by a *control period* of at least ten days during which fractional and twenty-four-hour urine specimens are analyzed daily for glucose and, if positive, for ketone bodies and both fasting and postprandial blood sugar levels are determined each day. If blood and urinary glucose remain within acceptable limits as defined above, the patient needs neither insulin nor oral drug and has proved himself an unsuitable subject.

If hyperglycemia and glycosuria appear or continue during the control period, the drug to be tested is added to the regimen, with no other change, for the next ten days (*test period*), during which comparable data are collected and signs of toxicity watched for.

A *recovery period* of similar length terminates the observations.

If during the test period normal or nearly normal glucose levels are achieved, it can be concluded that the compound is effective for the patient in question and possibly for others of a similar type. If good control is not obtained, the compound is not as good as insulin for this patient and the opposite conclusions can be drawn.

Ideally, a period with a placebo instead of the test substance should follow the recovery period, but this adds materially to the time required and is far less important in hospital than outpatient observations.

Obviously, this elaborate and time-consuming kind of study is not suitable for large numbers of patients or for the determination of long-term toxicity. Its purpose is to provide unassailable data on the effect of a given preparation in a few carefully selected subjects with diabetes of various types and degrees of severity. Only after the accumulation of this sort of information should the base of clinical testing be broadened to include ambulatory cases.

With respect to office or clinic patients, we are not concerned here with single-dose response tests of a few hours' duration but with the effectiveness and safety of drugs on a maintenance basis. The procedure follows the general scheme just presented but with two important modifications: Insulin must be withdrawn slowly rather than abruptly in order to guard against ketosis, and the "double-blind" method of administering the test drug and a placebo is imperative. The inherent difficulties of this kind of observation are mitigated to some extent by longer control, test and recovery periods; weekly visits at which blood sugar and quantitative (twenty-four-hour) urinary glucose are determined; written records of home urine tests made four times daily; and measurements of body weight.

Short-cuts in these procedures have been taken too often in the past, and the tendency to take them is currently increasing with the successive introduction of new forms of the sulfonylureas and other hypoglycemic agents. The fact that a new drug differs from its predecessor by only an atom or two is no guarantee that either its biologic activity or its safety is identical. Witness the example of carbutamide, in which merely the substitution of a methyl for an amino group converted that compound to one (tolbutamide) which is appreciably less toxic and lacks bactericidal properties while retaining essentially the same hypoglycemic potency. In the interest of sound medical practice and public safety, and despite the pressure of commercial competition, each new compound, however similar to others, deserves the same careful clinical testing as if its close relatives had never been heard of.

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THE TUBERCULOUS DIABETIC

The publication of a report on the management of the tuberculous diabetic by Luntz[1] has prompted this comment. Its purpose is to emphasize again a concluding statement by Luntz, to wit, "Acute bilateral pulmonary tuberculosis in a diabetic is a serious complication to be regarded as a medical emergency. It calls for immediate treatment in a special hospital unit with an effective dosage of combined chemotherapy for the tuberculosis and the stabilization of the diabetes as a matter of great urgency."

The validity of these conclusions cannot be questioned by any one who has had the opportunity to observe these cases. The tragic consequences of neglect of both diseases and, per contra, the remarkable success of combined therapeutic efforts in the past twenty years testify to the correctness of the conclusions.

The experience of Luntz was based, it is true, on only a short (one year) follow-up of eighty-four cases. He noted the usual sequence, tuberculosis complicating pre-existent diabetes in the majority of instances. The age distribution was also the usual one, with two peaks of predominance, twenty to thirty-nine and forty-five to sixty-four years, the first seeming to correspond to the maximal incidence of tuberculosis, the latter to the maximal incidence of diabetes. It would seem unnecessary to remind any practitioner again, in these days of mass X rays, of the dictum of at least yearly chest X rays in all diabetic patients and in particular in those with a break in tolerance or poor or difficult control. Such vigilance is imperative in the light of Luntz's finding of bilateral

disease in over half of his cases, in 68 per cent three or more zones involved and in 87 per cent cavitation present when first seen. This bespeaks advanced and profuse involvement. It signifies either delay or neglect either by the patient or his medical attendant. This is not a unique experience. It is noted in all institutions where these patients are segregated.

Dr. Luntz followed the recommendation of the Ministry of Health for special provision for tuberculous diabetic patients and organized a hospital unit, out-patient clinic and domiciliary service, thus providing continuity of treatment and supervision. Such ideal arrangements are not common by any means, although it is in operation at least in one of New York's institutions and should be in all others. This organization paid dividends. There was only one death in the ensuing year and this was not due to tuberculosis. Granted that one year is an insufficient period to assess the progress of tuberculous patients, the achievement of quiescence of disease in 83 per cent speaks for itself. The success of this program also seems evident from several indices: Reduction from an incidence of about 90 per cent positive sputum examinations to 6 per cent positives after one year; disappearance of cavitation in 83 per cent; decreases in sedimentation rate and pyrexia and gain in weight. These results compare favorably with those reported in nondiabetic tuberculous patients.[2]

The treatment program for the tuberculous infection was the usual combined chemotherapy, bed rest, collapse therapy including pneumothorax, pneumoperitoneum with and without phrenic nerve crush, thoracoplasty and lobar and segmental resection. Major surgery was well tolerated. The regulation of diabetes during and after the operative procedure followed conventional lines. The excellent results underline the fact that a tuberculous diabetic patient should be treated for the tuberculosis as thoroughly by all medical and sugical modalities as if his diabetes did not exist. But his diabetes must be controlled concomitantly so that he is as close to nutritional balance as possible. The Birmingham Group used measured diets to accomplish this, usually 2,500 calories, C—275, P—110, F—110, varying with the assessed nutritional requirements. These correspond closely to our ADA standard dietaries. Insulin, both soluble and depot, was given in various combinations, and distinct efforts were made to keep these patients aglycosuric and as nearly normoglycemic as possible.

The excellent results of this combined program of intense therapy for both diseases are similar to the experience of others.[3] It is my impression that the progressive improvement in prognosis over the years may be correlated better with the advancements in the therapy of tuberculosis than with changes in diabetes therapy. A final opinion on this point awaits a statistical analysis of a large series of patients. This is not to deny, by any means, the fundamental relationship between stabilization of the diabetic state and stabilization of the infection. No one will deny the grave prognosis to the infected individual without this control of his metabolic abnormality.

But the basic problem of the susceptibility of the diabetic to infection is still unsolved. The incidence of tuberculosis in diabetic subjects is several times that of the general population of similar age, sex, race and social status. Conversely, there seems to be little doubt that susceptibility to tuberculosis is decreased in the stabilized diabetic patient. This statement becomes more meaningful if we conceive of tuberculosis, according to Bloch,[4] as an intercellular, dormant, symbiotic infection awaiting the right combination of alterations in the "*microbiological environment of inflammation*" (Dubos)[5] to become active. The experiments of Dubos[6] on the effect of the nutritive state on this environment, particularly the effect of ketosis, strengthen this concept for the diabetic subject.

The lethal effect of artificially induced changes in the tricarboxylic acid cycle in Salmonella-infected mice demonstrated by Berry,[7] may be cited as another experimental example perhaps particularly applicable to the diabetic's metabolic dysfunction. Many such factors, nutritional, neural or endocrine-regulatory, biophysical and biochemical are being studied throughout the world and it would be naive, indeed, to select any one of them as the ultimate determinant of the diabetic patient's susceptibility.

As Bloch[4] has put it for tuberculosis: "During the chronic phase, the tuberculous infection remains stationary. Despite the continuous presence of living infectious organisms, clinical signs of tuberculosis are lacking. The animal (or man) has acquired a considerable degree of immunity against new infections, but at the same time he is liable to an exacerbation of his own condition after having been exposed to a variety of seemingly unrelated impacts such as nutritional or endocrine changes, or intercurrent infections other than tuberculosis."

These statements illustrate the acquired or phenotypic characteristics of disease and the numerous adaptations of both host and parasite necessary for the survival of either. But one must consider the genotype of both host and parasite. Natural resistance to infection is difficult

even to define and has proved much more difficult to assess. As yet, no specific alteration in any of the systems of natural resistance such as the Properdin one has been detected in the diabetic.

However, this does not mean that some alteration in an essential system, inherited concurrently and separately with his inherited metabolic abnormality, may not be present in the diabetic patient. If one considers that "genes control the potentiality of enzyme syntheses" (Spiegelman and Campbell)[8] then it does not seem too speculative to envisage a subtle inherited alteration in the enzymatic synthesis of the diabetic host's responsive metabolites when confronted by the aggressive metabolites of the parasite. Induced enzyme formation in the microorganism (Spiegelman and Campbell)[8] and metabolic adaptations in the mammalian organism (Knox)[9] must be conditioned by the genetic structure of both.

To express it in the words of Snyder,[10] "Each individual has a unique assembly of genes and will have his own mode of reaction to disease, whether it be presented through infection, trauma, stress or malnutrition, or wholly from within through biochemical error. The conviction that the genetic constitution is involved to a greater or lesser extent in all disease will serve as a stimulant to look beyond the secondary aspects of pathology and to search for the primary genic action in each case."

It remains to be seen whether the genotype of the diabetic may play an essential role in his peculiar susceptibility to infections other than through his known inherited metabolic abnormality. All we may state with any degree of confidence at present is that the intrinsic inherited defects in metabolism that characterize the diabetic state are factors in his susceptibility to infection.

The inescapable conclusion from all this would seem to be that these defects in his metabolism must be remedied or controlled to the best of our ability if the diabetic is to escape his predestined tendency to infection or to be rescued if infection occurs.

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BOOK REVIEW

THE LIPIDS: THEIR CHEMISTRY AND BIOCHEMISTRY. *Vol. III, by Harry J. Deuel, Jr. $25, pp. 1065, Interscience Publishers, Inc., New York, 1957.*

This is the third volume of Dr. Deuel's comprehensive treatise on the chemistry of the lipids. The present volume is published posthumously and together with its predecessors forms a fitting monument to the genius and indefatigable labors of Dr. Harry J. Deuel, Jr. The present volume is concerned with the biosynthesis, oxidation, metabolism, and nutritional value of lipids. There are fourteen chapters comprising some 1,000 pages. This book is an indispensable reference for biochemists working in this complex field. Chapter I deals with the problems of the digestion, absorption, transport and storage of lipids. Chapter II is a masterly detailed account of the biosynthesis of various forms of lipids in the animal body. It serves as a most valuable exposition of the development and the present status of this field. Chapter III covers the problems in oxidation and metabolism of the triglycerides, phospholipids, and fatty acids in the animal body. Chapter IV is an able exposition of the vexed question of the conversion of fat to carbohydrate. Deuel comes to the balanced conclusion that a net increase of carbohydrate from fat does not occur in the mammalian organism. The phospholipids are treated with respect to oxidation and metabolism in Chapter V. The role of the low molecular weight fatty acids, such as acetic, formic and propionic, in the intermediary metabolism of fat is treated in Chapter VI. The biochemistry of unusual forms of fatty acids, such as branch chain, hydroxy, and keto acids, etc., is treated in a separate chapter. Excellent and complete discussion of the sterol chemistry comprises some 100 pages in Chapter VII. The biochemistry of the fat soluble vitamins is treated in Chapters IX to XII. The discussion here is most thoroughgoing, of historical significance, and presents the modern developments most succinctly. Chapter XIII deals with the interesting biochemistry of the essential fatty acids, and the final chapter concerns itself with the nutritional value of fats. There is an excellent author and subject index. This particular volume of a series of three deserves high rank among the present available treatises on the rapidly developing field of lipid chemistry.