respect the definite absence of any appreciable degree of pulmonary oedema is recalled.

Alternatively, it may be argued that the acute cardiac failure was due to coronary ischaemia, purely and simply. Certainly there was aortic atheroma here, and this involved the wall in the immediate vicinity of the orifices of the coronary artery. Similar cases of sudden death among soldiers in training during the recent war were usually ascribed to coronary ischaemia. If the present case was due to that cause then the extreme dilatation of the right atrium requires explanation. It is certainly an interesting and apparently insoluble pathological problem.

THE COUGH SYRUP

BY

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While syrups are commonly used as correctives for the disagreeable taste of medicines, there is probably no one group of drugs so consistently prescribed and dispensed in a syrupy vehicle as are expectorants and antitussives. Many drugs in this category could be prescribed as tablets, pills, capsules, etc., and any undesirable taste thus effectively dealt with; but they continue, for the most part, to be given in the form of a syrup. A good proportion of the syrups listed in the British and United States *Pharmacopoeias* contain drugs commonly held to be expectorant, while the number of non-official and patent cough syrups is legion. These considerations lead to the question of what, if any, are the pharmacological and therapeutic effects of syrups *per se* in the treatment of cough, and whether there is any justification for their continued use in cough medicines.

Historical

Why and when cough syrups were first used is a moot question in the investigation of which many interesting facts may be brought to light. Sugar, the basis of syrups, was first manufactured from the sugar-cane in Bengal, where it was called *sharkarā*, an old Sanskrit word which meant a substance made up of small grains (Flückiger and Hanbury, 1879). Etymologically the word *sharkarā* or *śarkarā* is the root of many modern words, such as sugar, sucrose, saccharin, syrup, sherbet, etc. From the Sanskrit the Persians changed the word to *shakar* and the Arabians to *sukkar*; in early Latin it became *saccharum*, and by mediaeval times had altered to *succarum*: from these words there was a gradual transition to the early French word *sukere*, then *sucre*, to the early English *sugre*, then *suger*, and finally to *sugar*. About the 8th century the cultivation and manufacture of sugar spread eastward from India to China, the Malay and the Pacific Islands, and westward through Persia to the Arabian Empire. Arabian physicians, especially Rhazes and Avicenna, are usually credited with introducing syrups into the therapeutic armamentarium. The word "syrup" is generally said to originate from an Arabic word, *sharab*, which meant a drink, but it is obvious that this Arabic word was derived from the more ancient Sanskrit source. It is interesting to note also that our word "candy" may be traced back to the Arabic word *kandāt*, which meant a lump of sugar.

No evidence has been found that any one physician was responsible for the introduction of the cough syrup, and it seems most likely that the common people found, by trial and error, that sugar or syrups or candy held in the mouth would relieve a cough. In recent years Gordonoff (1935) has shown, using modern techniques, that the sucking of candy has a pharmacological effect upon the respiratory tract, which he interpreted as meaning an increased output of bronchial or respiratory-tract fluid. In a later extensive review of the physiology and pharmacology of expectorants Gordonoff (1938) has made the statement, without references, that sugars were ancient folk-remedies for colds. Should this be true—and it would appear to be correct from what evidence is available, or rather lack of evidence to the contrary—it is readily apparent how cough syrups were introduced into medical practice, because

the early pharmacopoeias were, to a large extent, compilations of folk-remedies of earlier days. The retention of the cough syrup in subsequent editions of the pharmacopoeias and in the practice of medicine is readily understood when one looks over the list of drugs of disagreeable taste described in textbooks of materia medica and therapeutics of the last 200 years and even to-day—e.g., Beckman (1945).

Gordonoff (1935, 1938) claims to have proved that syrups do act as expectorants by augmenting the output of bronchial or respiratory-tract fluid. He noted that the duration of action is short, and hence advised giving syrups at intervals of about two hours. He also reported that maltose and sucrose, but not lactose, had expectorant properties.

Antitussive Action of Syrup in Man

Syrupus, B.P., was given in doses of two teaspoonfuls t.i.d. or q.i.d. to 28 patients complaining of cough due, for the most part, to an attack of the common cold. I interviewed these people at short intervals, and recorded the results of "therapy" as effective or ineffective in relieving the cough. Where there was any doubt as to the syrup's having had an antitussive action the case was listed as ineffective. It should be mentioned that the patients did not know what medicine they were getting. Those who obtained relief from cough with syrup reported, on the average, that the antitussive effect lasted about two hours. In this small series of cases 68% got complete relief from cough, and in the remaining 32% there was little or no antitussive effect. Allowing for the subjective factor, which could not be controlled because a true control group was not possible, it seems reasonable to conclude that syrup alone actually did have some antitussive properties. In view of the fact, as will be described below, that syrup given by stomach tube to animals did not augment the output of respiratory-tract fluid, and in view of the short antitussive action of the syrup in man, it seems most reasonable to conclude that syrup taken by mouth exerted a linctus-like action by soothing the irritated pharynx and upper respiratory tract—irritation which presumably was responsible for cough in approximately two-thirds of the patients studied. The evidence from these experiments would favour the retention of syrup as a vehicle for expectorant and antitussive medicines. The results suggest that when an expectorant mixture is given in a syrupy vehicle the syrup exerts an immediate direct demulcent action, while in an hour or two the effective expectorant drugs in the mixture take over the same function but in a different way—namely, by augmenting the output of respiratory-tract fluid.

Syrups and the Output of Respiratory-tract Fluid

It was next investigated whether syrups alone have a true expectorant action, as claimed by Gordonoff. There is no unanimous agreement on the definition of an expectorant. Faced with this problem, when research on expectorants was begun a number of years ago in this department of the university, the decision was made to leave in abeyance the question of a definition and to investigate those pharmacological and therapeutic properties of reputed expectorants which might offer an explanation of their mode of action. Older methods for studying the nature of expectorant action were tried and discarded for one reason or another. The first new method used was to measure the water content of the tracheal, bronchial, and alveolar portions of the respiratory tract before, and at intervals after, administration of an expectorant drug. The technique was applied to a study of the creosotes and guaiacols (Boyd and Johnston, 1940; Connell, Johnston, and Boyd, 1940) and, while reasonably satisfactory, the procedure was cumbersome, time-consuming, and, more seriously, it did not provide the information most desired, so that it too was abandoned.

Gunn (1927) has stated: "If it were as easy to determine the quantity of bronchial secretions as it is to measure the amount of urine, there would be by this time no such vagueness in regard to the effect of expectorants as still exists." The problem, therefore, was to find a satisfactory method for quantitatively measuring the output of bronchial secretion or, as is used in this laboratory, respiratory-tract fluid (R.T.F.)—a term which does not designate the site of origin, at present imperfectly understood, of this fluid in the respiratory tract. Perry and Boyd (1941) eventually worked out a technique for determining the exact output of this fluid and of providing a means whereby

it could be collected and analysed. This method, with subsequent modifications, improvements, and variations (Boyd, Jackson, and Ronan, 1943; Boyd and Ronan, 1942; Boyd and MacLachlan, 1944; Boyd, Perry, and Stevens, 1944), consists essentially in collecting R.T.F. through a T-cannula ligated into the trachea of lightly anaesthetized or decerebrate animals, with the inhaled air warmed to body temperature and saturated with water vapour. By means of this technique it has to date been possible to measure the effect upon the output and composition of R.T.F. of the following drugs: ammonium chloride, ammonium carbonate, and thymol (Perry and Boyd, 1941); various guaiacols and creosotes (Stevens, Ronan, Sourkes, and Boyd, 1943); sympathicomimetic amines (Boyd, Jackson, and Ronan, 1943); ether (Boyd and Munro, 1943); inhalation of ammonia (Boyd, MacLachlan, and Perry, 1944) and steam (Boyd, Perry, and Stevens, 1944); paregoric, camphor, benzoic acid, and alcohol (Boyd and MacLachlan, 1944); theophylline ethylenediamine, potassium citrate, and chloroform (Boyd, Palmer, and Pearson, 1946); ipecacuanha (Perry and Boyd, 1941; Boyd, Palmer, and Pearson, 1946); organic and inorganic iodides (Boyd, Blanchaer, *et al.*, 1945), volatile oils, balsams, terpene hydrate, and terebene (Boyd and Pearson, 1946); parasympatheticomimetic drugs and atropine sulphate (Boyd and Lapp, 1946; Lapp and Boyd, 1946; Boyd and Munro, 1943); sulphonamides (Boyd and Dorrance, 1946) and expectorant saponins and related drugs (Boyd and Palmer, 1946). Further studies are in progress.

In the investigation described here, the same technique was applied to a study of the effect of several pharmacopoeial syrups on the rate of output of R.T.F. in approximately 200 animals, including guinea-pigs, rabbits, and cats. The general procedure was to arrange the animals for collection of R.T.F., and at the end of three hours, when the rate of output had been at a plateau level for two hours, administer the respective syrup by stomach tube. The dosage ranged from 0.1 to 10 ml. per kilogramme body weight, and when the volume was below 10 ml. per kg. it was made up to that volume with water. In previous studies from this laboratory it has been repeatedly shown that water given by stomach tube in doses up to 10 ml. per kg. body weight has no effect upon the output of R.T.F. On the average, somewhat over twenty animals were used for each syrup given to each species. To standardize the presentation of results the mean output of R.T.F. per kg. body weight per hour was first determined for the two control hours immediately preceding the administration of the syrups. The mean output each hour afterwards was then found, and any increase in the rate of excretion expressed as a percentage of the initial control two-hour output. In calculating these means all values from all doses of syrups were included, since no syrup, with the possible exception of syrup of tolu, had any significant effect on the output of R.T.F. in any of the doses studied. The results thus determined are presented in the accompanying Table.

Table Showing Effect of Several Pharmacopoeial Syrups on Rate of Output of Respiratory-tract Fluid in Animals

Syrup	Species	Change in Output of R.T.F.			
		1st Hour	2nd Hour	3rd Hour	4th Hour
Simple syrup	Rabbit	% +6	% 0	% -10	% -15
	Cat	-13	-11	-16	+7
Wild cherry	Rabbit	-22	+16	+8	-22
	Guinea-pig	-24	-26	-20	-21
Squill	Cat	-18	-16	-14	-9
	Rabbit	-2	+21	+18	+8
Liquorice	Cat	+32	+33	+47	+37
Tolu	Rabbit	+93	+43	+28	+4
	Cat	+10	+6	+28	+21

Syrupus, *B.P.*, syrupus pruni serotinae, *B.P.*, syrupus scillae, *B.P.*, syrupus zingiberis, *B.P.*, and syrupus glycyrrhizae, *U.S.P.*, had no significant effect on the rate of output of R.T.F., even in doses which would correspond to a pint (568 ml.) or quart (1.14 l.) taken by mouth by an average man, on a body-weight basis. Syrupus tolutanus, *B.P.*, slightly augmented the output of R.T.F. in cats and rabbits. From the results with this group of syrups it is apparent that the syrup in a cough syrup has little or no effect on the rate of output of R.T.F. when it is given by stomach tube.

Conclusions

From the results of these experiments on animals and man the following conclusions are indicated. First, the syrupy vehicle of a cough syrup exerts a short demulcent effect on the mucosa of the pharynx and upper respiratory tract, and if cough is due to irritation of this mucosa the syrup has an antitussive effect *per se*. Secondly, when the bulk of the volume of syrup enters the stomach it has little or no expectorant property in itself, in the sense that it does not increase the rate of output of soothing respiratory-tract fluid. Thirdly, effective expectorant drugs added to the syrup begin to exert an antitussive action, again in the sense that they increase the output of respiratory-tract fluid, at about the time that the local antitussive action of the syrup alone has begun to wear off. These experiments offer a logical explanation of the time-honoured use of expectorants in a vehicle of syrup, producing a cough syrup, and at the same time justify the continued use of this form of prescribing and medication.

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Medical Memoranda

An Accessory Liver in an African

While accessory spleens are commonly found at necropsy both in Europeans and in Africans, accessory livers are extremely rare. Rolleston and McNee (1929) were able to record only a very few cases, and in the literature available to me since their publication I have not been able to find reports of other cases. Thus this record of the occurrence of an accessory liver in an African may be of interest.

In the body of an adult male African of unknown tribe, dying of bronchopneumonia, a dark tumour, shaped like a fat cigar, about 3.5 by 1 cm. in its greatest dimensions, was found adherent to and partly embedded in the anterior surface of the pancreas at about the junction of the head and body, the longest axis being transverse. It was attached by a delicate pedicle which disappeared into the substance of the pancreas and, under the circumstances of the necropsy, was not traced further. The tumour was not attached to the liver. It was of darker colour than the true liver, which had no anatomical abnormalities.

Microscopically it proved to be hepatic tissue showing the normal liver architecture, enclosed in a delicate fibrous-tissue capsule with arteries, veins, and bile ducts running beneath the capsule, and these left the accessory liver at a small hilum and ran into the pancreas. Both the true liver and the accessory liver showed pathological changes, but these were much more pronounced in the accessory organ. They consisted of collections of fibroblasts and chronic inflammatory cells in the portal areas, with an increased amount of fibrous tissue surrounding and partially delimiting the periphery of some of the lobules. The rather dilated central veins were surrounded by liver cells containing considerable amounts of fat in large and small droplets, but the peripheral cells were free of fat. Considerably increased amounts of pigment were present—as granules in the Kupffer cells, in the sinusoids near the periphery as amorphous masses, and in the portal cell collections. All these changes were much more noticeable in the accessory liver.