No. 16.—L., aged 20. Pain in chest; cough. Temperature 101° each night for three weeks. Signs of pleural effusion; confirmed by exploratory needle. Complement fixation test negative on November 2nd, 1920. *Post-mortem* examination six weeks after above test showed malignant growth in left lung and effusion into pleural cavity. Primary growth in ovary.

No. 17.—G. H., war pensioner. Cough; sputum; pain in chest. Stated he coughed up four pints of blood in April, 1920. Weight 8 st. 3 lb. Sputum negative. No crepitations. Complement fixation test negative on December 1st, 1920. *Re-examination*: Pain in abdomen after food. No crepitations. Weight 8 st. 4 lb. Sputum negative. Complement fixation test negative on October 5th, 1921.

No. 18.—S. Cough; sputum; pain in back. Debility six months. Sputum negative four times. No crepitations. Complement fixation test negative on July 14th, 1920. *Re-examination*: No fresh symptoms. Has been at work since last seen. Complement fixation test weakly positive on June 4th, 1921. Examination of sputum seven months later positive. Brother died of pulmonary tuberculosis in October, 1921. Contact. Complement fixation test strongly positive on February 11th, 1922.

No. 19.—E. W. Cough; sputum. Haemoptysis (streaks) in May, 1920. Loss of weight; feels ill. Temperature 99.6°. Weight 8 st. 5 lb. Sputum negative. Complement fixation test negative on September 27th, 1920. *Re-examination*: Feels well; no cough. Weight 8 st. 5 lb. Temperature 98°. No crepitations. Complement fixation test negative on November 8th, 1921.

No. 20.—T. P. Cough; sputum; dyspnoea. Weight 8 st. 4 lb. No crepitations. Sputum negative. Complement fixation test negative on September 24th, 1920. *Re-examination*: Feels better; still has dyspnoea. Weight 9 st. 3 lb. No crepitations. Complement fixation test negative on April 22nd, 1921.

Comments.

A study of the above cases will show that the clinical condition at the time of the first test justified a strong suspicion of pulmonary tuberculosis. In all of them some combination of cough, sputum, fatigue, loss of weight, pyrexia, haemoptysis, and pain in the chest was present—in fact all the common symptoms of pulmonary tuberculosis. The frequency of haemoptysis is a striking feature.

A study of the re-examination notes will show an absence of any further evidence of the disease some ten to twenty months later. The too frequent absence of sputum reports when the patients were re-examined is due to the absence of any sputum. In no case did apical crepitations appear at the later examination, and almost all cases were examined by post-graduates as well as the writers. No. 18 had a weak positive complement fixation test at the re-examination, and the sputum was found positive seven months after the positive complement fixation test; but he had been a "contact" till four months after the second test was taken when his brother died, so the infection may have occurred between the first and second tests. Many patients had regained their normal health, some had improved, and others were unchanged. Two of the fifty cases died, and *post-mortem* examinations showed malignant growths of the lung or pleura as the cause of death. After the lapse of ten to twenty months or even longer forty-nine had not developed any definite evidence of pulmonary tuberculosis, nor, with a few exceptions, were they even under treatment.

It is the absence of the development of any more definite evidence of tuberculous infection in all but one of these suspicious cases in the course of ten to twenty months afterwards that would appear to us to offer striking evidence in favour of the accuracy of the test and to demonstrate its value in the exclusion of active pulmonary tuberculosis.

We wish to thank the Lady Almoner of the Brompton Hospital for her valuable help in tracing the patients.

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At a meeting of the Manchester Pathological Society on February 8th, with Mr. Howson Ray in the chair, Dr. J. A. Murray, Director of the Cancer Research Fund, demonstrated the pathological anatomy of experimentally induced squamous carcinoma of the skin of the mouse following repeated and long-continued application of coal tar. Lantern slides were shown illustrating the growth of the tumours, their metastases and dissemination, and the invasion of the subjacent tissues. Reference was made to the application of autoplasmic implantation of tumour fragments to bring out the powers of growth of the altered epithelium when removed from the direct irritating influence of the tar and of bacterial infection. By this method of artificial metastasis it was possible to demonstrate the malignancy of growths at a very early period. The relative advantages were discussed of other successful methods of inducing cancerous changes.

D

EVIDENCE OF PANCREATIC DISORDER IN RICKETS.*

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MANY observers have been working on the factors concerned in the production of rickets, and recently special prominence has been given to the view that the problem is intimately bound up with the question of diet, more especially with the amount and quality of the fats. It is urged also that carbohydrates play an important part, but as to the explanation of these two facts there is still considerable difference of opinion.

The well-known vitamin deficiency theory ascribes the production of rickets to a lack of the vitamin A, which is fat-soluble; but with regard to the carbohydrate part of the problem, no observer seems to have given a satisfactory explanation. In this communication the importance of both fats and carbohydrates is taken into account, but the conclusions to be drawn from the investigations made point in a different direction. As a result of the examination of cases of acute rickets in children, distinct evidence was found of pancreatic disorder, as determined by an increase (1) in urinary diastase, and (2) in faecal fat content.

1. The Diastatic Power of the Urine.

By means of its diastatic enzyme normal urine is able to hydrolyse starch solution to a mixture of products which give no colour with iodine solution. Wohlgemuth expressed this property of urine quantitatively by means of "units," the number of units of diastase being given by the number of cubic centimetres of 0.1 per cent. starch solution digested by 1 c.cm. of urine.

Method.

The usual method is to put up a series of test tubes, each being filled as follows:

Test tubes:	1.	2.	3.	4.	...	12.
Starch 0.1%	2 c.cm.	2 c.cm.	2 c.cm.	2 c.cm.	...	2 c.cm.
Urine ...	0.3 c.cm.	0.2 c.cm.	0.1 c.cm.	0.09 c.cm.	...	0.01 c.cm.
Saline...	0.7 c.cm.	0.8 c.cm.	0.9 c.cm.	1 c.cm.	...	1 c.cm.

The starch solution is put in first, then the urine, and the saline is run in last, in order to wash the first two down to the bottom of the tube.

The tubes are incubated in a water bath at 37° C. for half an hour, are then cooled under tap water, and enough N/50 iodine solution to produce a permanent colour is added to each tube. The tube immediately preceding one with a mauve tint is taken as that in which the 2 c.cm. of starch solution is just digested by the urine. Suppose 0.1 c.cm. of urine digests 2 c.cm. of starch solution, then 1 c.cm. of urine would digest 20 c.cm. of starch solution—that is, there would be 20 units of diastase present.

Towards the end of this series of diastase reactions, I modified the original method so as to take into account the hydrogen-ion concentration of the urine. The diastatic enzyme works best at a hydrogen-ion concentration of pH 6.1 (Michaelis), and since the pH of the urine varies normally between pH 4.5 to pH 7 it is obvious that unless the reaction of the urine is pH 6.1, the diastatic power will be decreased. The newer technique is to bring the urine's hydrogen-ion concentration to approximately pH 6.1 by diluting it with a buffer solution of phosphates and then determining the diastase as in the ordinary method. A description of this method will be given elsewhere, but it should be pointed out that it can only increase a low reading of the ordinary method, and can never decrease it.

The normal number of diastatic units in urine lies between 6 and 30. Any increase is said to indicate pancreatitis, with the possible exception of cases of eclampsia, in which the diastatic power is said to be high.

In Table I are given the figures from a series of cases of acute rickets; all are high enough to warrant a diagnosis of pancreatitis. The mean of 17 cases is 154 diastatic units.

These results were controlled by the examination of a series of normal children of about the same age as the rickety cases; as will be seen from Table III, the results were all low. As some observers maintain that there is a general infection in rickets, series of septic cases showing no rickets, and with and without fever, were examined (Table III). It was also thought advisable to make control observations on a series of cases where there was bone erosion (Table III).

* A report to the Medical Research Council.

All these cases gave low results. The diastase was found to be higher than normal in three cases of acute osteomyelitis—namely, 66, 50, 66 units—but this was very much below the mean of the rickety cases, which was 154. Convalescent cases of rickets, as will be seen from Table II, did not show this high diastatic power. They gave an average of 14.5 units.

TABLE I.—*Acute Rickets (17 Cases).*

Age.	Sex.	Diastase.	Fat in Faeces per Cent.	Age.	Sex.	Diastase.	Fat in Faeces per Cent.
2	M	100	65	2	F	150	78
3	M	200	80	4½	F	70	50
3	M	200	89	2	M	200	90
9/12	F	200	90	9/12	F	150	79
1	M	100	70	1	M	100	89
2	M	150	80	1½	F	100	60
2½	M	200	60	2	M	200	65
4	F	150	70	4	M	150	78
3	M	200	80				

Total diastatic units ... 2520. Mean ... 154.
Total fat in faeces per cent. ... 1273. Mean ... 75.

TABLE II.—*Rickets, Subacute or after Treatment (8 Cases).*

Diastase.	Fat in Faeces per Cent.	Remarks.
10	20	No. 1 in Table I, six months after.
25	25	No. 2 in Table I, six months after.
33	56	No. 3 in Table I, three months after.
7	25	No. 4 in Table I, two months after.
7	20	No. 5 in Table I, two months after.
7	28	No. 7 in Table I, twelve months after.
22	38	After six months' treatment.
20	30	After three months' treatment.

TABLE III.—*Controls for Diastase and Fat in Faeces.*

Condition of Cases.	No of Cases Investigated.	Average Diastase.	Average Fat in Faeces per Cent.
Normal children ...	10	16	20
Septic cases, with no fever ...	6	20	22
Septic cases, with fever ...	7	13	—
Bone erosion, mainly new growth involving bone	9	10	—

2. The Fat Content of the Faeces.

Normal dry faeces contain 25 per cent. of fat by weight at a maximum. Any increase above this is usually regarded as pathological. If the increase consists mainly of unsplit fats it is assumed that the pancreatic lipase is at fault, and pancreatitis is suspected. It is, of course, essential that there be no great increase in the fat diet, otherwise the high faecal fat content might be explained by a simple passage through the intestines of an excess of fat in the diet.

The rickety cases investigated were on ordinary diet, and the faeces were collected and dried very carefully. The fat content was then estimated by means of the Schmidt-Werner process. Table I shows that in all the faeces obtained from cases of acute rickets the fat content was greatly increased—a mean of 75 per cent. against the normal of 25 per cent.

Controls.—This result was controlled by examining a series of non-rickety children of about the same age and on the same diet; it will be seen from Table III that all the readings were low—an average of 20 per cent. As in the case of the diastase reactions, convalescent cases did not show this high faecal fat content (Table II).

3. Acidosis in Rickets.

The urine of 10 cases of acute rickets was examined for acetone bodies, and it was found that 9 cases gave quite a

strongly positive Rothera's test. The other case only gave a very faint pink colour. Of the 9 cases, 6 gave a very faint ferric chloride test for aceto-acetic acid, but both the Rothera and ferric chloride tests became negative after a few weeks of treatment.

In a recent article Dr. Amy Hodgson² reported the results of a detailed analysis of the urine of 13 children with active rickets; she found marked evidence of an acidosis, as determined by the ammonia ratio—that is:

NH₃ per cent.
N₂ per cent.

The mean of her 13 cases was 14.3 per cent., as compared with 6.2 per cent. for a series of normal healthy children.

Without entering into a discussion of the exact pathology of the acidosis frequently found in children, it seems clear from these observations that rickets must be added to the list of diseases in which it occurs.

Consideration of Results.

The results obtained—namely, a high diastatic power of the urine and a high faecal fat content—suggest a diagnosis of a pancreatic lesion. The large amount of unsplit fat in the faeces shows that it must be associated with reduced secretion of pancreatic juice. Exactly what bearing these facts have upon the pathology of rickets it is difficult at first sight to say.

It has been taught for some long time past that the fatty acids, when liberated from the neutral fats by the action of the pancreatic lipase, form soaps with the metallic bases, especially with calcium; the resulting calcium soap, being soluble in bile, is absorbed. If this is the most important mode of calcium absorption, the importance of inadequate pancreatic secretion at once becomes obvious, because there would be poor fat digestion and, consequently, poor production of fatty acids. This would lead to deficient calcium absorption, and therefore to calcium starvation, which has been stated to occur in rickets.

This theory is being tested by noticing the effect of fatty acids on calcium absorption, both in rickety and in normal children. The experiments are in too early a stage yet to warrant a definite statement being made. Since there is a deficiency of pancreatic secretion a new line of treatment suggests itself—namely, that of giving a pancreatic extract which contains lipase. A number of cases are now being treated with this extract in the hopes that it will digest fats in the intestine, and thereby give an adequate amount of free fatty acids for the absorption of calcium.

It is interesting to note that in German cases have been treated with calcium soaps of fatty acids.³ The scientific basis of this mode of treatment was not stated, but the views put forward in this paper seem to offer an explanation.

It is quite likely that this pancreatic lesion is the result of an intoxication, probably bacterial in origin. Investigations are now in progress to determine, if possible, the source of the intoxication and infection.

In conclusion, I have to express my thanks for much very valuable advice and criticism from Professor McIntosh and Dr. E. L. Kennaway, and also to acknowledge the kindness of the surgeons of the Royal National Orthopaedic Hospital for allowing me to investigate their cases.

Summary.

1. The diastatic power of the urine is greatly increased in rickets, the mean of 17 cases being 154.
2. The diastatic power falls to normal during convalescence.
3. The fat in the faeces is increased in rickets, the mean being 75 per cent., as compared with 20 per cent. for a series of non-rickety children.
4. From the above observations it is suggested that there is a pancreatic lesion in rickets, and a possible explanation of its bearing on the disease is given—namely, that there is a poor production of fatty acids, and consequently a poor absorption of calcium.
5. Attention is called to the acidosis of rickets.
6. In consideration of the above results cases of rickets are being treated with pancreatic extract containing lipase.

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