therapy in a series of 25 infants has been excellent. Thus the following conclusions are tenable:

1. The use of sodium bicarbonate in severe cases of acidosis is safe and satisfactory.

2. The withdrawal of large samples of blood from infants for extensive laboratory tests is unnecessary and may be harmful.

3. The CO_2 combining power affords a guide to therapy.

4. The maintenance of fluid intake, oral and/or parenteral is of prime importance in this disorder.

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THE CHOLAGOGIC AND CHOLERETIC EFFECT OF SODIUM NICOTINATE

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INTRODUCTION

MARKED elevation of the indirect reacting bilirubin of serum follows the intravenous injection of 30 mgs. of sodium nicotinate in normal subjects (7,6,10). It reaches a maximum value 60-90 minutes after the injection and slowly returns to the original level in 6 to 8 hours. The mechanism of the hyperbilirubinemic effect of sodium nicotinate and its application to the study of the metabolism of biliary pigments and to the diagnosis of liver disorders have been described in a previous communication (10). In the course of that study, evidence was obtained that the drug possessed marked cholagogic effect. This observation is confirmed and extended by further findings presented in this paper.

EXPERIMENTS AND RESULTS

Eighteen healthy adults, who had been fasting for the past twelve hours, volunteered for the following experiment. A Rehfuss tube was passed into the duodenum under fluoroscopic control and its extremity connected with a volumetric drainage bottle. The results were similar in all volunteers. Few cc. of yellow colored bile were obtained in some subjects, but the scanty flow soon stopped altogether. Half an hour later, when the subject had become well used to the presence of the tube, thirty mgs. of sodium nicotinate in 10 cc. of saline solution were injected intravenously at the speed on about 30 seconds per cc. The injection was followed by a generalized flushing, particularly evident over the face and extremities, and, at the same time, the subject experienced a marked feeling of warmth. These effects of the drug usually regressed in two to five minutes time.

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Ten minutes after completing the injection of sodium nicotinate, a copious rhythmical flow of bile began, in the quantity of 2 to 4 cc. per minute. About 10 to 15 cc. of light colored fluid (bile A) were collected in the first 2 to 6 minutes. From 175 to 200 cc of dark brown colored bile (bile B) followed in the next 20-25 minutes. Finally, 40-50 more cc. of golden yellow colored bile (bile C) were obtained slowly during another half an hour, at the end of which the flow stopped altogether. The collected samples revealed a concentration of bilirubin and biliary salts in the range of normal values. The total volume of bile collected was of 220-270 cc., a figure much higher than the 50-110 cc. usually obtainable with the stimulation by means of hypertonic magnesium sulphate solutions.

It appeared then that the solution nicotinate technic produced a more pronounced cholagogic effect than the Meltzer-Lyon's procedure. To further demonstrate this a Rehfuss tube was again passed in the duodenum of three more healthy subjects. Bile flow was first stimulated by means of duodenal instillation of 100 cc. of a 25% solution of $MgSO_4$. When bile could no longer be obtained, sodium nicotinate was injected intravenously. Following this, between 105 and 175 cc. more of mixed bile were collected, in one hour time. The intravenous injection of 100 mgs. of nicotinamide, which is not followed by elevation of the serum bilirubin level (10), also had a similar but much less pronounced cholagogic effect. Nicotinic acid and nicotinamide were also moderately active when given orally.

As the samples of bile collected during the experimental period were of much larger volume but did not present higher concentration of bilirubin or biliary salts, the effect of sodium nicotinate in normal subjects appeared to be mainly cholagogic. A clinical case who came to our observation, however, offered the opportunity of showing that sodium nicotinate and nicotinamide may also possess choleretic action when retention of biliary pigments is present. The patient, deeply jaundiced with evidence of serious liver damage, had a

TABLE I: The effect of the intravenous injection of sodium nicotinate on the serum bilirubin and bile bilirubin and biliary salts level in a patient suffering from chronic hepatocholangitis with surgical biliary fistula.

Time after injection (hours)	0	1	2	3	4	5	6	7	8	24	48
Serum, total bilirubin mgs%	5.09	7.49	8.09	8.31	8.64	8.29	7.94	7.60	7.34	7.50	7.02
Serum, direct reacting bilirubin mgs%	1.18	1.54	1.87	2.18	2.36	2.29	2.24	2.11	2.00	1.54	1.27
Serum, total bilirubin mgs%	0.52*	1.94	4.82	11.73	18.61	16.43	15.27	13.28	10.47	7.32	5.28
Bile, biliary salts 0/00	2	4	8	16	32	16	16	16	8	4	2

*The strikingly low initial value of bile bilirubin concentration was likely due to the impaired liver function of the patient.

TABLE II: The effect of prolonged treatment with nicotinamide (300 mgs. a day, intramuscularly) on the serum level of bilirubin and biliary salts, bilirubin concentration in bile and urine, and fecal and urinary urobilinogen in a patient with severe hepatic dysfunction presenting a surgical biliary fistula.

Day of treatment	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Serum																
Total bilirubin (mgs.%)	5.14	4.88	4.64	4.59	3.57	2.49	2.45	1.98	2.51	2.42	3.73	3.89	4.10	4.45	4.90	4.85
Direct reacting bilirubin (mgs.%)	1.91	1.67	1.63	1.75	1.81	1.75	1.22	0.93	1.21	1.37	1.54	1.62	1.73	1.89	1.76	1.79
Bile salts 0/00	4	4	4	4	4	0	0	2	0	4	8	4	4	4	4	4
Bile																
Total bilirubin (mgs.%)	2.4	2.8	3.5	4.2	5.0	5.6	10.2	13.5	7.8	11.5	6.2	4.1	3.8	2.7	3.0	3.4
Bile salts 0/00	32	64	32	128	128	64	256	256	64	32	32	16	8	8	16	8
Urine																
Bilirubin (mgs.%)	2.5	1.8	0.7	0.4	0.4	0.3	0.1	0.8	0.9	0.2	0.6	1.7	1.8	2.6	2.4	2.1
Urobilinogen (mgs.%)	12.6	11.7	12.0	13.0	13.2	14.9	16.0	17.5	21.3	19.2		14.1	12.5	10.7	9.4	10.3
Feces																
Urobilinogen (mgs.%)	10.2	12.0	14.1	19.7	24.8	32.6	51.4	47.5	52.0	55.4	34.9	32.15	28.9	27.2	19.4	23.5

biliary fistula established for the treatment of a chronic hepatocholangitis. The case made possible not only the study of the possible choleretic effect of sodium nicotinate and nicotinamide, but also the correlation of the changes in serum bilirubin level with those of the bile concentration of bilirubin, following the administration of the drugs. The serum total and direct reacting bilirubin and the bile bilirubin level were followed at one-hour intervals for eight hours after the intravenous injection of 30 mgs. of sodium nicotinate, and then again after 24 and 48 hours. Serum bilirubin and bilirubin concentration in the fistula bile were determined with the methods of Jendrassik and Grof (5,4). The analytical results are presented in Table I. They indicate that the injection of sodium nicotinate was followed by stimulation of the biliary excretion of bilirubin, still moderately evident after 48 hours. Also the concentration of biliary salts in the bile (determined with the method of Cottet, 2) was moderately increased from the fourth to the eighth hour of the experiment.

After a 4 week rest, the same patient was given 300 mgs. of nicotinamide intramuscularly for a period of 15 days. Concentration of bilirubin in the bile, fecal and urinary urobilinogen, urinary bilirubin and serum bilirubin were followed at the same time. Urinary bilirubin was determined with the quantitative method of Jendrassik and Grof (4) and fecal and urinary urobilinigen with the method of Watson (12). The results show that, while the bilirubin level in serum decreased slightly, the excretion of pigments through the bile fistula and in the feces increased rapidly during the early phase of the treatment. During the second week of therapy, however, all values slowly returned to the original ones (Table 2).

DISCUSSION

The results presented in this paper show that sodium nicotinate and nicotinamide, given either intravenously or orally, possess cholagogic action. In case of retention of biliary pigments a choleretic effect can also be demonstrated.

The significance of these results in the study of the metabolism of the biliary pigments has been commented in a previous communication (10). It may be added here that the present findings seem to support the observations of Villa (11), who claimed that treatment with nicotinic acid and nicotinamide produced a striking remission of jaundice in different types of hepatic dysfunction with "reversible" liver damage. No resolutive therapeutic effect was observed in cases with severe impairment of the function of the liver. Villa's findings have been confirmed by other authors (1,9,3,8). In the case under observation, a single intravenous injection of sodium nicotinate and continued treatment with nicotinamide temporarily increased the excretion of bile pigments, at the same time lowering the bilirubin level of serum. They failed, however, to influence favorably the further course of the condition, as could have been expected due to the serious impairment of liver function.

SUMMARY

Sodium nicotinate and nicotinamide, given both orally and parenterally, possess an evident cholagogic effect in healthy subjects. A temporary cholagogic and choleretic effect with decrease of the serum bilirubin level was observed in a patient with severe jaundice presenting a biliary fistula established surgically for the treatment of chronic hepatocholangitis.

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