The natural history of this condition is that of a defect of maturation. The disability shows neither the intermittency and tendency to recurrence of the emotionally determined speech difficulty such as stammering nor the rapid response to treatment with which we are familiar in those cases of temporary consonant substitution to which we have limited our use of the term "dyslalia." In our view the lesion in developmental dysarthria is analogous to that of spastic diplegia in nature if not in situation. The site of the lesion is problematical. It is certainly suprabulbar, and would seem to depend on a focal cerebral dysgenesis essentially similar to but more limited in extent than that with which we are familiar in spastic diplegia. It is for these reasons that we have adopted the term "developmental dysarthria," first suggested to us by Dr. C. Worster Drought (personal communication, 1952), to describe these cases and as the title of the present paper.

Diagnosis

Developmental dysarthria must be separated on the one hand from the dysarthria of cerebral palsy, and on the other from severe dyslalia. Where the dysarthria is part of a persisting minimal spastic diplegia recognition requires nothing more than careful physical examination. The differentiation of developmental dysarthria from the group of articulatory defects for which we reserve the term "dyslalia" is, however, not always easy and may be impossible without testing the response to treatment; but in most instances the distinction can be made on the basis of a careful history and examination.

In developmental dysarthria speech is slow and clumsy and, in severe examples, punctuated by explosive words and phrases. The child is unable to imitate speech quickly and easily, and the chief defect of pronunciation is omission with or without substitution of consonants. Many such children show the characteristic appearances and defective movements of tongue and palate already described and identical with those seen in cerebral palsy. In some children, however, the movements are apparently normal except when the muscles are used in articulation. The specific clumsiness evident under such circumstances appears to depend on a disturbance of function, an articulatory dyspraxia, arising at a higher level of the nervous system than is involved in cases where neuromuscular function is visibly abnormal. In a considerable proportion of dysarthric children there is also a history of slow development of language and a poor vocabulary with persisting difficulty in reading.

In the child with severe dyslalia, on the other hand, language develops at the normal time and speech is fluent even if unintelligible. There is no abnormality in the movements of the lips, tongue, or palate, and the defect of pronunciation is largely one of multiple consonant substitutions. The most striking difference between the two conditions lies in the response to treatment. Whereas in dysarthria recovery is slow, in dyslalia normal speech should be reached within three to twelve months from the start of consistent treatment. That these two broad groups of articulatory defects exist is obvious in everyday experience, and, whereas developmental dysarthria is structurally determined, dyslalia would appear to be a functional disorder of speech which responds quickly to guidance and treatment.

Summary

Within the general context of dysarthria in childhood we wish to draw attention to a group of children in whom dysarthria is unassociated with any neuromuscular abnormality elsewhere. The clinical features suggest that this is a structurally determined condition, for which the term "developmental dysarthria" would be fitting.

We have seen a smaller number of children also covered by this term in whom we suspect that the defect is essentially an articulatory dyspraxia.

The condition may or may not be associated with delayed development of language and difficulty in reading.

The outlook varies with the severity of the defect and the intelligence of the child; response to consistent treatment is usually slow, and occasionally the difficulty persists into adult life.

We value the opportunity which our colleagues have given us to study these children, and would like to express our thanks to Sir James Spence for his encouragement and advice. We are also grateful to Mr. R. F. Garside, of the department of psychological medicine, who assessed the children's mental development

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ESTIMATION OF INTRINSIC FACTOR OF CASTLE BY USE OF RADIOACTIVE VITAMIN B_{12}

BY

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Pernicious anaemia is attributed to the failure of absorption of vitamin B_{12} in the absence of the secretion by the stomach of the substance known as intrinsic factor (Castle, 1951). The preparation of pure vitamin B_{12} labelled with radioactive cobalt (Co^{60}) (Chaiet, Rosenblum, and Woodbury, 1950) presented a method of assessing the absorption of orally administered vitamin B_{12} and thus of detecting intrinsic factor activity. Heinle and his colleagues (1952) estimated the radioactivity appearing in the faeces after an oral dose of 0.5 μg. of radioactive vitamin B_{12}. They found that between 72 and 96% of the radioactivity in this test dose was recovered from the faeces of four patients with pernicious anaemia unless a source of intrinsic factor was given simultaneously, when the recovery was less than 30%. In two normal subjects on three occasions they recovered no radioactivity, but on one occasion in one subject, when he was convalescing from pneumonia, 42% was recovered. A. D. Welch (1952, personal communication) indicated the difficulties encountered in these early experiments owing to the low specific activity (60 μc./mg.) of the radioactive vitamin B_{12} used.

Using radioactive vitamin B_{12} of higher specific activity (245 μc./mg.), Meyer (1953) recovered from the faeces between 89 and 99% of a 1-μg. test dose in four patients with pernicious anaemia and between 15 and 59% in seven control subjects. Significant reduction in the recovery of radioactivity, however, did not occur consistently when a source of intrinsic factor was given with the radioactive vitamin B_{12}.

The preparation by Lester Smith (1952) of radioactive vitamin B_{12} of high specific activity (420 μc./mg.) has enabled us to extend these experiments.

*In receipt of a British Council Scholarship.

Method

Vitamin B_{12} labelled with radioactive cobalt (Co^{60}) was given to a group of control patients with normal haematological findings and to patients with pernicious anaemia, and the radioactivity appearing in the faeces was measured.

A standard dose of 0.5 μg. of radioactive vitamin B_{12} containing approximately 0.2 μc. of radioactivity was given by mouth in about 100 ml. of water. No food was allowed after 10 p.m. on the previous evening and for two hours after the dose had been taken, but the patient was allowed one cup of tea first thing in the morning (at least two hours before the dose was given); apart from this the patient took a normal diet. The stools were passed direct into glass containers and were collected until at least one contained less than 1% of the radioactivity of the test dose. No aperients were allowed for 24 hours before or after the test dose. Repeated tests were made on most of the patients in order to diminish the possibility of error due to incomplete collection of the stools. If this was suspected the test was discounted.

Each stool specimen was transferred quantitatively to a domestic electric mixer with enough water to allow the faeces to be blended to a uniform homogeneous suspension, which was then transferred quantitatively to a beaker and weighed. After further mixing an aliquot was transferred to a stoppered glass bottle and set aside for estimation of the contained radioactivity.

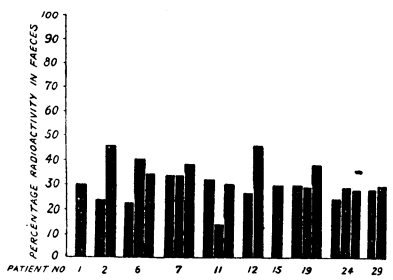

FIG. 1.—Recovery of radioactivity from faeces after an oral dose of 0.5 μg. of radioactive vitamin B_{12} in 10 control patients.

The radioactivity of the specimens was estimated by means of a scintillation counter comprising a crystal of sodium iodide 2½ in. (6.3 cm.) in diameter and a photomultiplier and scaling unit supplied by A.E.R.E., Harwell. Each specimen was weighed out into a 30 by 50 mm. glass weighing - bottle, which was stood on a thin brass tray over the crystal. The tray had raised edges, which ensured that each bottle was held in the same place.

Counting was carried out with a photomultiplier voltage of 2 kV and a discriminator bias of 12 volts. Under these conditions background counts of between 120 and 160 a minute were obtained, the efficiency of the counter for Co^{60} being approximately 8%. It was found that the empty weighing-bottles gave counts of 10 to 30 a minute above background, and so each bottle was first counted empty to obtain the true background.

Then 50 g. of each of the faecal suspensions was weighed out in duplicate and the radioactivity counted. Since the specific gravity of the stools is approximately one, differences in volume were negligible. The counts obtained with the specimens were compared with that of 50 ml. of a standard solution containing one-tenth of a test dose. Each specimen was counted in duplicate for five minutes and an average taken of the two results. If, however, these differed by more than 2% (when expressed as a percentage of the total dose administered) further aliquots were counted.

TABLE I.—*Radioactivity in Faeces After Oral Dose* (0.5 μg.) *of Radioactive Vitamin* B_{12} *in* 10 *Control Subjects*

Patient	Age	Sex	Diagnosis	Date	Total Radioactivity in Faeces as Percentage of Dose
1	46	F	Benign hypertension	4/11/52	30
2	64	M	Duodenal ulcer	18/11/52	24
				7/4/53	45
				13/4/53	60*
6	57	F	Fractured neck of femur	7/1/53	22
				16/1/53	40
				23/1/53	34
7	65	F	Fractured neck of femur Hypochromic anaemia Mild senile parkinsonism	7/1/53	34
				16/1/53	34
				23/1/53	38
11	78	F	Fractured neck of femur Mild cerebral arterio-sclerosis	6/2/53	32
				16/2/53	14
				27/2/53	30
12	82	F	Fractured neck of femur Osteoarthritis of hips	6/2/53	26
				10/3/53	45
15	65	F	Peripheral neuritis	3/3/53	30
19	45	M	Duodenal ulcer	28/2/53	30
				9/3/53	29
				16/3/53	37
24	50	F	Benign hypertension	21/3/53	25
				31/3/53	29
				8/4/53	28
29	56	M	Gastric ulcer	14/4/53	28
				20/4/53	30

* See text.

Results

Normals

Radioactive vitamin B_{12} was given to 10 patients who were in hospital for various complaints but who were considered to be haematologically normal, except for patient No. 7, who had a moderate hypochromic anaemia (haemoglobin 9.8 g.%) following the nailing of a fractured femoral neck and who was receiving ferrous sulphate. These patients were mostly in the same age group as our patients with pernicious anaemia. Their diagnoses and the results obtained with radioactive vitamin B_{12} are shown in Table I and Fig. 1.

These results show that in the normal patient between 20 and 40% of the radioactivity in a test dose of 0.5 μg. of radioactive vitamin B_{12} usually appears in the faeces. In the third test on patient No. 2 the recovery was 60%. He was at the time suffering from an upper respiratory infection. Recoveries of between 45 and 60% have also been

TABLE II.—*Radioactivity in Faeces After Oral Dose* (0.5 μg.) *of Radioactive Vitamin* B_{12} *in* 13 *Patients with Pernicious Anaemia*

Patient	Age	Sex	Duration of Disease	Date	Total Radioactivity in Faeces as Percentage of Dose
4	62	F	2 years	29/11/52	90
				30/12/52	95
				12/1/53	91
	55	F	19 ,,	31/12/52	87
				13/1/53	86
				16/2/53	90
8	66	M	27 ,,	10/1/53	92
				21/1/53	91
				6/2/53	99
13	69	M	2½ ,,	7/2/53	92
				16/5/53	76
16	80	F	21 ,,	17/2/53	95
				9/3/53	91
20	67	F	3 months	6/3/53	84
				12/3/53	79
21	72	F	19 years	10/3/53	86
				1/4/53	98
22	76	M	17 ,,	17/3/53	85
				31/3/53	79
				7/4/53	81
23	61	M	2 ,,	20/3/53	81
				7/4/53	79
28	70	M	3 ,,	10/4/53	79
				4/5/53	99
				11/5/53	101
30	74	F	1 year	28/4/53	95
				27/5/53	91
31	73	F	12 years	8/5/53	90
32	60	M	19 ,,	26/4/53	90

obtained in four other patients during the course of infections. It seems that infections interfere with the test, and we have therefore excluded from the figures the results of the third test on No. 2.

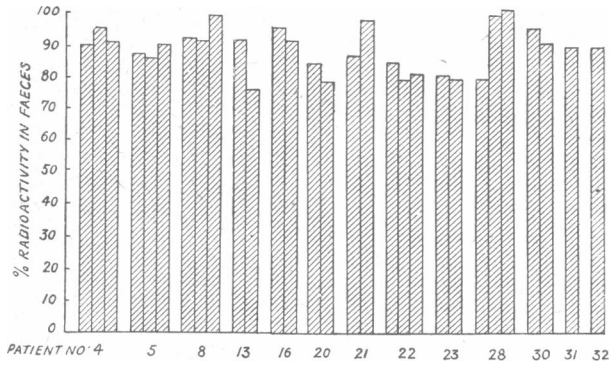

FIG. 2.—Recovery of radioactivity from faeces after an oral dose of 0.5 μg. of radioactive vitamin B_{12} in 13 patients with pernicious anaemia.

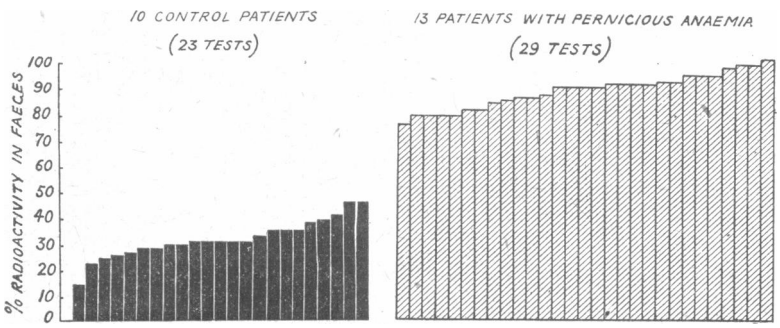

FIG. 3.—Comparison of recoveries of radioactivity from faeces after oral doses of 0.5 μg. of radioactive vitamin B_{12} in 10 control patients and 13 patients with pernicious anaemia.

TABLE III.—*Effect on the Recovery of Radioactivity from the Faeces of Giving a Source of Intrinsic Factor with an Oral Dose of Radioactive Vitamin B_{12} in Eight Patients with Pernicious Anaemia*

Patient	Date	Material Given	Total Radioactivity in Faeces as Percentage of Dose of B_{12} Given
20	6/3/53	0·5 μg. B_{12}	84
	12/3/53	,,	79
	18/3/53	,, and 100 ml. human gastric juice (Pool A)	34
	24/3/53	,, ,, ,, ,,	32
22	17/3/53	,,	85
	24/3/53	,, ,, ,, (Pool B)	59
	31/3/53	,,	79
	7/4/53	,,	81
	14/4/53	,, ,, ,, (Pool C)	54
23	20/3/53	,,	81
	27/3/53	,, ,, ,, (Pool B)	57
	7/4/53	,,	79
	14/4/53	,, ,, ,, (Pool C)	52
13	7/2/53	,,	92
	14/2/53	,, and 100 ml. gastric mucosal extract (T2)	53
	21/2/53	,, ,, ,, (T4)	43
	16/5/53	,,	76
21	10/3/53	,,	86
	10/4/53	,, ,, ,, (T7)	44
	1/5/53	,,	98
30	28/4/53	,,	95
	18/5/53	,, and 10 mg. " fraction B "	60
	27/5/53	,,	91
31	8/5/53	,,	90
	15/5/53	,, ,, ,, ,,	49
32	26/4/53	,,	90
	27/5/53	,, ,, ,, ,,	66

Pernicious Anaemia

Radioactive vitamin B_{12} was given to 13 patients who had had classical pernicious anaemia for various periods. All except patients Nos. 4 and 20 were in good remission under treatment with vitamin B_{12} (" cytamen "). Nos. 4 and 20 have both responded excellently to injections of vitamin B_{12} started after their first test with radioactive vitamin B_{12} had been completed.

The results obtained are shown in Table II and Fig. 2. In these patients between 76 and 101% of the radioactivity in the test dose was recovered from the faeces. Fig. 3 summarizes the results obtained in the normal patients and those with pernicious anaemia.

It might be argued that the apparent failure of absorption of the radioactive vitamin B_{12} in these treated patients with pernicious anaemia was due to their tissues being saturated with vitamin B_{12}. The test was therefore repeated, giving a source of intrinsic factor together with the vitamin B_{12}. Patients Nos. 20, 22, and 23 received radioactive vitamin B_{12} mixed with 100 ml. of pooled neutralized normal human gastric juice. Nos. 13 and 21 received as their source of intrinsic factor watery extracts of gastric mucosa. Nos. 30, 31, and 32 were given radioactive vitamin B_{12} with 10 mg. of an ammonium-sulphate-precipitated fraction of hog stomach mucosa (" fraction B ") prepared by the method of Prusoff *et al.* (1950).

The results of these experiments are shown in Table III and Fig. 4. It will be seen that the amount of radioactivity recovered from the faeces was diminished whenever a source of intrinsic factor was given, although it seems that the various preparations differed in potency.

Discussion

Our results confirm those of Heinle and his colleagues (1952) in that we find that there is a gross difference between the percentage of radioactivity of 0.5 μg. of labelled vitamin B_{12} recovered from the faeces in normal subjects and in patients with pernicious anaemia. However, the addition of preparations containing intrinsic factor to the test dose reduced the faecal recovery of radioactivity considerably less than in their experiments. This difference is probably in part due to the greater accuracy resulting from the use of radioactive vitamin B_{12} of higher specific activity, and in part to variations in potency of the sources of intrinsic factor.

It is interesting that even the normal subjects in our series did not absorb completely this small amount of vitamin B_{12}. It must be emphasized that it is the Co^{60} which is being estimated, and that this is not necessarily still in a molecule

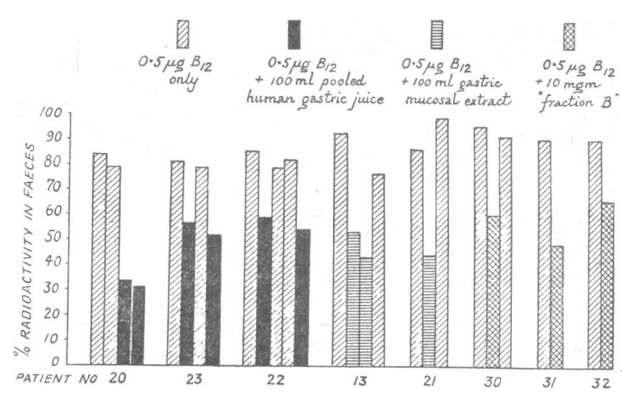

FIG. 4.—Effect on recovery of radioactivity from faeces of giving a source of intrinsic factor with an oral dose of 0.5 μg. of radioactive vitamin B_{12} in eight patients with pernicious anaemia.

of vitamin B_{12}. Moreover, if some vitamin B_{12} is destroyed in the gastro-intestinal tract with the liberation of free ions of cobalt, it is possible that some of the latter might be absorbed as such.

Some of our patients with pernicious anaemia seem to have absorbed a fraction of the radioactive vitamin B_{12}, and this may indicate, as Goldhamer (1936) first suggested, that some patients with pernicious anaemia secrete traces of intrinsic factor. The significance of our figures depends chiefly on the accuracy of the stool collections. Experience in this department with radioactive iron (Fe^{59}), which was given by mouth and recovered from the red blood corpuscles and from the faeces, supports the view that incompleteness of stool collection is unlikely to account for all the radioactivity which was not recovered.

It appears that this technique offers a simple measure of intrinsic factor activity in the patient, and that it may also be used to assay preparations for their content of intrinsic factor. It has many advantages over the clinical assay, which requires patients with pernicious anaemia in relapse, but it has the disadvantage that it is an indirect test which depends on the absorptive power of the gastro-intestinal tract at the time at which the test dose is given. Preliminary evidence of the effect of infections suggests that the absorption of vitamin B_{12} is easily interfered with in the normal subject. Further investigation of this point is in progress.

Summary

The absorption of vitamin B_{12} has been assessed by measuring the radioactivity in the faeces after an oral dose of 0.5 μg. of vitamin B_{12} labelled with Co^{60}.

In 10 patients with normal haematological findings a mean of 31.0% (standard deviation, 6.9%) of the radioactivity in the test dose was recovered from the faeces. In 13 patients with pernicious anaemia a mean of 88.7% (standard deviation, 6.8%) was recovered.

Sources of intrinsic factor given with radioactive vitamin B_{12} to patients with pernicious anaemia reduced greatly the percentage of the test dose recovered.

It is a pleasure to express our thanks to Professor L. J. Witts for allowing us to study patients under his care and for his constant help and encouragement; Dr. L. Z. Cosin for allowing us to study patients under his care in the Cowley Road Hospital; Dr. Lester Smith, of Glaxo, Ltd., for supplies of radioactive vitamin B_{12}; Dr. Arnold Welch for the "fraction B"; Dr. W. B. Taylor for the gastric mucosal extracts; Mr. Ray Oliver for advice and assistance in the radioactivity measurements; Dr. John Badenoch for help and advice; and Miss Barbara Hunt for technical assistance. This work was in part supported by a grant to Professor L. J. Witts from the Medical Research Council.

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The World Health Organization has recently issued the report of the discussion at the third European Seminar for Sanitary Engineers which was held in London from October 27 to November 1, 1952. The book is entitled *Design and Operation of Septic Tanks*, and among topics discussed are the treatment of small sewage plants, the design of small sewage works, and comparative studies of septic tanks. It is published in the Monograph Series (No. 18), price 7s. 6d., and is obtainable through H.M. Stationery Office, London, or direct from the Sales Section, Palais des Nations, Geneva.

RESEARCHES IN AETIOLOGY OF NON-SPECIFIC URETHRITIS*

BY

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General Observations

Non-specific urethritis (N.S.U.) is one of the most perplexing conditions encountered in the British venereal diseases clinic to-day. When complicated by Reiter's syndrome its disabling powers are considerable. In the clinics of England and Wales in 1951 there were 10,794 cases of non-specific urethritis, as compared with 14,975 male cases of gonorrhoea.

Although the condition is usually acquired venereally in the male, it is possible that the female may on occasion be infected non-venereally, which would explain the slight non-venereal bias. Thus in 100 cases of gonorrhoea the last sexual risk had been a casual exposure in 60%, whereas in 100 cases of non-specific urethritis the comparable figure was only 40%. Also, of 640 subjects of non-specific urethritis studied 35.3% were married, whereas of 603 male subjects of gonorrhoea only 25% were married. Persons suffering from non-specific urethritis were of slightly older age groups than those with gonorrhoea, and more likely to be in a "white collar" occupation—both observations perhaps being reflections of the marital status.

Some observers (for example, Coutts of Chile) have suggested that the practice of oral and/or anal coitus may frequently be responsible for the transmission of non-specific urethritis. This would not appear to be the case in Great Britain, for such practices were admitted by only 6% of 50 patients with non-specific urethritis so questioned, as against 9% of 100 other patients attending the venereal diseases clinic during the same period.

The incubation period of non-specific urethritis is often longer than that of gonorrhoea. Of two groups, each of 150 cases, 52% of patients with non-specific urethritis had incubation periods of over seven days, as compared with only 32% (in itself a high figure) in the case of patients with gonorrhoea.

Ignoring established rare causes, the following have variously been regarded as possibly responsible for the bulk of cases: (1) bacteria; (2) pleuropneumonia-like organisms; (3) trichomonads; (4) spirochaetes; and (5) a virus. This study was limited mainly to a consideration of bacterial and viral causes.

Bacterial Urethritis

It has for some time been fashionable to divide non-specific urethritis into bacterial and abacterial urethritis, depending on whether bacteria are seen in the urethral smears. Some 301 urethral cultures were made at King Edward VII Hospital, Windsor (pathologist, E. Sayle), on consecutive patients with non-specific urethritis, before and after treatment with the orally administered antibiotics, and on controls. As a result it is considered that "bacterial urethritis" is not a common entity and that the bacteria found are usually commensals (Table I).

*Being a summary of the report presented to the British Medical Association at the conclusion of the term of office as Insole Research Scholar.