ESTIMATION OF HEPATIC EFFICIENCY.

REPORT ON

THE EXPERIMENTAL INVESTIGATION OF A NEW TEST BASED
ON THE USE OF SODIUM SALICYLATE.

BY

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ROCH AND SCHIFF (Geneva) in 1921 suggested a new test of hepatic function based on the use of sodium salicylate, and H. Thiers in 1927¹ described a modification of their method. A brief account of this test appeared in the *British Medical Journal*,² and the present paper records some experiences with the test, the work having been undertaken on the suggestion of Dr. J. R. Marrack, chemical pathologist of the Hale Clinical Laboratory, as such a simple test—if universally accepted as reliable—would be of great value in diagnosis.

Nature of the Test.

H. Thiers "states that a normal adult can assimilate a dose of 0.04 gram (=3/5 grain) of sodium salicylate, no trace of salicylic acid being found subsequently in the urine. If the liver is damaged salicylic acid appears in the urine passed during the second to the seventh hour after the ingestion of the sodium salicylate." In the preliminary experiments described below the method used by Thiers—namely, extraction of the urine in a flask, and then testing the extract for salicylic acid with dilute ferric chloride—was closely followed, and positive results were obtained with a normal adult. During the later experiments the method of extraction was improved (as shown by the tabulated results) by using a glass-stoppered separating funnel, and it was proved that as much salicylic acid was excreted by normal adults as by those with diseased livers.

Preliminary Experiments.

After preparing the three solutions required for the test, a patient with a diseased liver (Case A, Table II) was selected for the first trial, and as the results obtained seemed to confirm the claim made for it, the next test was done with a healthy adult (Case 1, Table I). The same

TABLE I.—Normal Cases.

No.	Age.	Date of Test.	Urine specimens.	Test for salicylic acid.	Standard to match the colour.	Remarks.
					c.cm. or mg.	
1	55	1928. Jan. 23	1st 54 2nd 206	Neg Pos.	— 0.5	Special care given to extractions in 1a, the second trial on same adult.
1a	"	Jan. 26	1st 43 2nd 136	P.s. Pos.	0.25 0.75	
2	16	Jan. 27	1st 40 2nd 135	Pos. Pos.	0.25 0.75	
3	32	Feb. 11	1st 8 2nd 176	Pos. Pos.	0.18 0.1	Extraction not complete. See a and Note 1. 20 times more than No. 3.
3a	"	"	* same specimen	P.s.	2.0	
4	28	Feb. 22	1st 34 2nd 181	Pos. Pos.	0.37 1.5	Improved yield explained in Note 4.

results were obtained as with Case A, and thus were contrary to the statement on which the test is said to be based. It was therefore considered advisable to repeat the test on the same healthy adult. Salicylic acid was again found present in the second specimen of urine and, this time, in the first specimen also (Case 1a, Table I). The result with the second specimen in Case 1 was thus confirmed, and the negative result with the first specimen could be explained as possibly due to inexperience with the method, and to the apparatus used for extraction being to some extent unsuitable.

These results raised a very grave doubt as to the reliability of the statement that normal adults could assimilate sodium salicylate and no trace of salicylic acid would

appear in the urine, especially as a reference to the pharmacology of salicylic acid showed that "it appears in the urine very soon after its ingestion [ten to thirty minutes], but the elimination goes on slowly."³

Later Work.

These trials were done to remove this doubt, and the test was carried out with three other healthy adults and three more patients with diseased livers. Details with results have been tabulated below, followed by notes on the laboratory work. The cases referred to in Table I were four healthy adults who had never had any illness suggestive of liver disease, and they were therefore chosen as normal adults, all being males, their ages ranging from 16 to 55 years. Table II refers to four cases treated in

TABLE II.—Cases with Hepatic Disease Present.

No.	Sex.	Age.	Date of Test.	Diagnosis.	Urine specimens.	Test for salicylic acid.	Standard to match the colour.	Remarks.
							c.cm.	
A	M.	58	1928. Jan. 18	Cirrhosis of liver and tertiary syphilis	1st 22 2nd 71	Neg. Pos.	— 0.5	No bile in urine.
B	F.	66	Feb. 14	Carcinoma of pancreas	1st 36 2nd 92	Pos. Pos.	0.1 0.5	Bile present. See Note 5.
C	M.	25	Mar. 1	Catarrhal jaundice	1st 52 2nd 26	Pos. Pos.	0.2 0.4	Bile present. See Note 6.
D	M.	70	Mar. 8	Cirrhosis of liver and ascites	1st 45 2nd 130	Pos. Pos.	0.25 2.0	Bile present. See Note 7.

the hospital, having diseased livers as shown in the "Diagnosis" column of the table. The first specimen of urine was collected one hour after the dose of salicylate was given, and the second specimen four hours later.

Notes on the Laboratory Work.

1. The chief aim was to detect any trace of salicylic acid present in the urine, and not merely follow a procedure which might give a negative result although a trace was in fact present. A comparison between the results of Cases 3 and 3a illustrates how a negative result may occur as a consequence of some incomplete extraction, as, when the second specimen of urine in Case 3 was re-extracted, twenty times more salicylic acid was proved present than was found by the first extraction. The only negative results obtained occurred with the two cases first tried, and one of these at least was proved as probably incorrect by the second trial giving positive results (Case 1a), as already explained.

2. The first specimen of urine in every case ranged from 22 c.cm. to 78 c.cm., and so the entire specimen in each case was used for the extractions.

3. The second specimens ranged from 71 c.cm. to 216 c.cm., and as these were not too inconvenient to extract the entire specimen was again used, except in Case C, where it was halved for the purpose explained below.

4. In the earlier extractions the ether was shaken up with the urine in the 8-oz. wide-mouthed stoppered bottle used for collection, and the separation of the emulsion was performed by transferring successive portions of the mixture to a glass-stoppered burette; but the bottle stoppers did not fit very well, the process was somewhat messy, and the separation was tedious. So after the experience with Case 3—where the salicylic acid (proved present in both specimens) was so much less than in the previous cases—a conical glass-stoppered separating funnel was obtained and used for the re-extraction in Case 3a, and for all the later extractions.

5. In cases B, C, and D bile pigment was present in the urine, and was extracted by the ether along with the salicylic acid. In case B the ethereal layer was not completely evaporated before adding to the ferric chloride, and on mixing the liquids the aqueous layer showed a distinct purple tinge while most of the bile pigment remained in the ethereal layer. In Cases C, 3a, 4, and D the ethereal extract was evaporated to a small bulk, and the bile pigment combined with the violet colour due to the salicylic acid, the resultant colour being a brown.

6. To test whether extraction by rotating vigorously in a beaker with ether could be complete, the urine of Case C was thus treated, and then, after separation of the ether (by use of the separating funnel), the urine was re-extracted by shaking with a fresh lot of ether in the funnel. The extraction of the first

specimen of urine in the beaker proved to be complete, the re-extraction giving no salicylic acid. The second urine specimen was halved, and one half (108 c.cm.) was extracted twice as above, the other half being used as a check by extracting once only by vigorously shaking in the separating funnel. In this instance the beaker method gave no colour indicative of the presence of salicylic acid, whereas the second extraction gave a distinct trace (a, Case C). The check half of the urine gave a more distinct trace (b, Case C). These results, therefore, indicate that the open beaker method is the less reliable of the two.

7. In Case D the extract gave a more decided colour reaction than any of the others with bile pigment present, and it was interesting to find that the effect of the yellow bile pigment could be exactly imitated in the tubes with the violet standards by mixing with a few drops of the yellow solution of potassium chromate.

Summary.

The foregoing is a report on work done in trying a new test for hepatic efficiency, based on the use of sodium salicylate, as described in the *British Medical Journal*.

The preliminary work consisted in trying the test on a selected patient, and then comparing the result with that obtained with a normal adult. As the results were the same in both cases further investigation was considered necessary, especially as a doubt arose about the reliability of the statement that "normal adults could assimilate a 3/5-grain dose of sodium salicylate, no trace appearing later in the urine."

The later experiments were carried out with three more normal adults and other three cases with damaged livers, all the results being shown in tabular form, followed by a discussion of the tables in the form of notes, explaining how and why the method of extracting the salicylic acid was slightly varied, and pointing out that bile pigment modified the violet colour of the salicylic acid test to a brown, which could be matched in the standard colour tubes by the addition of potassium chromate.

Conclusion.

1. The tables show that salicylic acid appeared in the urine of each of the four healthy adults after the ingestion of a small dose of sodium salicylate, as well as in that of four other cases with damaged livers.

2. Its appearance in the urine of the first hour confirms the statement quoted in reference to the pharmacology of salicylic acid, and does not support Thiers's statement.

3. The tables show that no distinction can be made by means of this test between the four normal adults and the four cases with damaged livers.

From the above results it is concluded that this test, as described in the publication referred to, can be of no use in classifying cases with damaged livers, or in measuring the extent of the damage.

REFERENCES.

- ¹ H. Thiers: *Lyon Médical*, May, 1927.
- ² *British Medical Journal*, February 11th, 1928, p. 231.
- ³ W. Hale-White: *Materia Medica*, edition 1920, p. 490.

BRONZED DIABETES IN A WOMAN.

BY

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I VENTURE to publish these notes on account of the rarity of bronzed diabetes in women, and because this case seems to have run an unusual course. The patient was seen at the maximum of bronzing by three other medical practitioners, who could suggest no other diagnosis; one who had previously seen a case (in a man) thought the bronzing typical.

The clinical details available are as follows.

Family History.—The grandparents all lived to advanced ages; the father died of uraemic coma at the age of 74, and the mother died of the same complaint at the age of 70. There were eight children, of whom the patient was the eldest. She was perhaps mentally the brightest of a not very bright family. The next in age, a male, died of "cancer of the liver," aged 30; he was

congenitally blind. The third, also a male, died of epilepsy at the age of 30. The fourth, a female, is living, mentally deficient and congenitally blind. The fifth, a male, is living and is normal. The sixth, also a male, is alive and normal, but mentally he is rather dull. The seventh, a female, is living; she is mentally deficient and congenitally blind. The eighth, a male, is living, and is normal. None of them show any signs of syphilis, and two who have been examined (the fourth and seventh) give negative Wassermann reactions.

Personal History.—This gives nothing of importance. The patient was a very stout woman, but exceedingly active. Her chief ailments have been flatulent dyspepsia and some cardiac insufficiency. She had had no medical attention for five years.

Clinical Details.

On November 11th, 1927, the patient was deeply jaundiced, with anorexia, but no sickness and no diarrhoea. She had become much thinner since the previous May, the loss of flesh coinciding with extreme thirst.

The liver was easily felt two inches below the costal margin, and the spleen about the same. Both were smooth, regular, and soft. The liver was slightly tender. Nothing else abnormal was found. The heart sounds were normal, but muffled, and the lungs were normal. The urine contained much bile pigment, but no albumin; sugar was present in large quantity. At this time there were on the forehead and forearms what appeared to be a few freckles.

The jaundice cleared up under treatment in ten days. The patient was put on a strict non-carbohydrate diet. The urine sugar rapidly diminished, and early in December, 1927, the urine contained only a trace. A blood examination gave 65 per cent. haemoglobin and a normal white cell count.

On December 12th there was a sudden rise in the urinary sugar, and acetone was present. The patient became partially comatose, and had apparently marked pain over the spleen. She remained in this condition, sometimes rousing and sometimes completely unconscious, for a month, the heart gradually getting weaker and dropsy developing; but the sugar had completely disappeared from the urine on December 20th, and was never found again until just before her death.

During this period pigmentation became very apparent, involving the face, neck, forearms, and both groins, with scattered patches on the abdomen, back, and both thighs. The pigmented spots were of all sizes up to a threepenny piece, many coalescing. Her face presented a curious appearance—a mottling of yellow shading up to deep bronze on a skin almost mauve in colour. There was incontinence of urine and faeces, and bedsores developed. By this time the liver and spleen both reached halfway from the costal margins to the umbilicus.

From the middle of January, 1928, she began to improve. The heart regained its tone; her colour became normal except for the bronzing; the bedsores healed; the appetite returned. In July she was downstairs, walking in the garden, and doing needlework. The bronzing was beginning to fade. From now on she was seen and the urine examined at fourteen-day intervals.

On November 9th, 1928, five days after the last visit, she suddenly complained of feeling very ill—"just as I did before." The urine was found to contain a fair amount of sugar. She became comatose on November 10th, and died the following day.

Post-mortem Findings.

Only a partial necropsy was allowed. There appeared to be no pigmentation of the peritoneum. There was little free fluid, and this was clear. No abnormal mass or tumour could be found. The liver was about two and a half times its normal size, and appeared uniformly enlarged. It was smooth, rather soft, and pale; it was densely adherent posteriorly. The gall-bladder and duct were normal. The spleen measured roughly 9 in. by 5 in.; it was smooth, extremely friable, and adherent to the periphery and omentum. Both kidneys were enlarged and soft. The heart was enlarged and infiltrated with fat; the valves showed no disease. There was some staining of the pericardium, but not enough to be definitely called pigmentation.

Pathologist's Report

Portion of Spleen.—There is general slight chronic perisplenitis. The pulp is soft. A few dark points are seen. The Malpighian bodies are not easily distinguished and not much fibrosis can be discerned.

Liver.—There is generalized monolobular cirrhosis with much yellow pigmentation along the prolongation of Glisson's capsule. The liver substance is fatty.

Pancreas.—The glandular tissue is largely replaced by fat. No pigmentation can be distinguished.

Suprarenals.—Soft, but normal.

Kidney.—It is slightly enlarged and soft. The cortex is not clearly diminished; it is pigmented and yellow. The capsule strips leaving a number of arterio-sclerotic depressed patches of various sizes. The pyramids show whitish streaks towards the papillae.

Microscopic Examination.

Spleen.—The pulp is of a loose fibrotic texture; the Malpighian bodies are atrophied. The trabeculae appear normal, but bacillary emboli are present in some of the vessels. There are no gross lesions anywhere to be seen. Many of the cells contain pigment granules, and free granules are also present, but it is not possible to say how much of this is due to post-mortem change. The iron reaction of the spleen is feeble and consists of occasional blue granules.