ping on the abdomen of the frog. Perhaps the best explanation is furnished by the state called "shock," using the term, as Prince¹² suggests, to denote "a sudden and profound depression or inhibition of the nervous centers, as a reflex result of so sudden and extensive injury to the pancreas itself, without requiring the mediation of the semilunar ganglion."

I have appended below a tabulated list of the cases hitherto reported; its careful study will serve to emphasize the importance of the subject of pancreatic hemorrhage, both from a clinical and a medicolegal viewpoint. I have endeavored to exclude those cases of acute pancreatitis and other morbid states in which there was only slight hemorrhagic infiltration occurring as a symptom. Oppositely, I have selected those cases in which the symptoms pointed to marked or fatal internal hemorrhage suddenly developed and the hemorrhage was confirmed by necropsy. The cases previously reported in a classic article by Dr. R. H. Fitz¹³, 16 in number, are included in the subjoined table. Draper¹⁴ had previously reported a series of cases of sudden death from pancreatic hemorrhage, of which six are also embraced in my table. There are to be found in the literature a large number of cases which I omitted, concerning which, however, there is room for a difference of opinion as to the cause of death, for the reason that all other obvious direct causes of death could not be reliably excluded. Judged by this test, few if any of the cases narrated in my table will be regarded as doubtful instances of pancreatic hemorrhage. It will be observed, also, that while most cases terminate quite acutely or even suddenly, others in which a fatal ending is attributable to pancreatic hemorrhage reached death more gradually, interrupted even by remitting periods.

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A STUDY OF CODEIN AND ITS SALTS.*

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Codein has been employed since its discovery in 1832 for various affections accompanied by pain, as a substitute for morphin, which had been in use for seventeen years before the above date. The drug has gained a prominence not hitherto accorded it, with the appearance of epidemic influenza and its sequelæ throughout this country during the severe winter just past.

Codein is administered alone or as one of its salts. It forms combinations with the mineral and organic acids, which are much more soluble than the alkaloid itself. The *acetate*, *citrate*, *hydrobromate*, *hydrochlorate*, *hydroiodate*, *nitrate* and *sulphate* have physical and therapeutic properties in common and are soluble in

from five to twenty parts of cold water, more so in hot water, from which they recrystallize to a certain extent on cooling. The *phosphate* is a white crystalline powder, soluble in four parts of cold water, and is especially suited for hypodermic use, as it is less irritating than any of the other salts. It is largely employed in this form in continental Europe. The *salicylate* is said to possess, besides analgesic, antirheumatic properties while the *valerianate* is especially beneficial in nervous troubles. All the salts of codein are subject to the general rules of incompatibility.

Kunkel¹ found, in his experiments on dogs and guinea-pigs, that codein has a powerfully irritating effect, producing convulsions in the extremities and the muscles of the neck, and where death results, it is due to its influence on the cerebellum and medulla oblongata. It acts on the circulatory apparatus, inflames the parts with which it comes into immediate contact, and its effect is greater when taken up by the cellular tissues than when absorbed through the stomach.

There are many contradictory reports regarding the action of this drug. Thus Hagen² states that it checks the urinary secretion, while most observers hold that it increases the amount of urine. Again, most writers speak of its advantage in not causing gastric disturbances, but its administration has been repeatedly followed by such excessive nausea and vomiting that it had to be altogether discontinued, as even a greatly diminished dose had the same effect as a larger one. These effects on the stomach are rarely seen when the drug is given in combination with one of the coal-tar preparations, such as acetanilid, probably due to the controlling influence of the latter on the cerebral centers.

Kersch³, in experimenting on dogs and cats, confirms the observations of Trousseau that the first effect of codein is paralysis of the hinder limbs and contraction of the pupils. Another characteristic symptom in animals is the frequent micturition, setting in as early as one hour after the injection of the drug in poisonous doses, whereas morphin causes retention of urine. Quite different was the action of the heart. In codeinized, deeply comatose animals, the pulse and respiration were accelerated, while the reverse was the case in morphinized animals. This acceleration occurred only in those animals having received a lethal dose and shortly before death, a symptom of paralysis of the vasomotor centers.

Reiner⁴, quoting Schröder, states that the physiologic action of codein in small, narcotic doses on the intestinal canal is to reduce peristaltic action; large, poisonous doses produce bloody diarrhea. This does not apply to the human being, as therapeutic doses are never followed by constipation, nor is the appetite diminished, as is the case with morphin.

With regard to the pupils, in therapeutic doses, no especial changes take place, but in toxic doses considerable dilatation is present. Locally, neither codein nor morphin produces mydriasis, so that the dilatation is a secondary phenomenon, in contradistinction to such substances as atropin and hyoscin, which act directly on the pupils. The blood-pressure is not influenced by codein, the pulse but slightly and respiration is slowed at first in toxic doses, and later returns to normal or above it.

THERAPEUTICS.

Cohen⁵ thinks the dose as given in most text-books is too large. While the drug may safely be given, if necessary, in doses of from 2 to 6 grains, on the basis that its narcotic power is but one-fourth that of morphin,

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yet, in medicinal usage, its dose need not ordinarily be greater than would be the dose of morphin in the same conditions, and he frequently gives 1-16 grain and rarely exceeds $\frac{1}{2}$ grain. It should, however, be repeated much more frequently than would be safe with morphin, and one advantage over the latter is the safety of frequent repetition. The greatest advantage of codein over morphin, however, is that it is less likely to create a morbid drug habit, and that in the unfortunate cases in which its long and continued use becomes necessary, it does not cause the distressing results that a similar use of morphin often entails. As compared with morphin, the sedative and hypnotic effects are greater, its anodyne and narcotic effects less. In addition it appears to have a special influence on inflammation of the serous membranes and thus to be useful in checking the spread of pleuritis and peritonitis. On the normal secretions its effects are less marked than those of morphin, and in moderate doses, constipation, dryness of the throat, diminution of urine and of perspiration are not usually produced.

In epidemic bronchitis it is a valuable remedy for the relief of the harassing pain of the cough, and when combined with one of the coal-tar antipyretics, the analgesic effects become more pronounced. It is a favorite drug in the cough of phthisis and chronic bronchitis, and its sedative influence is highly satisfactory, clinical data having shown it to be the best succedaneum for opium. Another advantage of codein over morphin, one of special value in bronchial catarrh, is that the patients not only cough less but also expectorate more easily than on morphin. The cough-dispelling power of codein is such as to make it indispensable in phthisic patients, and a point of great importance in these cases is that it does not impair the appetite or digestion, and can therefore be used uninterruptedly for months.

That codein has the power of diminishing the excretion of sugar in cases of diabetes mellitus is shown by the leading authorities, who recommend it as the only drug in the medicinal treatment of that disease. Thus Tyson⁶ gives it in doses of $\frac{1}{4}$ gr. each day. Hare⁷ recommends it in ascending doses beginning with from 1 to 5 gr. thrice a day. Wood and Fitz⁸ order it in $\frac{1}{2}$ gr. doses three times a day to be rapidly increased until 30 or 40 gr. are taken *per diem*. Anders⁹ gives codein sulphate in increasing doses, commencing with $\frac{1}{4}$ gr. three times daily, and augmenting the dose by $\frac{1}{4}$ gr. every second day, until 2 gr. are taken three times a day. Osler¹⁰ gives $\frac{1}{2}$ gr. three times daily, which may be gradually increased to 6 or 8 gr. in twenty-four hours. Strümpell¹¹ differs from most observers in regard to the action of this drug. He says, "it is a noteworthy fact that the alkaloids of opium, such as morphin and codein, possess much less value than opium itself in the treatment of diabetes mellitus."

Lauder-Brunton¹² was the first to use codein in abdominal pains, following the investigations of Barbier and Berthe, who showed that it exerts a specific action on the sympathetic nerve. He found it relieved the violent pains in a case of perityphlitis in 1-gr. doses; in another of abdominal tumor, $\frac{1}{2}$ gr. of the drug, and in a third case, one of fecal impaction, 1 gr. sufficed to relieve the pains without disturbing the function of the intestines. He also employed it successfully for the pains from carcinoma of the liver and pancreas. More recently, Slaughter¹³ gives preference to codein to relieve the pains in appendicitis. Freund¹⁴ used it in diseases of women and found that pain of uterine

origin, whether accompanying dysmenorrhea, acute or chronic diseases, can be temporarily relieved, but never to such an extent as with morphin or opium. In cases of abundant exudation in the pelvic peritoneum and connective tissue, codein was not very successful; furthermore, the drug can not be recommended as an anodyne in tubal disease. On the other hand, codein has a great and usually very prompt influence on pain proceeding from the ovaries, such as due to displacement or prolapse, oöphoritis, acute or chronic perioöphoritis and ovarian neuralgia; the pains invariably diminish even after small doses and in most cases disappear entirely as long as the action of the drug continues.

As a sedative in the insane, Dornblüth¹⁵ gave it internally in 448 cases, and codein phosphate hypodermically in 34 cases. In all but 2 of the cases it quieted the patients in from three to twelve hours. The doses were gauged according to the degree of excitation present. In maniac conditions it has a weaker action than hyoscin, but he prefers it when the latter causes hallucinations. It was found very useful in all cases where anxiety, precordial distress and insomnia were present.

Codein as a sedative and anodyne is more useful and appropriate than morphin or opium, where a mild effect is desired. In the treatment of the morphin habit, Schmidt¹⁶ employed injections of a 10 per cent. solution of the phosphate. It moderates the symptoms attending the withdrawal of morphin, even to the point of tolerance; it does not prolong the duration of the treatment, causes the morphin craving to vanish permanently, and disagreeable collateral effects, which develop with the increase in dose, prevent the abuse of this narcotic as a remedy. Professor Rosenthal¹⁷ of Vienna also uses the hydrochlorate for this purpose, giving 1-3 to $\frac{1}{2}$ gr. and, separately, 30 to 45 gr. of sodium bromid in solution as an adjuvant.

TOXICOLOGY.

Codein does not cause chronic poisoning, as it has no cumulative effect. Although it possesses decided toxic properties, cases of poisoning from the drug are rare, which may be explained by the greater cost as compared to morphin, opium, or the preparations containing these, and by reason that it is not generally known to the laity, even by name. The following cases are reported in the literature on the subject, most of them presenting severe symptoms, but all terminating in recovery:

CASE 1.—Myrtle¹⁸ reports a diabetic patient who became greatly depressed on account of the death within a short interval of each other, of his mother and brother, and who also had glycosuria. He took a pill containing 4 gr. of codein and 1-20 gr. of strychnin, and soon after had a severe attack of vertigo, collapse and contracted pupils. The latter as well as the admixture of strychnin make the genesis of the intoxication somewhat doubtful.

CASE 2.—Ambroso¹⁹ reports a child 2 years old with the following symptoms: Cadaveric appearance, cool extremities, pulse and heart-beat could not be felt; abdomen distended by meteorisms; pupils widely dilated; secretions arrested. He had taken 1 gram of codein in 150 c.c. mistura gummosa and 30 c.c. syrupus ipecacuanhæ within the course of a few hours. Treatment was as for opium poisoning.

CASE 3.—Walsh's²⁰ patient, 21 years old, and in the advanced stages of phthisis, with suicidal intent, swallowed a quantity of cough mixture containing codein, of which he took about 8 gr. Much of this was probably vomited, as it was taken on an empty stomach,

but for the same reason a great deal must have been absorbed in the interval of a quarter of an hour that elapsed before emetics could be made to act. The most noteworthy symptoms seem to have been the intense irritation of the sensory nerve endings and altered blood-pressure. Possibly many of the manifestations were marked or modified by the phthisical condition.

CASE 4.—Mettenheimer²¹ reports that an elderly woman suffering from bronchitis was ordered pills of codein, $\frac{1}{2}$ gr. every three hours. She took four pills at one dose. Violent vomiting set in with abdominal pain, no action from bowels, suppression of urine; great somnolence but no deep sleep; pupils contracted, pulse and respiration accelerated, but this may have been due to fear and excitement. The myosis continued for several days with complete anorexia and abnormal sensitiveness of the abdomen. Urinary secretion was re-established after twenty-six hours, and somnolence disappeared on the third day. The vomiting was evidently due to cerebral irritation, as the tongue remained clean during the period of loss of appetite.

CASE 5.—Béla Medva²² cited the case of a female aged 72 years, who took twenty-five pills containing 0.50 grams ($7\frac{1}{2}$ gr.) of codein with suicidal intent. Half an hour later she experienced a sense of warmth, vertigo and suffocation; semiconscious and somnolent; tossed about in a restless manner and scratched every part of the body; skin scarlet red, which coloration disappeared on pressure, but returned when this was removed; eyes bulging and weeping, conjunctiva deeply injected, pupils fully dilated and reacted slowly; entire body felt clammy; face swollen, turgid and reddened; twitching of fascial muscles and extremities, more marked in the lower extremities; knee-jerk exaggerated; pressure or pricking at first not felt by patient, later exquisitely sensitive; respiration superficial, pulse 116, soft and weak. Recovery resulted after deep coma lasting twenty-four hours.

CASE 6.—Spratling²³ reports the case of a young woman who took sixteen pills of codein. She had suffered for some months from a painful disease and had been ordered to take the drug for the relief of pain and persistent insomnia. An hour after taking she had considerable nausea, vomited some, was awake, but extremely restless and irritable. She could not lie in one position and tossed from side to side. Frequent convulsive movements of the entire muscular system existed, more marked in the upper extremities and head, with intense irritation of the skin all over the body, most annoying along the flexor surfaces of the forearm and on the back. The pupils were fixed to pin-point contraction; respiration, 12 per minute. She had great thirst and an uncomfortable feeling of fullness in the head.

CASE 7.—Roy²⁴ ordered codein for a boy aged 11 years. The father, a druggist, gave him 1 gr. with elixir calisaya. Great restlessness set in within an hour; respiration shallow and diminished; pulse, 100; pupils contracted. The symptoms lasted several hours.

CASE 8.—The author, for a female child aged 2 years, ordered a cough mixture of codein, wild cherry and tolu syrups, which was given in larger and oftener repeated doses than directed. When she had taken in all about 2 gr. of the drug, alarming symptoms of poisoning set in, such as deep coma, shallow respiration and reduced to 4 per minute, with pulse 120, and pupils dilated. The comatose condition lasted several hours and only yielded to the most active measures; flagellations with towels wrung out in cold water, electricity, hypodermics of strychnin and atropin.

CONCLUSIONS.

1. Codein is a most valuable drug as a sedative in the various forms of cough. It is an excellent anodyne in the pains of pelvic and abdominal origin, where morphin is contraindicated and where the intestinal function should not be deranged. It is the best remedy in the medicinal treatment of diabetes mellitus.

2. It is best administered in the form of a sulphate for internal use and as a phosphate hypodermically.

3. Poisonous doses produce great restlessness, intense irritation of the entire body, spasms of the muscular system, and generally dilatation of the pupils.

4. No fatal case of codein poison is recorded.

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SYNTHETIC CHEMISTRY,

ITS CONTRIBUTIONS TO MODERN THERAPEUTICS.*

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Synthetic chemistry is that department of chemistry which investigates the combination of elements or radicals under circumstances favorable to the formation of chemical compounds. It is the combining of separate elements or subordinates into new forms. In its restricted sense a synthetic compound is understood to be a body now made by artificial means, which formerly was believed to be capable of being formed only by vital action, such as urea, salicylic acid, or alcohol. The chemistry of the hydrocarbon compounds which consist of carbon united with hydrogen in definite series and which include the fatty and aromatic compounds, affords a number of illustrations of the achievements of synthetic chemistry, many of which are now of recognized therapeutic value.

Lavoisier wrote, in 1789, that: "Chemistry consists in the decomposition of substances; its object is to examine separately the various elements which enter into the composition of products. The study of chemistry advances toward its goal by division and subdivision." Synthetic chemistry reverses this proposition, and we now recognize the truth of the statement that the reverse operation is not only a part of chemistry, but also that it is to-day its most important department.

In former years, we were taught that chemistry was divided into two departments: organic and inorganic; organic chemistry comprising such compounds as were produced only within the tissues of animal and vegetable life, inorganic chemistry the elements and compounds of the mineral or inorganic world. We now know that no

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