congenital syphilis, typhoid and para-typhoid fever, malaria, tuberculosis, scarlet fever, diphtheria and pertussis can easily be excluded on the basis both of clinical and laboratory findings.

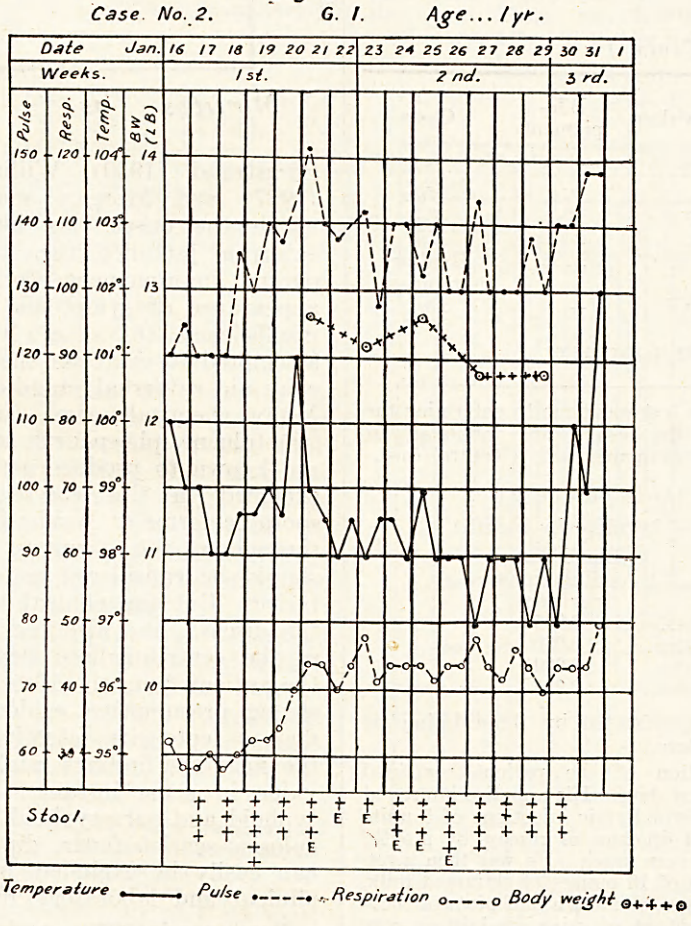
Bergstrand (1930), and Findlay, Dunlop and Brown (1931) have expressed the view that epidemic catarrhal jaundice is probably due to a virus infection, which though pathogenic for man cannot be inoculated into experimental animals. It is possible that acute necrosis of the liver is due to super-added toxæmia in a patient whose liver has been previously damaged by such virus and has not recovered fully after a primary attack. Opie (1910) found acute hepatic necrosis from a combined action of chloroform and *B. coli*. Hurst and Hurst (1928)

produced more marked changes by combining the action of manganese chloride and *B. coli*. Findlay *et al.* (1931) showed that the extent of necrosis is far greater with combined arsaphamin and *B. coli* than with either of them alone. One of us (S. P. B.) observed in a fair number of cases of infantile cirrhosis of the liver, secondary infections with streptococci, *B. coli, B. fæcalis,* etc., and isolated them from the puncture fluid of the liver and in some instances confirmed these findings by post-mortem examination. Moon (1932) has conclusively demonstrated streptococci in histological specimens of the liver and Bergstrand recovered *Streptococcus viridans* in pure form from the duodenum. Macdonald (1918) reported secondary infection with streptococci in acute necrosis of the liver.

was not recent and was probably connected with the throat infection. The rhythm was regular—90 per minute. There was no extra-systole. The deep jaundice, the irregular rise of temperature, and œdema of the whole body could not be attributed to a cardiac lesion.

A marked disturbance of the functions of the liver is demonstrated by the results of the lævulose-tolerance test. It has been universally accepted that in healthy subjects the blood-sugar level shows hardly any variation after the administration of lævulose, but in disorders of the liver alimentary hyperglycæmia is noticed. It will be seen that in this case the blood-sugar level has increased 35 milligrammes per cent over the initial value which is far from normal. Poynton and Wyllie (1926) noted blood-sugar

Fig 3.



In this case streptococcal infection on the top of a catarrhal jaundice is a reasonable possibility, although a definite proof is difficult to get. There was no jugular pulsation in the neck and the boy suffered no distress whilst lying on his back. There was an enlarged heart with a valvular lesion, but there was no tenderness of the tip of the fingers or toes, no sign of embolism, spleen neither enlarged nor tender, no arteritis of peripheral vessels, no finger clubbing, and no petechiæ noticed. The cardiac lesion

value, which is 'slightly below the average, being 0.053 and 0.056 respectively' in their cases. The initial blood-sugar value in our case, namely 0.065, is definitely below the average in this country. Mann (1927) reported in a recent paper that the complete or even incomplete extirpation of the liver in experimental dogs produces loss of sight and hearing, and coma with concomitant development of hypoglycæmia, ending in death. This could be avoided by repeated administration of sugar.

In our case the symptoms of hypoglycæmia and insulin shock were prevented for a time by the repeated administration of glucose, but after a certain length of time the patient developed loss of sight and hearing, and coma supervened ending in death. This might be due to the sudden disability of a large portion of the liver resembling a partial extirpation, as in experimental animals, because the train of symptoms simulated very much those produced in experimental animals.

In our case the almost constant presence of lævulose in the urine except just before death is remarkable. Then sugar that was reported to be present in the urine on the 16th January was perhaps lævulose, as it was not polarimetrically examined at the time. Lævulose was excreted in the urine both on a mixed diet and on administration of lævulose by mouth, and therefore it could not be considered that it was only a diminished lævulose tolerance, as is seen in functional disorders of the liver, but *lævulose diabetes*, because lævulose was present even on starvation or when a mixed diet was given. Warkany (1927) reported such an instance of essential lævulosuria in a child suffering from cirrhosis of the liver of tuberculous origin. Barrenschen (1922) also reported a case and collected eleven others from the literature.

It is thus seen that the carbohydrate metabolism is markedly disturbed in this instance. Associated with lævulosuria there is definite hypoglycæmia, which can be reasonably compared with the glycæmic reaction of the diabetic. On oral administration of lævulose, there is a rise of blood-sugar level, which is not seen in normal subjects. This disturbance is undoubtedly due to changes in the liver and perhaps can be explained only on the following assumptions :—

1. Inability of the liver to convert lævulose into dextrose or glycogen.
2. Inability to store glycogen.

The positive van den Bergh reactions, both 'direct' and 'indirect', which suggest obstruction of the bile passages with fair degree of liver damage, and the clinical signs, namely, jaundice, ascites, enlarged liver, etc., all point to gross disorder of the liver, and lævulosuria is another manifestation of this disorder. That the liver was poor in glycogen store is obvious, because the blood-sugar level on fasting was very low.

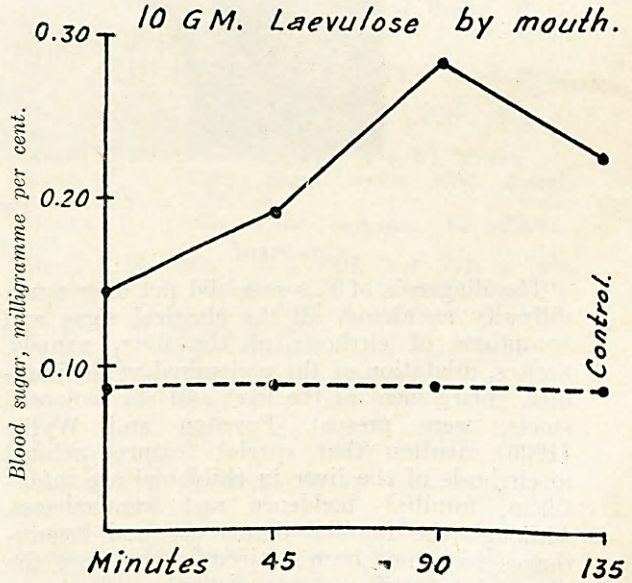
Case 2.—G. I., a boy, aged 12 months, was born of healthy parents at full time. His parents used to live in Madras and came to Calcutta only in November 1932. Both the parents are healthy and the mother has had no miscarriages. There is no history of syphilis, or alcohol. The health of the other children is good. The child had been fed with diluted cow's milk and butter-milk since a few days after birth, and was seldom breast-fed. The only previous illness that he had had was slight fever and cough, and occasional diarrhœa. On the 2nd January, 1933, he had a little cough and, on the 6th, fever. Three days later he is reported to have passed greyish stools and on the 12th February he developed jaundice, which gradually deepened. On the 16th January he was admitted to the hospital with deep jaundice, ascites and in a very low condition. For the temperature, pulse rate, respiration and body weight *vide* figure 3.

On admission to the hospital the patient was found to be deeply jaundiced and emaciated. He presented an anxious, irritable and anæmic appearance. Muscles and subcutaneous fat were very much reduced and turgor was severe. The skin and conjunctivæ were tinged deep yellow. Veins were dilated and prominent on the chest and abdomen, and showed centripetal distribution. The fontanelle was open and two finger-breadths in width. The child had not cut any teeth. He could not sit, stand, nor speak. His body-weight was 12.8 pounds and height 27 inches. The abdomen was protuberant, its girth being 17.75 inches, with ascites. The liver was enlarged two finger-breadths below the costal margin. It was hard, uniformly smooth and not tender. The spleen was just palpable. The thorax was symmetrical and moved equally on both sides with respiration. Signs of bronchitis were present in both the lungs. There was no evidence of disease of the nervous or any other system.

Investigations.—Van den Bergh's test was strongly positive both for 'direct' and 'indirect' reactions. On examining the blood on the 17th January the erythrocytes amounted to 3,150,000 and leucocytes 36,900 per cubic millimetre of which 83 per cent were polymorphonuclears, 14 per cent lymphocytes, 1 per cent mononuclears and 2 per cent eosinophiles. Hæmoglobin was 50 per cent. The Wassermann reaction was negative. Microscopical examination of the stool revealed nothing except the ova of trichuris and culture of the stool showed *B. pseudo-carolinus*. The fat-content of the stool was found to be 2.26 per cent total fat, of which 1.06 per cent was saponified fat, 1.16 per cent non-saponified fat, 0.62 per cent fatty acid and 0.44 per cent neutral fat. Urine examination showed nothing, but lævulose appeared on the administration of 10 grammes of lævulose by the mouth. On culturing a catheter specimen, *B. pseudo-carolinus*, non-lactose

Figure 4

Case No. 2.....*G. I.* .....*Age* 1 *year.*



fermenters and some fine colonies of streptococci were noticed. The results of the lævulose-tolerance test are given in table III.

Röntgenological examination of the skeletal bones showed no rickety or syphilitic change (*vide* skiagram).

TABLE III (*vide* FIGURE 4)
(Ten grammes of lævulose by mouth)

	Blood sugar, milligramme per cent.
Fasting ..	0.149
After 45 minutes	0.190
After 90 minutes	0.280
After 135 minutes	0.220

Progress.—His condition improved transiently on administration of three drachms of glucose by the mouth, and giving 3 to 7 units of insulin hypodermically daily. About a week after admission he developed constipation and troublesome tympanitis, and died on the 1st February, *i.e.*, within 4 weeks of the onset of the first symptom. The course of the disease is represented graphically in figure 3 and a picture of the patient is seen in figure 5. No autopsy was permitted.

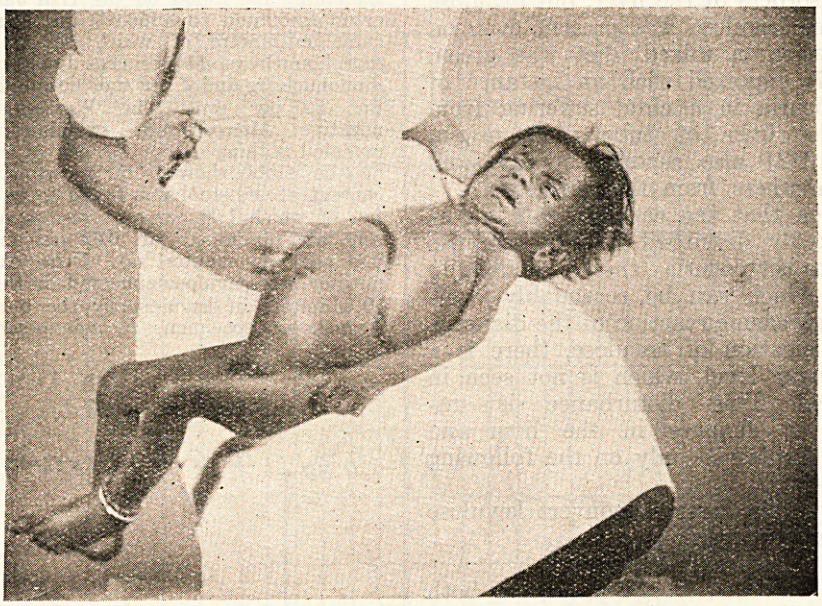


Figure 5

Comment

The diagnosis of this case did not offer much difficulty as almost all the classical signs and symptoms of cirrhosis of the liver, namely, ascites, dilatation of the abdominal veins, jaundice, enlargement of the liver and clay-coloured stools, were present. Poynton and Wyllie (1926) mention that special features related to cirrhosis of the liver in childhood are infantilism, familial incidence and hæmorrhages. Although the familial occurrence and hæmorrhages have not been noticed in this case the signs of infantilism were distinct and unmistakable. Small stature, delayed dentition, open fontanelle, and inability to sit, stand or speak, might be considered as of rickety origin but röntgenological examination of the skeletal bones revealed none of the characteristic changes of rickets. In figure 6, if the skiagram of the wrist of this case is compared with that of a case of rickets, the difference will be obvious to all. In contra-distinction to the view of Naegeli and his collaborators (1931) who observed leucopenia and characteristic granules in the mononuclears, and also to the Mexican series of cases where leucopenia was observed, we have found leucocytosis in this case as well as in many other similar cases. The course of the disease in this instance was unusually rapid and this is perhaps due to the fact that the patient was debilitated and had been artificially fed from the very beginning. On the basis of clinical and laboratory findings, it is impossible to distinguish this case imported from South India from those seen locally. Strongly positive 'direct' and 'indirect' van den Bergh reactions suggest that there was both obstruction of the bile passages and destruction of the liver cells. There was also definite sign of hepatic inefficiency, as shown by the lævulose-tolerance test. As will be seen from the figure there was very marked deviation of the blood-sugar level, after the administration of 10 grammes lævulose. The rise amounted to as much as 131 milligrammes per cent over the initial blood-sugar level as compared to the rise in normal cases. Hyperglycæmia is also a notable feature which is seen in this case as well as in others of a similar nature.

The search for an explanation of the cirrhosis has given rise to much speculation. Known causes of this disease, syphilis, the alcohol habit, tuberculosis, malaria, kala-azar, congenital malformations of the hepatic system, and acute infections, the rôle of which has been particularly stressed by Osler (1903), could be

definitely excluded. A parasitic type of cirrhosis is known, in which various forms of schistosome are concerned. No parasites or ova were discovered in this case. In many such cases where the origin remains obscure, a

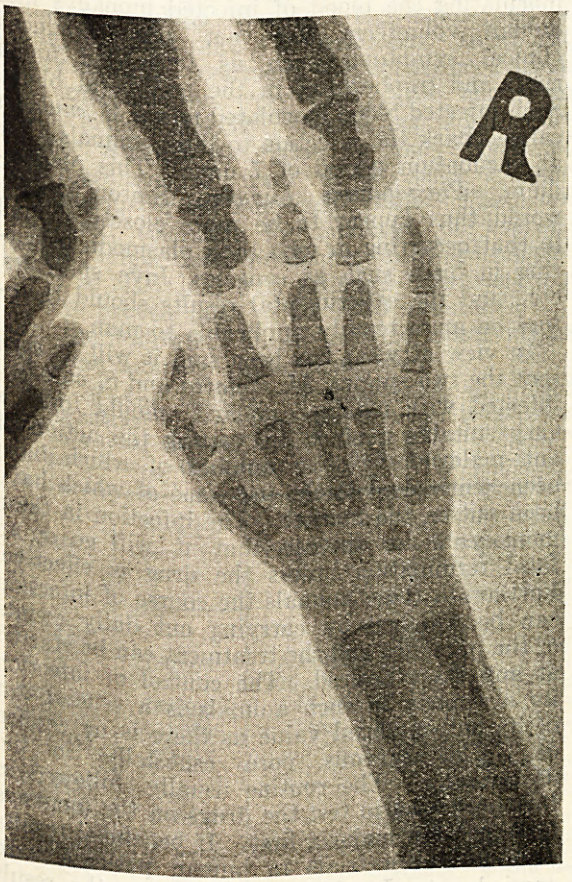


Figure 6
Skiagram

toxin of chemical, metabolic or bacterial origin is perhaps at work. Rolleston (1912) suggested 'a local result of a chronic general toxæmia, with the conveyance of the toxin to the smaller bile ducts by means of the hepatic artery'. Theories differ as to the character of the poison. It is likely that a toxic substance is produced under certain circumstances, which might act as a provocative agent. deRaadt (1930) thought that conditions, which greatly and for a long period increase the conversion of intestinal ammonia into urea by the liver, result in cirrhosis. A diet containing a small amount of nitrogen, such as strictly vegetable diet, would then act in this way. Many difficulties beset the determination of the exact ætiology of the cirrhosis of the liver. At the present stage of our knowledge it is impossible to state anything definite about the nature, origin and pathogenesis of these cases. It must be left to the future for discussion and determination.

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STUDIES ON THE ACTION OF ATEBRIN IN PLASMODIUM INFECTION OF MONKEYS

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NAPIER and Campbell (1932) found that the blood of a monkey imported from the Malay States—*Macaca irus*—contained a protozoal parasite in the red blood corpuscles resembling the malarial parasite. This monkey did not seem to be in any way affected by this infection, which was never intense and which was not always patent, even when a careful and prolonged examination of the blood was made. A few cubic centimetres of the blood of this monkey, in citrated saline injected intravenously into a *Macaca mulatta*, the common monkey occurring in Bengal and many parts of India, transferred the infection to the latter animal.

(*Continued from previous column*)

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