Apart from some small haemorrhages in the pericardium and upper ileum and conspicuous reactive changes in the upper abdominal lymph nodes, there were no important changes in other organs.

Discussion

The clinical picture—a febrile illness followed by jaundice, with a relapsing course—is strongly suggestive of virus hepatitis. The necropsy and histological findings are those of liver scarring and regeneration following parenchymal cell loss, and are compatible with a viral aetiology (Lucké, 1944). A toxic origin would appear to be excluded by the negative history, and it therefore seems reasonable to regard the case as one of subacute infective hepatitis; homologous serum jaundice may give rise to identical pathological changes, but there was no story of an appropriate injection or transfusion. The changes in blood, bone marrow, and other organs leave no doubt that a severe agranulocytosis developed and was responsible for the fatal outcome. It remains to consider the possible cause of the agranulocytosis.

Drug toxicity can be excluded, for none of the drugs which are commonly responsible was administered. Barbiturates have only rarely been thought to cause granulopenia, and the single dose of pentobarbitone given can hardly be held to blame.

Overaction of the spleen is unlikely to have been present, for evidence of increased sequestration and phagocytosis of leucocytes in this organ (von Haam and Awny, 1948) is lacking; in addition, hypoplasia of the marrow is exceptional in hypersplenism. A pre-existing *chronic hypoplastic neutropenia* (Spaet and Dameshek, 1952) can be ruled out on account of the satisfactory past history.

The possibility of *hepatic failure* must be taken into account: Sherlock (1955) refers to a patient with cirrhosis in whom polymorphs were absent from the blood, returning as liver function improved. Our patient was drowsy, but in the absence of supporting evidence severe liver failure must be regarded as improbable.

Finally, a relationship with *infection* has to be considered. A similar question arises also with certain other fevers, including measles, mumps, and influenza (Whitby and Britton, 1953), in which agranulocytosis occurs as a rare complication; in each of these diseases, in common with hepatitis, a neutropenia is common in the ordinary course of the illness. Two possibilities suggest themselves: that the hepatitis virus alone may have caused the agranulocytosis, with secondary infection as a result, or that the secondary infection itself may have played some causative role. Robertson (1949) has emphasized the importance of infection in aggravating the granulopenia when marrow depression is due to drugs; he also refers to a case of glandular fever with moderate neutropenia, in which a streptococcal throat infection led to a severe drop in neutrophils, with prompt improvement after the start of penicillin treatment. In the present instance the first alternative cannot be excluded, but we suggest that the second offers a more attractive explanation—secondary infection occurring when marrow function was already depressed as a result of the virus disease, and in turn precipitating severe leucopenia. The failure of antibiotic treatment, which is usually so effective, can be attributed to the antibiotic-resistant staphylococci in the lesions, and it seems likely that these organisms were there from the earliest stages.

Summary

A case is reported of fatal agranulocytosis developing late in the course of severe hepatitis, thought to have been of viral origin. The agranulocytosis cannot be attributed to drugs, and a relationship with hypersplenism is improbable, while the presence of severe hepatic failure seems unlikely; it is suggested that it may have resulted from secondary infection occurring at a time when marrow function was already depressed as a result of the virus disease.

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GLOSSOPHARYNGEAL BREATHING

ITS VALUE IN RESPIRATORY MUSCLE PARALYSIS OF POLIOMYELITIS

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In 1951 Dail, in the U.S.A., described the mechanism of this interesting and, for the human, abnormal form of breathing as observed in a series of 15 patients. A further report by Dail, Affeldt, and Collier (1955) brought the number under observation up to 100 with a correspondingly enhanced experience and comment. Our purpose is to bring to the notice of those faced with the problem of the respiratory muscle defect in the post-acute and chronic stages of poliomyelitis the experiences of the American observers, and also to describe the results of the attainment of this aid to breathing in a few of the patients in the respiratory unit of this hospital.

Description of the Technique

Glossopharyngeal breathing was so named by Dail because of the anatomical structures which take part in the process. It has also aptly been called "gulping" and "frog-breathing" because of its similarity to the breathing mechanism of amphibians. It has been stated that the method has been used by divers to allow for longer periods of submersion and may have been spontaneously developed by some poliomyelitis patients and used for years without recognition. Dail (1951) quotes the case of a patient whom he had observed to be using his mouth and throat in what appeared to be a swallowing action, but which further observations showed to be a gulping of air trapped by the pharynx and then forced through the larynx. It was later shown that each gulp could trap from 30–60 ml. of air and that from 10–20 or more of such gulps constituted a single inspiration. Breathing could continue in this fashion for minutes or hours.

In an excellent manual of instruction for glossopharyngeal breathing (G.P.B.) prepared by Dail, Zumwalt, and Adkins (1955) a description of the mechanism, based on observations and studies of more than 100 patients and 50 normal persons who had learned the technique, is summarized as follows: "There is a stroke-like action of the tongue together with constricting action of the pharynx pumping air through the larynx. The air accumulates step-like in the lungs. Each full 'inspiration' consists normally of about 10 or more such strokes, at the end of which air is released from the lungs in a manner similar to ordinary expiration."

Each stroke is regarded as a cycle consisting of four distinct steps. These steps are illustrated and described in the accompanying illustration. We are indebted to the authors and to the editors of the *Journal of the American Medical Association* for permission to reproduce it here.

Steps taken during one "stroke" of glossopharyngeal breathing. Step 1: a mouthful and throatful of air is taken, depressing the tongue, jaw, and larynx to get maximum volume. Step 2: the lips are closed and the soft palate raised to trap the air. Step 3: the jaw, floor of the mouth, and larynx are raised. This, together with progressive motion of tongue, forces air through the opened larynx. Step 4: after as much air as possible is forced through the larynx, it is closed and the air is retained in the lungs until the cycle is reinitiated.

Application of the Technique

There are now many patients in this country who, as a result of poliomyelitis, have reduced breathing capacity. The reduction is not infrequently almost complete failure, but in most cases, even in those who have achieved only partial release from mechanical assistance, there is sufficient recovery to allow of continued existence in reasonable comfort. Where normal breathing-muscles are inadequate much of the ventilation is carried out by the accessory muscles, such as the sternocleidomastoids and platysmata, and in some cases also by the abdominal muscles, which may have escaped damage. A considerable degree of stability and absence of distress are achieved in these chronic patients even when their efforts produce small tidal exchanges and a vital capacity in many cases of less than 700 ml. (about one-fifth of normal) in the adult—in some, indeed, as low as 300 ml. However, where existence is largely dependent on such accessory muscle groups the patient must be helped by mechanical means when he becomes tired or when he needs to sleep. In many cases he can be released from mechanical aid only for brief periods daily.

While it is for those in the severely limited class that G.P.B. may be particularly useful as an aid to partial release from mechanical aids, Dail and his associates (1955) have pointed out that complete dependence on the respirator is not the only indication for its use but that G.P.B. has also a most useful application in increasing the amount of time free from the machine. In addition, it appears to have a most useful function in those who, though they no longer require a respirator, have nevertheless inadequate capacity for forceful coughing and are therefore subject to lung complications such as atelectasis.

Capacity to Learn Glossopharyngeal Breathing

The technique may be acquired spontaneously, as, for example, in efforts to remain free from the respirator, and indeed one of our patients (Case 4) developed it in this way. Another of our patients found that in efforts to increase spirometer readings she gulped extra air (Case 3). Dail and his associates (1955) state that, while some patients have

learned the technique in one lesson, others required many lessons covering a period of several months. Having acquired it, however, it was found that in the majority several weeks of practice were required to achieve improvement both in the effectiveness of the "gulp"—that is, an increase in the quantity of air trapped in the stroke—and in the endurance for continuation of G.P.B. over lengthening periods of time. These observers also stated that for the new pupil three months should usually be allowed for learning and developing G.P.B.

In Dail's series of 100 cases, G.P.B. was learned at widely varying stages of recovery following on the onset of the disease, the earliest being at two months and the latest four years after onset. Two of our cases have exceeded the latter figure, having been paralysed more than five and seven years respectively (Cases 2 and 6). Therefore the duration of paralysis, however long, does not appear to be a limiting factor in the attainment of G.P.B.; although in our small series it has appeared to us that the younger patients may be expected to have less difficulty in acquiring G.P.B. and in a shorter period than older ones. The youngest in Dail's series was 4 years old and the oldest a man of 47, and it was found that relatively few children learned the technique. About one-quarter of his 100 patients learned the method without appreciable help from others, 5 developed it spontaneously, 15 were taught by other patients, and 55 were instructed by hospital staff.

Uses of Glossopharyngeal Breathing

Dail, Affeldt, and Collier (1955) stated that benefit from use of the method cannot be claimed unless there is evidence of increase in vital capacity, and, furthermore, that the capacity to remain free from mechanical aid by the use of G.P.B. should be at least five times that without it. They mention three classes of patients who were subjects of study based on their functional disability: (a) those who were unable to be free from mechanical aids for any appreciable time without G.P.B.; (b) those who used it as an aid to spontaneous breathing and would otherwise be fatigued; and (c) respiratory cripples who used it as an aid to chest-stretching and coughing.

The volume of air propelled by each stroke in Dail's groups was measured as averaging nearly 60 ml., and he and his colleagues estimated that effective use of the method required a stroke volume equal to approximately 1% of the predicted normal vital capacity in patients with very severe respiratory defect.

Case 1 in our series (see Table) is an excellent example of almost complete dependence on G.P.B., while Case 3 fits into the category of those who use it to supplement their ordinary capacity at intervals. Cases 2, 4, and 5 are examples of those who benefit from it chiefly in the assistance it gives in coughing or chest-stretching. Case 4 uses it also to supplement his efforts when he is under stress—for example, when undergoing active physical exercises for rehabilitation.

Report of Cases

Measurements showing the effects of G.P.B. on the respiratory mechanics of 6 patients are presented in the Table. Case 6 was, however, not available for complete data.

Case 1.—Woman aged 38. The onset of poliomyelitis was in October, 1956. She has been left with almost complete quadriplegia and severe paralysis of the respiratory muscles. She commenced G.P.B. in March, 1957, and the period of freedom from mechanical respiration progressively increased, so that after one month she could remain free of mechanical aid for more than three hours. Now she can remain out of the respirator for as long as 8–10 hours continuously and without obvious fatigue. She has also learned to eat when out of the machine, and while doing so she uses the accessory muscles of respiration. Her normal vital capacity is only 200 ml., but with G.P.B. she can trap up to 1,900 ml. Each phase of maintenance G.P.B. comprises

Individual Data Showing Volume Relations Between Unassisted Breathing and Glossopharyngeal Breathing as well as the Effect of G.P.B. on Chest Expansion and "Expulsive Force"

Case	Sex and Age (Yrs.)	Vital Capacity (V.C.)		Expected V.C. (Baldwin <i>et al.</i> , 1948)	Vital Capacity as Percentage of Expected Normal		Average Volume of Each Gulp During G.P.B.	Maximum Chest Expansion				"Expulsive" Force"	
		Unassisted	Assisted with G.P.B.		Unassisted	Assisted with G.P.B.		Voluntary Breathing		Assisted with G.P.B.		Unassisted	Assisted with G.P.B.
								9th c.c.*	4th c.c.	9th c.c.	4th c.c.		
		(ml.)	(ml.)	(ml.)	(%)	(%)	(ml.)	(cm.)	(cm.)	(cm.)	(cm.)	(cm. H ₂ O)	(cm. H ₂ O)
1	F 38	200	1,900	2,889	7	64	60	-0.5†	0.2	2.7	3.0	2	15
2	M 27	550	1,800	4,380	12.5	41	40	0.3	1.7	1.0	3.0	6	16
3	F 19	600	1,850	3,098	19	60	90	0	0.5	1.5	3.0	12	20
4	M 30	550	3,500	4,344	13	80	120	0.2	0.2	5.0	1.5	4	25
5	M 36	800	1,800	4,154	19	43	25	2.0	1.0	4.0	3.0	10	19
6	F 23	350	700‡	—	—	—	—	—	—	—	—	—	—

* c.c. Costal cartilage.

† Measured by blowing into a standard testing machine for mechanical respirators (Smith-Clarke design, by Cape Engineering Co.).

‡ Paradoxical movement of the chest due to paralysis of diaphragm and lower intercostal muscles.

§ Only two hours after learning the technique.

6-8 gulps, each of approximately 60 ml., giving a tidal volume of 360-480 ml. Her glossopharyngeal breathing rate is about 14 a minute. The acquisition of G.P.B. has greatly simplified the problem of nursing and physiotherapy. She can be taken to the bath, for trips in her wheel-chair, and even for car rides.

Case 2.—Man aged 27. This patient was taught G.P.B. within three days of admission to our unit in August of this year. He has been a chronic respirator case for more than five years, relying almost entirely on accessory muscles and therefore needing a respirator to sleep. His readmission to hospital was precipitated by an ominous reduction in vital capacity to 350 ml. from the usual level of about 800 ml. His vital capacity now is only 550 ml., but after G.P.B. he can blow 1,800 ml. into the spirometer. However, it is expected that with further practice his G.P.B. efficiency will increase. At the moment he traps an average of 40 ml. per gulp.

Case 3.—Young woman aged 19. Admitted to hospital a year ago with very severe paralytic poliomyelitis. Originally treated in cabinet respirator; later weaned through cuirass and rocking bed. She has now been free from mechanical aid for approximately two months. This patient was found to have developed G.P.B. spontaneously and without consciousness of the technique. It appears that she found that in efforts to increase her spirometry readings she gulped air, and this was probably the origin of her ability for G.P.B. Her present vital capacity is only 600 ml. With G.P.B. it totals 1,850 ml., and she uses it for occasional deep breaths—for example, for coughing.

Case 4.—Man aged 30. Has had paralytic poliomyelitis for about 21 months. He developed G.P.B. spontaneously, and with it he can increase his vital capacity of 550 ml. to no less than 3,500 ml. While gulping he produces an audible pumping sound not unlike that of air under compression in a tyre pump. He uses G.P.B. for stretching his chest and coughing, and also to supplement his normal capacity when doing his exercises. He can manage his usual tidal exchange by the use of remnants of ordinary muscles of respiration supplemented by accessory muscles during the day. At night he requires to sleep on a rocking bed.

Case 5.—Man aged 36. Developed poliomyelitis in March, 1957, and needed a cabinet respirator continuously for many weeks. He now has a vital capacity of 800 ml., but needs a rocking bed for sleep. He has been taught G.P.B. during the past fortnight and can now gulp so as to increase his vital capacity to 1,800 ml. His present gulp traps about 25 ml. We expect the efficiency of his G.P.B. to increase with further practice.

Case 6.—Woman aged 23. A chronic respirator patient of seven years' duration requiring the cabinet respirator for the greater part of each 24 hours. While on a visit to London (in her cabinet) she was admitted to our unit for examination and for trial of other breathing apparatus—for example, rocking bed. During the eight hours she was in our unit

she learned the technique of G.P.B. On simple tests before her departure in the late afternoon it was found that her vital capacity was increased from 350 to 700 ml. with G.P.B. Her capacity to count in one breath was increased from 12, using her accessory muscles, to 24 when supplemented with G.P.B. Since her return home she has written to us as follows: "I am now able to do frog-breathing almost imperceptibly apart from the gulping movement in my throat. It has given me so much more confidence to go further away from home and from my iron lung. Last week I made a journey to town by train—about eight miles (12.87 km.)—and spent four hours there before coming back home, which is something I had never ventured to do previously. Also it means I am always able to get sufficient breath to make my voice carry all over the house."

Discussion

Since Dail's original observations further studies on glossopharyngeal breathing have been carried out in many centres in the U.S.A. (Collier, Dail, and Affeldt, 1956; Zumwalt, Adkins, Dail, and Affeldt, 1956; Loeser, 1956; Feigelson, Dickenson, Talner, and Wilson, 1956). The advantages derived by the patient are basically due to his ability to amplify his inspiratory volume unaided by mechanical respirators. Thus he becomes less dependent on machines during waking hours and is assured of a safety factor in case of electrical breakdown or power cuts. The increased volume of air trapped in the lungs also helps the patient to produce a better cough and with it an ability to clear his lungs of secretions. However, the cough mechanism is also dependent on functioning abdominal muscles and diaphragm, and severe involvement of these will diminish the cough effort considerably even though the patient is a good frog-breather (Feigelson *et al.*, 1956). In such patients, however, a good expulsive effort can be produced with the help of an assistant squeezing the lower chest and upper abdomen during the expiratory phase of G.P.B. Efficient frog-breathers can stretch the chest intermittently, and this helps in reducing or preventing rigidity, which alone could seriously interfere with the efficiency of ventilation. Additionally, the deep breathing achieved must be of considerable value in reducing the risk of atelectasis.

In addition to its medical advantages frog-breathing provides considerable social and psychological help to these cripples. It allows them, with certain limitations, to visit their homes, to do shopping, and go for car rides. If the limb paralysis is not severe they may even be able to earn their living, and we are hoping that one of our patients (Case 5) will eventually be able to resume his occupation as a schoolteacher.

There are, however, certain limitations to what G.P.B. can achieve. The patient cannot do it during sleep, and if his unassisted vital capacity is very low and largely or entirely carried out by accessory muscles he will certainly need a respirator for sleeping.

Although it would appear that in the U.S.A. many tracheotomized patients have learned G.P.B., we have not so far succeeded with two patients now on intermittent positive pressure breathing. There are difficulties in preventing leaks from the tracheostome which could be minimized by using suitable plugs as recently developed in the U.S.A. (Dail, personal communication, 1957). These patients, we think, are psychologically ill-adapted also, particularly where they have been for a long time "addicted" to intermittent positive pressure breathing.

A patient cannot eat during frog-breathing. However, one of our patients (Case 1) uses her accessory muscles of respiration while masticating and returns to frog-breathing after she has swallowed. With this combination she can consume an average meal in less than half an hour.

If illness develops, the energy required to perform G.P.B. may be lacking and the patient will require assistance by artificial respiration.

The presence of an irritant—for example, food particles or mucus near the glottis—may cause guarding and temporarily diminished ability for efficient G.P.B. An assistant may be required to help by chest squeezing during expiration to facilitate its dislodgment.

Glossopharyngeal breathing may be regarded as a form of intermittent positive pressure respiration. If the inspiratory phase is prolonged the venous return to the heart is progressively reduced as the intrathoracic pressure rises; thus the cardiac output progressively diminishes, and it has been observed to coincide with a reduction in blood pressure. Most patients complain of lightheadedness for a few seconds after maximal G.P.B., presumably due to transient cerebral anaemia. However, when G.P.B. is carried out to provide maintenance tidal exchange there appears to be no lessening in cardiac output. Dail and his co-workers (Collier *et al.*, 1956) maintain that if the tidal exchange is kept below one litre, provided also that the inspiratory phase is not very prolonged, there is no significant change in cardiac output.

Summary

The usefulness of glossopharyngeal breathing (G.P.B.) in chronic poliomyelitis patients with respiratory paralysis is described. Case reports of six patients from this hospital who have learned the technique are presented and the value of G.P.B. is analysed in each case.

The basic advantage of G.P.B. is the enhanced ability of the patient to increase his vital capacity, which makes him less dependent on respirators and increases his power to cough and stretch his chest. The social and psychological advantages of this type of breathing are stressed.

It can be concluded, without reserve, that G.P.B. is of great value to seriously handicapped patients and that more use of this technique should be made in all centres where post-acute and chronic poliomyelitis patients are cared for.

We wish to record our thanks to the staff and patients of the poliomyelitis unit for their help and co-operation in this study. Our thanks are also due to Mr. E. J. Tunnicliffe, of Electronic and X-ray Applications Ltd., London, for loan of the Monaghan spirometer with which many of the measurements were made.

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PSYCHOSIS DUE TO ISONIAZID

BY

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During the five years in which isoniazid has been in general use in the treatment of tuberculosis, the only toxic manifestations frequently reported have been those involving the central nervous system. A few cases of encephalitis have occurred (Biehl and Nimitz, 1954; Mitchell, 1955) which may or may not have been due to the drug, but peripheral neuropathy and psychosis are both well-recognized side-effects which have not infrequently been encountered. Most attention has so far been focused on neuropathy, although it is usually only seen in those patients receiving dosage much larger than normal. Apart from cases with paraesthesia only, peripheral neuropathy must be exceedingly rare when isoniazid is given in conventional dosage (2–5 mg./kg.). On the other hand, where psychosis has been reported the relation to dosage is less obvious. In the M.R.C. (1952) trial, in which 173 cases received 200 mg. of isoniazid daily, there were no reports of peripheral neuritis, but four cases developed nervous symptoms, in one of which these were persistent and severe enough to warrant stopping the drug and withdrawing the case from the trial. The purpose of this paper is to record five cases developing a psychosis whilst receiving isoniazid in dosage well within the normally accepted range.

Summary of Cases

Case No.	Duration of Isoniazid Before Onset	Dosage of Isoniazid (mg./kg.)	Possible Pre-disposing Factors	Pre-dominant Mental Symptoms	Treatment	Duration of Psychosis After Isoniazid Withdrawn
1	34 weeks	3.8	Oxytetracycline. P.A.S. intolerance	Hysteria	Nil	6 weeks
2	3–4 "	4.5	P.A.S. intolerance	Mania	I.M. vit. B complex; good response	8 months
3	7–8 "	2.6	Nil	Anxiety with paranoid symptoms	Nil	3–4 "
4	1 week	2.9	"	Schizoid reaction	I.M. nicotinic acid; partial response. I.M. vit. B complex	5 weeks
5	6–8 weeks	3.2	Chronic alcoholism. Oxytetracycline. Chlor-tetracycline	Depression	I.M. nicotinamide; good response	1 week

Case 1

A scaffolder aged 53 was admitted to the ward in July, 1954, with a cavity in the right upper lobe and a positive sputum. He had a long history of basal bronchiectasis with a recent acute episode treated with oxytetracycline. His general condition was, however, good and he was not appreciably toxic. He was given a 60-g. course of daily streptomycin with P.A.S. followed by isoniazid, 200 mg. daily (3.8 g./kg.) with P.A.S. After three months the P.A.S. was replaced by streptomycin owing to some mild gastric upset, but progress was otherwise satisfactory and he was co-operating well. In mid-January he complained of