sections from the post-mortem room sections by observing the fibrous tissue as by concentrating on the epithelial pattern. The epithelial changes designated chronic mastitis by the histologist and assumed to be precancerous were present in a small proportion of the control sections, but it was quite exceptional to find an excess of highly nucleated fibrous tissue in sections taken from patients not complaining of the symptoms of chronic mastitis. The clinician when he refers to chronic mastitis means a painful nodular breast, and an outstanding feature of the painful nodular breast is fibrosis with or without cysts. If now this fibrosis accompanies epithelial changes, which threaten cancer but rarely fulfil their threat, it is possible that the fibrous tissue may be produced in response to that threat and may play a part in preventing it from coming to fruition. Consequently it would be just those patients who are able to develop a fibrous-tissue reaction to epithelial overgrowth—that is, those who complain of the symptoms of chronic mastitis—who would be unlikely to develop cancer. The conception that the fibrosis of chronic mastitis is an expression of a local defence mechanism resolves the problem of the precancerous nature of this disease in conformity with both the histological and the clinical evidence. Moreover, it falls into line with the established procedure of Nature in dealing with infectious disease and provides the counterpart to the granulation tissue which is such a prominent feature of that process.

That the problem of the protective function of fibrous tissue is an exceedingly complicated one is appreciated from a consideration of the relative malignancy of the different types of carcinoma of the breast. The malignancy of a breast cancer cannot be assessed from the amount of fibrous tissue present, as would be the case if fibrosis were the only mechanism of defence against the malignant cell. Where so many factors operate, these may exert a predominating influence on the clinical picture. In the absence, for instance, of a certain degree of natural or acquired immunity no amount of fibrosis could of itself control the spread of the disease. One factor among many might only be expected to colour the whole picture when it was operating in its most intense form. Such an intensity of fibrosis is met with in the atrophic scirrhus: here the combination of fibrosis with the most anaplastic type of epithelial cell leads to a control of epithelial growth which may delay the spread of the disease for many years. Thus in those cancers where the morphology of the epithelial cell would lead us to expect a rapid growth but which lie dormant for years, and in chronic mastitis where precancerous changes suggest a malignant tendency which is not fulfilled, the only accompanying phenomenon observable is fibrosis. On that account the theory of the protective function of fibrous tissue against epithelial new growth is put forward as a working hypothesis. This appeal to the old tissue-tension theory of Waldeyer and Thiersch does not suffer from the objections to that theory in its original form. It is not suggested that an upset of the equilibrium between fibrous and epithelial tissue is the whole story of the development of cancer, but it is proposed that fibrosis is engendered by a tendency to epithelial overgrowth and that the fibrosis is one part of the complicated mechanism of defence against neoplastic disease comparable to granulation tissue in infectious disease.

Pathology of the "Fibromatoses"

Lastly, if this be so, it is pertinent to inquire whether there is a series of clinical conditions comparable to the chronic granulomata and expressive of a local tissue

reaction to the threat of malignant invasion elsewhere in the body. We have discussed the relation of chronic mastitis to this problem, but there is a class of clinical phenomena, which I will call the fibromatoses, which might repay investigation in this connexion. I refer to leucoplakia, Riedel's thyroiditis, fibrotic prostate, linitis plastica, and fibromatosis of the colon. An entirely satisfactory pathology has not as yet been assigned to these conditions, and in order to stimulate further investigation the suggestion is put forward that the fibromatoses, including chronic mastitis, may be the homologues in neoplastic disease of the infective granulomata.

Summary

The natural history of chronic mastitis is considered, and an analysis made of the evidence as to whether the condition is precancerous.

It is submitted that the fibrosis occurring in chronic mastitis is part of the mechanism of defence against neoplastic disease, comparable to granulation tissue in infectious disease.

The suggestion is made that the "fibromatoses" might repay investigation in connexion with the appearance of cancer in other parts of the body.

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BLOOD LAEVULOSE IN THE LAEVULOSE TOLERANCE TEST

WITH SPECIAL REFERENCE TO NORMAL STANDARDS

BY

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When laevulose reaches the normal liver by the portal veins it is rapidly utilized, part being oxidized and part stored as glycogen. The rate of utilization is almost as rapid as the rate of absorption from the intestine, so that very little laevulose reaches the general circulation after oral administration of the sugar. If the glycogenic function of the liver is impaired by disease the rate of utilization fails to keep pace with the rate of absorption, and an abnormally large amount of laevulose passes through the liver into the systemic blood stream. These facts provide the basis for the laevulose-tolerance test of hepatic function. In the past the method of performing the test has been to follow the changes in total blood sugar after a dose of laevulose, and it has been assumed that any increase above the fasting level is due to laevulose.

Recent Investigations

In recent years methods have been developed for the analysis of blood laevulose, and various authors have made fresh investigations of the laevulose-tolerance test in which the blood laevulose has been directly estimated

(Scott, 1935; Stewart, Scarborough, and Davidson, 1937, 1938; Steinitz, 1937; Herbert and Davison, 1938). All these workers agree in their main conclusions, which are as follows. The blood glucose may either rise or fall during the test, so that the rise in total blood sugar does not give a measure of blood laevulose, and results based on total blood sugar may be misleading. The normal range of variation is narrower for blood laevulose than for total blood sugar. In a wide variety of non-hepatic diseases the blood-laevulose curves are normal. In arteriosclerosis Stewart *et al.* found deficient laevulose tolerance, but so far this is the only exception to the rule that the results are normal in the absence of liver disease. In uncomplicated diabetes the total blood sugar may show a considerable rise after the dose of laevulose, but the blood-laevulose curve is normal. Abnormally high rises in blood laevulose occur in a considerable proportion of cases of liver disease, though not in all. Evidently the liver has a large functional reserve, and the test does not reveal deficiency unless there is severe damage to the liver.

Necessity for a Normal Standard

These results show that the laevulose-tolerance test is sound in principle, and becomes more reliable in practice if it is based on analyses of blood laevulose instead of total blood sugar. There is, however, some discrepancy among different authors as to the standards which should be accepted as normal. This does not invalidate the main conclusions derived from their work, since in each study the findings in liver disease have been interpreted in relation to normal standards worked out by the same technique. But if blood-laevulose estimations are to be generally adopted for clinical use the normal range ought to be clearly defined. This is especially necessary, because in many cases of liver disease the peak of the blood-laevulose curve is only slightly above the upper limit of normal.

It is generally agreed that there is no measurable amount of laevulose in the blood in the fasting state. After the dose of laevulose (50 to 60 grammes) that substance appears in the blood, reaching a peak in one-half to one hour, and then falling. Scott examined six normal subjects and five cases of non-hepatic disease. He used his own method for the estimation of laevulose, which depends on a reaction between laevulose and bile salts. He found no laevulose in "fasting" blood and a maximum level never greater than 12 mg. per 100 c.cm. in venous blood. The other workers quoted used the diphenylamine method in various forms. It consists in the measurement of the blue colour produced when laevulose is heated with diphenylamine in acid solution. By this method one obtains a slight trace of colour in analysing "fasting" blood, but it is much too faint for accurate measurement. It seems probable that the differences in the figures obtained by different workers are due to the difficulty in allowing for this apparent fasting level. The colour is mainly due to the blood glucose, which reacts to a very slight extent with the diphenylamine. Steinitz, on the basis of over 200 tests in subjects without hepatic disease, stated that laevulose was absent from "fasting" blood and that the maximum level was never greater than 12 mg. per 100 c.cm. in venous blood, or 15 mg. per 100 c.cm. in cutaneous capillary blood. Stewart, Scarborough, and Davidson estimated the rise in blood laevulose above the apparent level in "fasting" blood, and found that normally this rise might amount to 20 mg. per 100 c.cm. in venous blood. Their figures all tended to be higher than those of other workers, since

their average peak in normal subjects was 12.8 mg. per 100 c.cm. They recognized that in their analyses the apparent fasting level was not precisely measured in each individual instance. Herbert and Davison found that the maximum normal rise above the apparent initial level was 15 mg. per 100 c.cm. (venous blood), and that only a small minority of cases showed peaks above 10 mg. per 100 c.cm.; but they made no analyses earlier than one hour after the test dose, and there was a possibility that some higher levels might have been found if the half-hour point had been included.

Herbert and Davison used Patterson's method for the estimation of blood laevulose. When their work was almost completed I evolved a new modification of the diphenylamine method (Herbert, 1938). This method is much more quickly carried out than the older procedures, and is therefore better suited to the needs of hospital laboratories.* It also gives much more intense colours, which can be measured with greater accuracy—a factor that is especially useful in dealing with "fasting" blood. The older methods gave a faint greenish-blue tinge, due to a mixture of a trace of blue, which is accounted for by the effect of glucose, and a trace of yellow from some unknown source. In the new method the yellow element becomes negligible in relation to the blue, and the glucose effect can be more precisely measured and allowed for.

The purpose of the present paper is to give the results obtained by this technique in subjects with healthy livers. For convenience the whole procedure will first be described.

Methods for Estimating Blood Laevulose

The dose of laevulose is 50 grammes for an adult, and for a child 1 gramme per kilogramme of body weight. It is given after a night's fast. Samples of venous blood, about 5 c.cm., are taken before the dose of laevulose, and at half an hour, one hour, and two hours after. Potassium oxalate is used as an anticoagulant; an excess of oxalate should be avoided.

ANALYSIS

Reagents:

- (1) 10 per cent. $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$.
- (2) 0.5N. NaOH.
- (3) Stock diphenylamine solution. 20 per cent. diphenylamine in alcohol.
- (4) Acid-alcohol-diphenylamine reagent: ethyl alcohol, 70 parts; concentrated HCl, 50 parts; stock diphenylamine solution, 6 parts. This reagent should not be more than a month old when used.
- (5) Stock laevulose solution, 1 per cent. in saturated benzoic acid. The laevulose should be desiccated before weighing.
- (6) Standard laevulose solutions (freshly prepared): (a) 1 c.cm. stock solution diluted to 200 c.cm. with water (2 c.cm. = 0.1 mg. laevulose). (b) 25 c.cm. of standard (a) diluted to 100 c.cm. (2 c.cm. = 0.025 mg. laevulose).

PROCEDURE

Take 2 c.cm. plasma in a 15 c.cm. centrifuge tube. Add 2 c.cm. water and 2 c.cm. 10 per cent. zinc sulphate solution. Close the tube with a rubber stopper and shake thoroughly. Add 2 c.cm. 0.5N NaOH and again shake thoroughly. Centrifuge the mixture well and pour the supernatant fluid through a small filter (Whatman No. 42 paper, 5.5 cm.). The yield of filtrate is just over 4 c.cm., which allows of duplicate

* It should be mentioned that another rapid method, based on a different principle, has recently been described by Jordan and Pryde (1938). So far there has been no report of the use of this technique in the laevulose-tolerance test.

analyses. In a pyrex test-tube (about $\frac{5}{8} \times 6$ in.), graduated at 10 c.cm., take 2 c.cm. filtrate and 6 c.cm. acid-alcohol-diphenylamine reagent. The standard laevulose solutions (2 c.cm. of each standard) are similarly treated. Place the tubes in a boiling-water bath for exactly fifteen minutes and then cool them rapidly in running water. Dilute with alcohol to the 10 c.cm. mark, and compare the colours in the colorimeter, using standard (b) for comparison with the filtrates from "fasting" plasma and standard (a) for the remainder.

CALCULATION

Let R_s = reading of standard
Let R_u = reading of unknown

The plasma laevulose, mg. per 100 c.cm., is given by the formulae:

$$\frac{R_s}{R_u} \times 20 \text{ when standard (a) is used;}$$

$$\frac{R_s}{R_u} \times 5 \text{ when standard (b) is used.}$$

If absolute figures for blood laevulose are required, the total blood sugar is estimated and a correction made for the effect of the blood glucose. The effect of 100 mg. glucose per 100 c.cm. is equal to that of 2.4 mg. laevulose per 100 c.cm.

In performing the laevulose-tolerance test in non-diabetic subjects it is justifiable to treat the glucose effect as constant throughout the test and to estimate the blood laevulose after the test dose from the rise above the apparent initial level. For diabetic subjects it is desirable to estimate the total sugar and make the correction, but even in diabetes the effect of the correction on the interpretation of the results is very small. The figures for plasma are identical with those for whole blood.

Results

The results obtained in twenty-six subjects without hepatic disease are given in Table I. The figures have not been corrected for the effect of glucose, except in the one case of diabetes. The apparent fasting level ranges from 1.5 to 3.5 mg. per 100 c.cm. Figures of this order are to be expected as due to the blood glucose. Very little, if any, laevulose is present in the fasting state. The maximum level may occur either at half an hour or at one hour after the test dose. The highest peak occurred in the case of diabetes, in which the rise above the initial level was 15 mg. per 100 c.cm. Of the remaining twenty-five subjects only three showed rises greater than 11 mg. per 100 c.cm. above the apparent initial level. If one takes a rise of 15 mg. per 100 c.cm. as the upper limit of normal, an adequate margin is allowed for the normal variation, since very few results fall in the upper part of the range. These figures are in general agreement with those of Scott and of Steinitz, and are definitely lower than those of Stewart, Scarborough, and Davidson. The standard now adopted is exactly the same as that used by Herbert and Davison. Although in individual cases the level half an hour after the test dose is often higher than at one hour, the inclusion of the half-hour point has not necessitated any extension of the normal range.

The level at two hours after the test dose is, in the present series, never greater than 6.2 mg. per 100 c.cm. above the apparent fasting level, but since in the earlier work the corresponding figures occasionally reached 10 mg. per 100 c.cm. it is safer to use the higher figure in considering whether or not the rise in any case of disease is unduly prolonged.

TABLE I.—Blood-laevalose Curves in Subjects without Hepatic Disease

Diagnosis	Apparent Plasma Laevulose mg. per 100 c.cm.				Rise above Apparent Initial Level mg. per 100 c.cm.		
	Before Laevulose	$\frac{1}{2}$ hr. after	1 hr. after	2 hrs. after	$\frac{1}{2}$ hr. after	1 hr. after	2 hrs. after
Normal	3.5	11.0	9.0	4.7	7.5	5.5	1.2
"	3.5	9.2	10.0	6.0	5.7	6.5	2.5
"	2.8	9.5	7.6	7.8	6.7	4.8	5.0
"	3.1	5.0	6.6	5.5	1.9	3.5	2.4
"	3.3	10.2	7.0	4.2	6.9	3.7	0.9
"	2.4	15.5	11.5	4.5	13.1	9.1	2.1
"	1.7	11.0	10.5	4.5	9.3	8.8	2.8
"	2.4	10.5	7.0	4.2	8.1	4.6	1.8
"	2.0	15.5	10.0	4.7	13.5	8.0	2.7
"	2.0	13.0	8.0	3.3	11.0	6.0	1.3
"	2.7	8.6	10.9	6.0	5.9	8.2	3.3
"	2.2	12.5	13.0	5.0	10.3	10.8	2.8
"	1.7	9.0	9.5	3.7	7.3	7.8	2.0
"	2.2	11.0	9.0	4.0	8.8	6.8	1.8
"	2.0	12.0	7.3	4.0	10.0	5.3	2.0
"	2.0	5.4	7.0	6.0	3.4	5.0	4.0
"	3.0	8.2	9.5	7.0	5.2	6.5	4.0
"	1.7	9.5	10.0	7.0	7.8	8.3	5.3
Skin pigmentation ..	1.5	14.0	12.0	4.0	12.5	10.5	2.5
Malignant ovarian cyst	2.0	10.0	11.0	4.5	8.0	9.0	2.5
Diabetes	2.0	14.0	17.0	4.0	12.0	15.0	2.0
Carcinoma of oesophagus	1.7	7.0	7.5	6.0	5.3	5.8	4.3
Hypertrophic gastritis	2.0	10.5	7.7	6.0	8.5	5.7	4.0
Subacute bacterial endocarditis	1.5	8.5	7.0	4.2	7.0	5.5	2.7
Splenic anaemia (four years after splenectomy)	3.0	10.0	10.0	7.5	7.0	7.0	4.5
Nutritional macrocytic anaemia	2.9	6.6	10.0	9.1	3.7	7.1	6.2

TABLE II

Diagnosis	Total Number of Cases	Number of Cases in which the Rise in Blood Laevulose per 100 c.cm. was :			
		Up to 10 mg.	11-15 mg.	16-20 mg.	Over 20 mg.
Normals and non-hepatic diseases	26	20	6	0	0
Hepatitis	2	0	0	1	1
Cirrhosis of liver ..	7	1	2	1	3
Malignant disease of liver	8	1*	2	5	0
Total liver diseases ..	17	2	4	7	4
Biliary obstruction ..	3	1	2	0	0

* This was a case of abdominal sarcoma, with only a few secondary nodules in the liver and no gross destruction of liver tissue.

A number of results in diseases of the liver have been obtained since the new analytical method was introduced, but as they merely provide additional illustrations of the facts established by earlier work they will not be described in detail. The cases in which the diagnosis could be definitely established are summarized in Table II. The majority of cases of hepatic disease show definitely high laevulose curves, though frequently the results are only slightly above the upper limit of normal. In some cases there is an early high peak followed by a rapid fall; in

others the blood-laeulose curve is not only raised but is also prolonged.

One case of carcinoma is of special interest as giving some indication of the extent of liver damage which must occur before the laeulose tolerance begins to show deficiency. The blood-laeulose curve, estimated five days before death, showed that the rise above the apparent initial level was, at half an hour after the dose of laeulose, 14 mg.; at one hour, 16 mg.; and at two hours, 10 mg. per 100 c.cm. This was a border-line result—only just outside the normal range. At necropsy the liver was found to be extensively disorganized by carcinoma, infarction, and necrosis, and it was estimated that about half the liver tissue had been destroyed. Now in such a case the condition resembles the result of partial hepatectomy. Little, if any, blood will pass from the portal veins to the hepatic veins through grossly damaged tissue. Almost all the blood which passes through the liver will traverse tissue of good functional capacity. It seems that in such circumstances a deficient laeulose tolerance indicates that at least half the liver tissue is out of action. In diffuse lesions, such as acute hepatitis, the condition is quite different, since all the circulatory paths through the liver will traverse damaged tissue, and this probably accounts for the fact that in acute hepatitis the laeulose tolerance is usually definitely deficient during the attack.

The diagnostic value of the test is limited by the existence of a large functional reserve in the liver. A normal result does not exclude liver disease. But, like renal function tests, the laeulose-tolerance test may give information as to the extent of the damage when a lesion has been recognized on clinical evidence. In some cases the test has diagnostic value; I have met with instances in which deficient laeulose tolerance has been demonstrated when the existence of liver disease could be neither proved nor excluded on the clinical evidence. The test may sometimes assist diagnosis—for example, in cases of unexplained haematemesis, unexplained anaemia, and in detecting hepatic cirrhosis in Banti's disease at a stage when the clinical evidence is inconclusive.

Summary

As a result of earlier work it has been shown that the laeulose-tolerance test becomes more reliable if the results are based on estimations of blood laeulose rather than total blood sugar.

My modification of the diphenylamine method for the estimation of blood laeulose has resulted in greater speed and accuracy of analysis.

Normal results for blood-laeulose curves obtained by this method are presented.

Some additional results in cases of liver disease are described.

I am indebted to the honorary medical and surgical staff of the Royal Victoria Infirmary for the opportunity to examine cases and for the use of clinical notes; to my colleagues on the pathological staff for histological and post-mortem data; and to the volunteers who offered themselves as subjects for the study of normal results.

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ASTHMA AS A SEQUEL OF NASAL INJURY

BY

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The association of asthma with disease of or pressure on areas of the nasal mucosa has been recognized for many years, and has often been made the basis of anti-asthmatic treatment. The importance of nasal pathology is, however, now much debated, and an authority has stated that "physicians nowadays are beginning to realize that it is only a minor cause in some cases and a major secondary effect in a majority of adults" (Bray, 1931). The importance of trauma in this respect has not been stressed, and as it may at times appear to play a part—not merely minor or secondary, but actually a sole part—in the production of asthma, the following two cases may be of interest.

Case I

The patient, a messenger girl aged 17, had been exceptionally healthy, without chest trouble of any kind, urticaria, migraine, or other allergic manifestations. The family history was similarly free. On June 27, 1932, she was flung from her bicycle, and her head struck the ground violently. She was admitted to Exmouth Hospital, where on examination she was found unconscious, with stertorous respiration, pupils dilated and non-reactant, and limbs flaccid, with occasional spasms. There was a tri-radiate wound, the largest limb of which extended upwards and to the left from the nasion for a distance of three inches, exposing the frontal bone. There was extensive bruising of the face, with haematomata of both orbits. There were also abrasions of hands, knees, and shins. The head wound was cleaned and dressed without suture. For five days the patient's condition appeared grave. Symptoms of cerebral concussion and irritation then disappeared rapidly, the wound closed, and in three weeks she was discharged at her own request. As the facial swelling subsided it was seen that there had been a fracture of the bones of the nose, with lateral displacement of moderate degree. This was not treated. She continued to attend as an out-patient, and appeared to have made a good recovery. There were no symptoms of chest trouble.

On August 7, 1932, she suddenly developed spasmodic dyspnoea of expiratory type, asthmatic in character, very severe, and relieved by adrenaline. Attacks of this kind continued in spite of treatment on usual medical lines, with local nebulae. Protein-sensitivity tests gave no result. In November she was referred to a hospital nose and throat department, where it was reported that there was deflection of the septum and scarring, definitely due to the accident, but that in view of the patient's chest condition operation was not advised. The asthmatic condition continued for a further period of sixteen months, with some improvement in the summer of 1933, but with prolonged attacks of great severity. The patient became kyphotic, dyspnoeic, and cyanosed, instead of stalwart and upstanding, with the clear colour that is often seen in the red-haired. She was quite unable to work, in spite of courses of vaccine and peptone treatment and breathing exercises.

In March, 1934, operation for resection of the septum was performed. The immediate effect of this was to some extent disappointing. Nasal obstruction was relieved, but the asthma continued, slowly diminishing in severity until May, 1935, since when the patient has had no attacks. Treatment of any kind ceased in February, 1935.

Case II

A retired lieutenant-commander, aged 40 and unmarried, had a history free from any chest trouble or allergic manifestation. The family history was similarly free. On August