retain its regular amount of hemoglobin and its usual number of red blood-cells is based on estimations of urobilin in the urine and stools. The increase in urobilin is thus considered by him a measure of blood destruction, and taken with the percentage of hemoglobin and red blood-counts, a measure as well of the work done by the hemopoietic organs. Many investigators have reported the finding of urobilin in pneumonia. Möller²⁷ with Billi's method²⁸ found urobilin in the serum of two pneumonia patients. Out of sixty patients, Conner and Roper²⁹ found urobilin in the blood, but none in the affected lung tissue, of ten who were in the last stages; nor were they able to show that it came from bacterial action on hemoglobin.

Prognostic Value in Cardiac Lesions.—Case 4 (that of H. B.) is typical and shows clearly the value of urobilinuria in estimating the amount of stasis in the liver in failure of cardiac compensation. With improvement and consequent decrease in the size and tenderness of the liver there was a rapid decrease in the amount of urobilin in the urine without a corresponding fall in the fecal excretion. A recurring period of decompensation was inaugurated by a premonitory increase in the urobilinuria. In general, liver stasis is accompanied by a marked urobilinuria. Its estimation serves as a guide by which one may follow the beneficial results of administered digitalis. Cases with cyanosis and with hypercythemia, but without marked liver engorgement, present no increase in the urobilin in urine. Fischler considers a urobilinuria which persists after compensation has been regained as evidence of a pathologic condition of the liver.

Migraine.—The increased urobilinuria found in Case 5 (that of M. B.) at the time of migraine attacks is suggestive, especially when considered in the light of the very effective treatment of Rachford,³⁴ which aims to prevent the periodic headaches by the persistent use of drugs thought to stimulate elimination from the liver. Too few cases have been observed to more than indicate the desirability of further investigation.

CONCLUSIONS

1. Simultaneous estimation of urobilin and urobilinogen in the stools and urine, after certain allowances are made for the state of the liver and intestinal peristalsis, permits valuable approximations to be drawn as to the amount of hemoglobin broken down within the body.

2. Urobilinuria may be used as an early indicator of the failure of the liver to functionate normally in alcoholic individuals with enlarged and tender livers.

3. While in a jaundiced individual the persistent failure to obtain positive tests for urobilinogen in the urine by the present methods points usually to absolute closure of the duct, there seems to be evidence against the correctness of the commonly accepted view that the only origin of urobilin is from the reduction of bilirubin in the intestine, this evidence consisting in the presence of not inconsiderable amounts of urobilin in the stools of patients in whom very little bilirubin (closure of the common bile-duct) or no bilirubin (closure of the common duct and a biliary fistula) reaches the intestine.

4. The urobilinuria and urobilinemia of pneumonia deserve more study as the occurrence of urobilin as such in the blood is apparently, by the present methods, found during life only in this disease, and it may indi-

cate that peculiar relations exist between urobilin and the factors accompanying cyanosis.

5. The discovery of a persistent urobilinuria should incite a careful study for all possible factors leading either to blood destruction or to parenchymatous or obstructive hepatic disorders.

MY EXPERIENCE WITH DIABETIC PATIENTS LIVING TEN OR MORE YEARS *

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It was a gratifying surprise to me to discover that sixty-seven of my patients with diabetes had lived, or were still alive; at least ten years after the onset of the disease. The discouragements which beset the life of the diabetic patient and his physician are so great that the brighter aspects of the disease should constantly be brought into the foreground. Furthermore, lessons are always to be learned from a study of the extreme aspects of any disease. Therefore it appears desirable to me to report on my cases of diabetes of long, rather than of short, duration.

Eleven per cent. of all the cases of diabetes which I have seen in private practice have had a duration of ten or more years; but the figures are far more favorable than this, because, out of these 505 cases, I have, at the present writing, been able to trace the outcome in only 394 cases. The proportion of cases of ten years' duration of which I know the present state, therefore, rises to 17 per cent., and yet this figure is too low, because a large number of the living patients have acquired their diabetes less than ten years ago. If I subtract this number, which is 141, from the number of diabetics of which I have discovered the outcome there remain 253 cases, representing the number which are actually eligible for statistics. Of this number, sixty-seven patients having lived ten or more years with the disease, we can say that 26 per cent., i. e., one in every four, may look forward to a duration of life of at least ten years from the onset of their malady.

The usual preponderance of diabetes in the male sex prevails. Of my sixty-seven patients forty were males.

The onset of the disease was at 16 years of age in one patient, and 69 in another. Contrary to expectation, nearly one-third of the patients acquired the disease under 40, and only five after the age of 60. The remainder were equally divided between the fifth and sixth decades.

TABLE 1.—TABULATION OF ONSET OF DIABETES IN SIXTY-SEVEN PATIENTS ACCORDING TO AGE

Age at Onset Years	Number of Cases
11-20	3
21-30	5
31-40	12
41-50	21
51-60	21
61-70	5

It is thus apparent at the outset that these cases of long duration were not simply due to the mild diabetes of elderly people.

The duration of life in one patient was thirty-five years, and in five others twenty years or more. Thirty-nine of my patients are still living, and of this number fourteen have had the disease at least fifteen years.

27. Möller: Berl. klin. Wchnschr., 1900, xlv1, 2303.

28. Billi: Foll. Haemat., 1906, III, 189; 1907, IV, 533.

29. Conner and Roper: Arch. Int. Med., 1908, II, 532.

34. Rachford: Med. News, 1903, lxxxIII, 630.

* Read in the Section on Practice of Medicine of the American Medical Association, at the Sixty-Third Annual Session, held at Atlantic City, June, 1912.

Practically all of the patients were of American extraction. Four were Hebrews and one was an Irishman.

Syphilis was known to me to exist in only five of the cases. I am sure, however, that it was present in a much larger proportion. All will agree that statistics on syphilis in diabetes are to-day of no value. Within a few years syphilis may reach a position of great importance in diabetes. I would call attention to the case reported by Umber, in which the diabetes was most favorably influenced by salvarsan. All should scan each new case of diabetes and its possible connection with syphilis with great care. No case of diabetes has come under my personal observation which has been favorably influenced by antisyphilitic treatment. I mean, however, to be most open-minded on the subject.

The severity of the disease is attested by the presence of acidosis in thirty-five of the cases, and also by the fact that of the twenty-eight patients who died, twelve died in coma. On the other hand, it is true that, contrary to the rule that the severity of the disease increases with its duration, a certain number of the cases became less severe as time advanced. Thus, fifteen were free from sugar before death occurred. Some of these cases too were of considerable severity and, as a rule, they were of long duration. So far as I am aware acidosis was absent in all but one of these cases. Of course, sugar may have persisted in an increased quantity in the blood, and yet been absent from the urine. But because of the absence of acidosis I am inclined to believe that the sugar in the blood did not reach, toward the end of the disease, a height above the normal level.

The cause of death was, as above stated, diabetic coma in twelve cases. In only eight cases was death directly attributable to arteriosclerotic conditions. Pulmonary tuberculosis was the cause in one patient. Contrast this with the probable statistics of twenty years ago. It is interesting that the patient who finally died with pulmonary tuberculosis represented one of the severest cases in the group, and yet toward the end of life the diabetes decreased in severity, yielding preference to the tuberculosis. I have several other examples of this sort. Pneumonia occurred three times, cancer once, and pernicious anemia once, as causes of death. The cause of death was not ascertained in two cases.

The classification of the cases is extremely difficult. Eight cases were pure diabetes and can be so grouped in the Naunyn sense. Fifty-two can be similarly grouped if we would include in this number thirty-two patients who were also obese and nine at the age of 59 or over. Five cases were of extremely mild type and might be grouped under glycosuria, though, better, I think as mild diabetes. One case was of a functional neurotic character and the remainder could not be classified.

How did it happen that these sixty-seven diabetics lived so long?

1. Obesity surpasses all other factors as an explanation. Twenty-six weighed over 200 pounds at some time or other of their lives, and thirty-five weighed at least 180 pounds. If we study the duration of life of the distinctively fat patients we find it to be fourteen years for the nine who died, and thirteen years for the seventeen who are still alive. In contrast to this, the duration of life for the fifteen patients of moderate weight now dead was thirteen years, and for the fourteen of moderate weight yet alive also thirteen years. The type of diabetes among the fat patients was mild. Presumably these same individuals would not have developed diabetes if they had maintained normal weight. Modern medicine demands the prevention

of obesity as prophylaxis against diabetes. I realize that another interpretation could be put on these figures, namely, that if there is a disposition to acquire diabetes, one had best be fat, but I believe most will agree that the figures can be better utilized as reason for prophylactic treatment against the onset of the disease rather than as prophylactic treatment against death after the disease has begun.

The loss of weight ranged from 109 pounds in one individual to a gain in weight of 1 pound in another. The usual loss of weight was 40 to 50 pounds.

TABLE 2.—TABULATION OF LOSS OF WEIGHT IN SIXTY-SEVEN DIABETICS

Loss of Weight Pounds	Number of Cases
0-10	7
11-20	4
21-30	13
31-40	9
41-50	9
51-60	6
61-70	2
71-80	1
81-90	0
91-100	0
101-110	1
Gain in weight	1
Unknown	14

2. Three qualities of temperament constitute a second reason why these patients lived so long. These qualities were common sense, courage and cheerfulness. These patients were not led into fads of treatment either by physicians or by the advertisements of patent medicines. They were practically all individuals of strong character who, realizing their disease, made up their minds to fight it through to the very end. They were not cowards. A cowardly diabetic has a poor prospect for life. Cheerfulness was more than noteworthy as a characteristic of these people. It was well-nigh universal.

3. There is hope in the fact that fifty-five of the sixty-seven patients received distinctly better treatment than the average diabetic patient. Eleven of the patients received treatment from men who stand exceptionally high in the profession. It is true that over and over again patients deny that they carry out careful treatment, but I think it is seldom, though it is occasionally so, that one meets a patient with diabetes of long standing who has not consciously or unconsciously followed rational methods of care.

4. Heredity plays a considerable rôle among the group. Sixteen, or 25 per cent., of the sixty-three patients whose cases are available for statistics in this regard had parents, brothers or sisters, cousins or aunts with the disease. This percentage is probably somewhat higher than the percentage of heredity in diabetes, but not really so much greater than is often the case. Undoubtedly, heredity will play a greater rôle in diabetes as time goes on, but it may not attain greater significance. Accuracy of vital statistics and better physicians enter into this condition. Two cases in the heredity group are of especial significance because the disease developed at the ages of 15 and 17, respectively; in fact, these were the youngest patients in my group. Another of my patients with marked heredity developed diabetes at the age of 13 but lived not quite ten years.

All cases which have come to my attention of youthful patients with diabetes living for such long periods of time have been hereditary. The case of Schmitz, quoted by Naunyn, was hereditary. Naunyn's own famous cases, Nos. 124, 173 and 32 were all hereditary cases, and he refers on pages 96 and 97 of the second edition of his book on diabetes to other cases with long duration in which I find that heredity was manifest.

Von Noorden calls attention to the fact that heredity may be a favorable factor for the duration of diabetes, though occasionally unfavorable if the type in the progenitors has been especially severe.

5. The diabetes was extremely mild in five of my cases, and the quantity of sugar in the urine in these five cases was not far from 1 per cent. In one of these cases, acidosis was present following an operation for appendicitis. In several of the cases a small quantity of sugar was present in the urine presumably for some time before the disease broke out in full force. I suspect that many more such cases will be found in the future.

6. The favorable outcome in a considerable percentage of the cases can be attributed to the early detection of the disease. Many of the patients were physicians and several learned of the diabetes through life-insurance. Approximately one-fourth of the patients discovered their diabetes in this manner, and thus presumably began treatment early. The early detection of the disease, therefore, is one of the best methods for obtaining favorable results for treatment.

Naunyn especially urges the importance and the good results of early treatment. The time is probably not far distant, if not already here, when the question will be asked of the diabetic "How long did the diabetes exist before it was discovered and who was your physician?" We are familiar with the same questions in tuberculosis. Who would have thought ten years, or even five years ago, that it might reflect on a physician if one of his patients developed typhoid fever? In ten years to come we may be blamed for the development of some cases of diabetes.

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ABSTRACT OF DISCUSSION

DR. THEODORE C. JANEWAY, New York: Success in the treatment of diabetes mellitus depends entirely on minute attention to detail and on the ability of the physician to persuade the patient to undergo the necessary hardships, which, however, should be made as little irksome as possible. There must of necessity be cooperation on the part of the patient; unless you can convince your patient of your ability to help him, you will not get this needed cooperation.

The treatment of the ordinary cases of diabetes is within the powers of any physician who is willing to give a little time and study to the underlying principles. The management of severe cases of diabetes requires special experience. Dr. Joslin has emphasized the real value of profiting by what we have learned from experience, carefully studied, in the hopefulness that comes from known power to help our patients. The same principle holds good, for instance, in the use of digitalis in heart disease; the man who always uses it carefully, and only when it is indicated, can accomplish results, and avoid many failures. In his future use of digitalis then he will show a confidence which goes a great way in promoting a good effect on the patient. This holds good over the whole domain of practical medicine.

If we have learned to carry these diabetic patients along and improve at least one-quarter of all of them so that they can live ten years or more, I think that we have been given a valuable lesson. There is no one in the country who is in a better position than Dr. Joslin to give us this lesson with the statistics that he has, and the thoroughness with which he has gathered them. My personal experience with these cases of diabetes has not been as great as his. I think rather more of the long-lived ones that I have records of have shown obesity. Dr. Joslin's patients, however, have been chiefly among the American-born population, more of mine among the Hebrews. One patient illustrates a phase of the question occasionally seen, an elderly obese individual, now nearly 80

years of age, diabetic for about twenty years, who has disregarded most of the rules laid down for him but is still alive. He has survived an appendix abscess since 70. For the last six years his diabetes has been moderately severe. Too much should not be said about such cases, for the disregard of proper dietetic measures usually produces very definite effects in hastening the progress of diabetes. Such a case shows, however, that the elderly obese diabetic may live long even without good treatment.

DR. JOHN A. LIGHTY, Pittsburgh: What was the percentage of these patients that Dr. Joslin has reported to the number of patients diabetic whom he has seen? An important point which I think should be emphasized, is the effect of the acute infections on these cases. Death in almost all my cases was due to some acute infection rather than because of the usually dreaded diabetic coma, such for instance as middle-ear disease, tonsillitis, pneumonia, pulmonary tuberculosis and other diseases which might be mentioned.

In looking over my case records a few weeks ago in preparation for a lecture to the students on the subject of diabetes mellitus, I found a point that impressed itself on me very much, and one that Dr. Joslin has brought out this morning, that these patients live longer than was ordinarily believed and longer than the text-books usually tell. One case in particular illustrates the hopefulness which should be entertained in regard to these cases. This patient was a young man, in the dangerous age, between 20 and 30, whose case was classed as acute, with a bad prognosis. He was eliminating 26 ounces of sugar during twenty-four hours. This man was gradually placed on a carbohydrate-free diet, and the amount of sugar fell gradually to three-fourths of an ounce per day. After two days' rest in bed the sugar entirely disappeared, and he slowly gained in weight. This case looks to be very hopeful. It illustrates what rest in addition to proper dietetics will do.

DR. G. W. McCASKEY, Ft. Wayne, Ind.: I am strongly inclined to think that we have a tendency to take an altogether too hopeless view of the progressive tendencies of diabetes mellitus, and am firmly convinced that an intelligent and careful management of these patients will tend very largely to increase the number of those who live many years, and who make, under favorable conditions, what is a substantial recovery. While we do not know much of the real pathology of the disease, we may say that it is a more or less complete breakdown in the glycolytic function of the body. This function is very complex. Certainly it is dependent in part on the internal secretion of the pancreas and probably on the glycolytic ferment discovered by Cohnheim in the muscle juices. Other factors still may be operative although at present unknown.

What we should aim to do is to study this function in so far as its limitations are concerned and endeavor if possible to broaden them. I believe that this can be done to a great extent in a considerable number of cases. The first thing to do is to determine whether the patient with diabetes will continue to have glycosuria on a starch- and sugar-free diet. If he does, the case is essentially unfavorable and the patient cannot be expected to improve very much or perhaps even survive very long. If the sugar in the urine disappears on the withdrawal of carbohydrates, then intelligent supervision of the patient's dietary may accomplish very much. He cannot, of course, be kept aglycosuric by completely withholding carbohydrates indefinitely, as this is not practical; but by reducing the quantity as much as possible and at frequent intervals entirely withdrawing them and giving this complex function rest, we may improve its capacity and widen its limitations and in a certain group of cases the patient may ultimately become able to assimilate and metabolize an increasing quantity of starch without the production of glycosuria. A full recognition of these facts will enable us to be of vast service to some of these patients who otherwise may drift along steadily becoming worse as months and years go by. In short, it is not sufficient at all, nor does it discharge our duty to the patient simply to tell him to take less starch; the quantity that he can assimilate must be carefully worked out from time to time and the treatment which is, of course, principally dietetic, must be intelligently directed along the lines indicated.

Dr. J. L. MILLER, Chicago: I would like to report two interesting cases. A woman had a glycosuria which had existed for a number of years; she developed an urticaria of very severe type which persisted for three or four months. Without any change in her diet or any special medication, the glycosuria disappeared. After the disappearance of the urticaria, however, the glycosuria returned.

The second patient was a woman, who passed 50 gm. of sugar a day. She was on a rigid diet. She had very severe uterine hemorrhages, and, as a result, was markedly anemic. A hysterectomy was performed. It was found that a carcinoma had developed on an old fibroid tumor. Several months later the patient returned and it was found that she was entirely free of sugar. To-day she is taking practically an unlimited amount of starch and is doing very well.

Dr. LOUIS G. HEYN, Cincinnati: At von Noorden's clinic and at different sanatoriums to which I had access in Vienna, I was impressed with the control the physician had over his patient and the good results to the diabetic patient accruing from a hospital residence. Great stress is laid on the patient's residence in a hospital or sanatorium, an important step in gaining control of the patient. Of greater importance perhaps than the control of the patient is the facility which close observation affords of determining the carbohydrate tolerance. Estimations may thus be carried over a definite length of time daily. What also seemed important to me was the manner in which physicians impressed their patients with the seriousness of their condition and the fearlessness which the physician displayed in handling the situation. For instance, the presence of acetone and acid bodies was usually disregarded, unless the acetone estimate was over 5 gm. daily. Let me say again that I consider of paramount importance the residence of diabetic patients in hospitals or sanatoriums. Most of them will not be required to remain longer than a few weeks.

Dr. ELLIOTT P. JOSLIN, Boston: One occasionally meets a patient who states that he has not had careful treatment, yet such a patient may live for a long period of time. I investigate such cases and usually find that such patients take much butter and cream and other fatty food and also change the character of their work. The head of a large life-insurance office told me that he had had diabetes for twenty years, and that he had never been treated for it. In reality, however, the diagnosis was made early and the patient being intelligent had followed a most careful diet all his life. I can report a case similar to that described by Dr. Miller. The patient had a very severe attack of diabetes; the glycosuria occurred in connection with a fibroid tumor of the uterus; when the fibroid was removed the glycosuria disappeared. I think that residence in a hospital should be but a short time, three weeks the maximum. When sent out, these individuals will be more willing to return for another period of treatment. They should be allowed to go about town and enjoy pleasures outside the institution. Rest for a week, however, often results in great benefit to them. The report of the case of urticaria occurring in the case of diabetes was extremely interesting, especially as it might throw some light on the etiology or on the treatment of this disease. There is no doubt also but that cases of diabetes in which tuberculosis is acquired require careful study; if tuberculosis develops in a diabetic patient, the diabetes usually recedes; just why I do not know.

Laboratory Typhoid Diagnosis.—Blood-cultures make possible an early and positive diagnosis. The typhoid bacilli can be recovered from the blood in a large percentage of cases as early as twenty-four hours after the onset of the illness. This is the most valuable aid in diagnosis during the first week, before the appearance of the Widal reaction. After the first week the percentage of successful blood-cultures take a decided drop. This method of examination is now even more of a necessity since the use of typhobacterin in the prophylaxis of typhoid fever. A positive Widal results quickly after the vaccination and persists for a varying period, making the agglutination reaction worthless in many cases.—Sledge in *Southern Med. Jour.*

SUCCESSFUL CULTIVATION OF MALARIAL PLASMODIA *

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NEW ORLEANS

In a former contribution¹ I first reported my success in cultivating *Plasmodium vivax*, *P. malariae*, and *P. falciparum*; and as much additional work has been completed since the appearance of that article, the present brief announcement of results to date is presented pending publication of the full technic and details.²

The work subsequent to that first described in the article above cited¹ was done in Central America in conjunction with Dr. Foster M. Johns on a research expedition equipped and sent to Panama by the Tulane School of Tropical Medicine and Hygiene.

In the course of this later work it was found that the malarial plasmodia can be grown in human serum, in Locke's fluid (from which calcium chlorid is omitted) and in human ascitic fluid. In the majority of cases it was found that dextrose must be added to the medium in order to secure growth of the parasites. The plasmodia grow in a thin layer near the top of the cell sediment, beneath which zone the parasites all die.

The parasites have been cultivated only in the red cells of human blood and are destroyed by the leukocytes as soon as they are liberated from the erythrocytes, and also by the serum, Locke's fluid, ascitic fluid, or, in fact, by any of the mediums experimented with.

Plasmodia develop readily in the red corpuscles, apparently digesting the substance of the corpuscles, and segmentation can be followed with great satisfaction in the cultures.

The most favorable temperature found for the cultivation of these protozoa is about 40 C. They will usually live at a lower temperature, but often will not grow, and as a rule will not multiply.

Positive cultures have been obtained from twenty-nine cases of estivo-autumnal malaria, six cases of tertian and one case of quartan. The cultures have been carried on as far as four generations from the parent culture and with proper attention to technic can doubtless be maintained indefinitely. Only the asexual cycle of the parasite has been observed in our cultures.³

It is hoped that those workers who are in a position to do so will confirm the work already done; those who are interested in the matter are referred to the full discussion.²

In conclusion I wish to thank the anonymous friend of the Tulane School of Tropical Medicine who, through the Dean of the Medical Department of Tulane University, contributed the fund which paid the expenses of the expedition; also the United Fruit Company which, through their manager, Mr. C. H. Ellis, furnished complimentary transportation for the members and apparatus of the party, and Colonel W. C. Gorgas, chief sanitary officer of the Canal Zone, with various members of his staff, who extended every help and courtesy during the expedition's stay in Panama.

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* Study 23, from the Laboratories of Tropical Medicine and Hygiene, under the direction of Creighton Wellman, Medical Department of the Tulane University of Louisiana.

1. Bass, C. C.: A New Conception of Immunity, *THE JOURNAL A. M. A.*, Nov. 4, 1911, p. 1534.

2. A complete discussion will appear in the October number of the *Journal of Experimental Medicine*.

3. Cultures, preparations and apparatus illustrating the foregoing work will be exhibited at the International Congress on Hygiene and Demography to be held at Washington, September 23-28.