circulation is defective, his extremities being almost invariably blue and cold. He has a tendency to bronchitis in the winter months. His limbs, with their bony framework, are short and thick, but there is no absolute distortion except a bowing of the tibiae with the convexity forwards. The hands and feet are short and broad, with stumpy fingers and toes. The feet are flat, and the second toe on each foot is smaller than normal and overrides the rest. His skin is universally harsh, dry, and resistant, and his muscles are firm, but not larger than normal. There are no local swellings about the body. His senses of touch, sight, and hearing, so far as can be ascertained, are normal, though perception is distinctly retarded. He has occasionally suffered from slight hæmorrhages from the bowels, and once, when he had two teeth drawn, he bled considerably. His tendon reactions and superficial reflexes are active. He has never had convulsions.

D. B., aged 6 years and 3 months, is 33 inches in height, and weighs 32½ lbs. He is the fourth child (a healthy boy and girl intervening between him and G.). He cut his first teeth early, and is said to have been bright as an infant, but he did not walk until he was 2 years and 3 months old. Although still characteristic of cretinism, his expression appears to denote more alertness than that of his brother. He talks very little and usually wears an air of contentment, smiling very readily. He is subject to fits of sulkiness, exactly similar to those mentioned in the case of G. He waddles when he walks, but can move much faster than his brother. He can even run. His head is fairly well shaped, somewhat flattened at the vertex, with a depression in the region of the anterior fontanelle, which is closed. His hair is normal. The root of the nose is broad and flat and the tip is rather turned up, the alæ and septum are thickened and the nostrils are broad. He has rather a big mouth, which shows a tendency to remain open, but he only occasionally protrudes the tongue. The lips are not everted, but the lower lip is larger than usual. His cheeks are not puffy and there is the normal furrow beneath the lower eyelids. He has a pale yellow complexion, the cheeks being rather more yellow than the rest of the face. He has his first set of teeth, which are set widely apart. His neck is short and thick, and he has a small thyroid gland of very much the same character as that of his brother. There are no pseudo-lipomata about the neck or body. His abdomen is prominent and has a small umbilical hernia, and his chest is remarkable in the fact that it quite retains the circular form of infancy. There is a slight heaving of the ribs. A faint systolic murmur is audible at the apex of the heart, but not at the angle of the scapula, and there is no increase in the area of cardiac dulness. The rest of his viscera appear to be normal. His limbs show the same peculiarities as his brother's, including that of the second toe in each foot. His perceptive faculties are probably somewhat more acute than his brother's, but it is difficult to determine to what extent; there can be no doubt of his being at the present moment of extremely limited intellectual capacity. His skin is harsh and firm to the touch, and his circulation is sluggish. His tendon reactions are active. During his stay in the hospital he has passed blood from the bowels on one occasion. This however may have been due to the constipation from which he has constantly suffered.

A distinction has recently been drawn by Dr. Bourneville¹ between endemic and sporadic cretins, which appears to be somewhat unnecessary. He lays stress on the fact that endemic cretins are descended from goitrous parents, while sporadic cretins are not. Speaking generally, this statement may be correct, but Dr. Bourneville also proceeds to separate the two forms on the ground of their anatomical quite as much as of their etiological differences. He points out that endemic cretins have brachycephalic heads, are very frequently goitrous, and have no "pseudo-lipomata;" while, on the contrary, sporadic cretins have dolichocephalic heads, are invariably without thyroid glands, and present the "pseudo-lipomata." It may be that the etiological conditions of the two forms of disease are different; our knowledge at present is so limited that we are hardly in a position to discuss the question, but when we turn to the clinical features we scarcely find the difference between them sufficiently great to warrant our accepting them as two totally distinct diseases.

In the first place, it must be acknowledged that, although in the endemic form the disease appears able to go a step further in its effects, that is, the mental and bodily degeneration may be greater than is known to occur in sporadic cretinism, the two forms not only present the closest identity of symptoms, but have now been conclusively proved to depend upon the same fundamental pathological conditions—namely, loss of function of the thyroid gland. Then as to details—not more than two-thirds of endemic cretins are affected with goitre,² while cases have been described in which the thyroid gland has been entirely absent. On the other hand, as regards the statement that all sporadic cretins are destitute of thyroid gland, the patients described above are instances of its presence, and the late Dr. Hilton Fagge mentioned one case in which there was a goitre. Dolichocephalic heads, as seen in the above cases, are the rule in sporadic cretins, but brachycephalic heads have been described. Finally, the "pseudo-lipomata," though frequently met with in sporadic cretins, are not invariable, and when present are not always permanent, and as regards their presumed invariable absence in endemic cretins, it has been plausibly suggested that they have not been systematically looked for.

Minor points of difference between the two forms are mentioned by Dr. Bourneville, but as they are still more differences of degree rather than of kind than the above, they need not further be dwelt upon. For my part, I am satisfied that the distinction between the two forms is sufficiently marked by the terms endemic and sporadic cretinism.

EXPERIMENTAL RESEARCH AS TO THE PHYSIOLOGICAL ACTION OF PARA- CRESOTIC ACID.

By M. CHARTERIS, M.D.,

Professor of Therapeutics and Materia Medica, University of Glasgow.

IN accordance with the promise made in a letter to the BRITISH MEDICAL JOURNAL of December 6th, 1890, I instituted a further series of experiments with regard to para-cresotic acid. This acid was forwarded to me by Messrs. Hopkins and Williams, London, and with it there was also sent at my request a sample of ortho-cresotic acid. Both these acids had been prepared from the corresponding cresols. I also obtained from another source samples of these acids, but, except for confirmatory purposes, they were not used, as their characters and melting points were identical with those obtained from Messrs. Hopkins and Williams.

Physical Characters.—*Para-cresotic acid*, melting point 150° C. to 151° C., a whitish powder, resembles the para-cresotic acid isolated from commercial salicylic acid by Professor Dunstan. The physiological action of this para-cresotic acid was stated at the meeting of the Pharmaceutical Society of London. *Ortho-cresotic acid*, melting point 163° C., distinct crystals. The only difference between it and the specimen of the ortho-cresotic acid received from Professor Dunstan was that in the latter the crystals were somewhat larger.

Physiological Experiments with Para-Cresotic Acid.—For this purpose two strong healthy rabbits were selected—(a) weighing 2½ lbs., (b) weighing 3½ lbs.

(a) To this animal an injection of 6 grains dissolved in rectified spirit was given. Fifteen minutes afterwards the fore-limbs slipped down, and the animal was unable to move easily. In forty-five minutes the hind limbs were stretched out, and a prone position was assumed. At the expiration of an hour and a half from receiving the injection the symptoms noted were "a prone position, great prostration, the head resting between the fore limbs, the breathing hurried and short." Three hours after the injection was given it died, the paralysis being complete half an hour before death.

(b) To this animal an injection of 8 grains similarly dissolved was given, and at the expiration of an hour other 4 grains. The result of the first injection was distinct disturbance, which deepened after the second injection into complete paralysis. Death occurred at the expiration of three hours. The same results followed upon injections of the two acids obtained

¹ *Progrès Médical*, Nos. 29, 30, 33, and 34, August, 1890.

² Baillarger and Krishaber, *Dict. Encycl. des Sci. Méd.*, Art. "Crétin."

from another source, the animals being of similar weight to *a* and *b*.

These experiments show that 6 grains of para-cresotic acid proved fatal in three hours to an animal weighing $2\frac{1}{2}$ lbs., and that 12 grains in the same time were fatal to an animal weighing $3\frac{1}{2}$ lbs. The lethal dose deduced from these experiments is thus about 3 grains per lb. weight of the animal. Smaller doses would doubtless cause death after a longer interval.

Physiological Experiments with Ortho-Cresotic Acid.—Two grains of this acid similarly dissolved were injected into a rabbit weighing $2\frac{1}{2}$ lbs. The animal from the time of receiving the injection remained in a dazed condition, with its eyes closed. Three hours afterwards paralysis of the fore-limbs commenced, and it died twelve hours after the injection had been given. The lethal action of this acid in no way differed from the specimen of the ortho-cresotic acid received from Professor Dunstan, and from other experiments unnecessary to detail I conclude that 1 grain per lb. weight of the animal is sufficient to cause death at intervals varying from twelve to thirty-six hours. After the completion of these experiments I resolved to try the ortho- and para-cresotic acids combined in certain proportions, and I found that the action was more immediate and pronounced than when they were given separately. Thus 1 grain of ortho-cresotic acid and 2 grains of para-cresotic acid caused death in three hours to an animal weighing about 2 lbs. This experiment repeated three times gave the same result in the same interval of time.

I further tried the combination of these acids with natural salicylic acid; 1 grain of para-cresotic acid, and 1 grain of ortho-cresotic acid were dissolved with 20 grains of natural salicylic acid and crystallised. Five grains of this powder dissolved in rectified spirit caused immediate action, and death occurred in the course of twelve hours, or, in other words, rather less than $\frac{1}{4}$ grain of para-cresotic acid, $\frac{1}{4}$ grain of ortho-cresotic acid, $4\frac{1}{2}$ grains natural salicylic acid were fatal to an animal weighing 2 lbs.

Chemical Experiments.—From these physiological experiments of the ortho- or para-cresotic acids, alone or combined, in the manner indicated, I was induced tentatively to try a few chemical experiments. I therefore added these acids respectively to the beautiful crystals of the natural acids, and dissolved and crystallised them from hot aqueous solutions.

1. By the above procedure it was found that when to 20 grains of natural salicylic acid (melting point 157°) was added 1 grain of ortho-cresotic acid, the result was a white powder (melting point 152.3°).

2. Twenty grains of natural salicylic acid with 1 grain of para-cresotic acid resulted in a white powder with a few distinct crystals, melting point 154° .

3. Guided by these facts, I tried the addition of 1 grain of ortho-cresotic and 1 grain of para-cresotic acids respectively to 60 grains of the natural acid. I subsequently tested the result of solution and crystallisation, and compared these with dissolving 60 grains of the natural acid without the addition of any foreign acid.

It was found that after two crystallisations the natural acid regained its original crystalline form, and that its melting point was unaltered. On the other hand, after two crystallisations, the natural acid with ortho-cresotic acid had a melting point 154.3° , and the natural acid with the para-cresotic acid a melting point 154° . In both cases there was a non-crystalline powder.

Further crystallisations, five in all, of the natural acid and the ortho-acid resulted in the formation of distinct crystals, somewhat smaller than those of the natural acid. Melting point, 156.0° , which is one degree less than the original melting point of the natural acid. Six crystallisations of the natural acid with para-cresotic acid showed a few distinct crystals, but by far the greater portion remained non-crystalline. Melting point, 154.5° . To the last solution in each case a little spirit was added.

The melting points were taken first at the Chemical Laboratory of the University of Glasgow, and subsequently the different samples were submitted to Mr. Tatlock, city analyst for Glasgow. The results were exactly the same, and for convenience of illustration and comparison are given in a tabular form.

Tabular Statement as to Melting Points.

	Melting Point.
1. Hopkins and Williams (natural salicylic acid) ...	157.0° C.
" (artificial) ...	156.0° C.
Characters of each distinct crystals.	
2. Equal parts of natural salicylic acid and ortho-cresotic acid ...	135.0° C.
Equal parts of natural salicylic acid and para-cresotic acid ...	128.5° C.
3. 20 grains natural salicylic acid and 1 grain ortho-cresotic acid ...	152.5° C.
4. 20 grains natural salicylic acid and 1 grain para-cresotic acid ...	152.0° C.
5. 60 grains natural salicylic acid and 1 grain ortho-cresotic acid ...	156.0° C.
6. 60 grains natural salicylic acid and 1 grain para-cresotic acid ...	154.5° C.
7. 97 grains natural salicylic acid } 2 " para-cresotic acid } 1 " ortho-cresotic } Characters similar to those of the British Pharmacopœia.	About 155.0° C.
8. Merck's artificial salicylic acid, melting point 157.0° C., similarly dissolved with ortho- or para-cresotic acids, and the different combinations crystallised gave the same results as regards the melting points.	

The explanation of these melting points belongs more to the province of the chemist than the physician, but whatever explanation may be offered by those competent to deal with it, the broad deduction cannot be minimised, that the presence of ortho- and para-cresotic acids in salicylic acid, renders it impure and lethal to small animals such as were experimented on. Their removal is a *sine quâ non* before commercial salicylic acid can be termed "physiologically pure."

In a research which has been carried on for some time at this laboratory, we find that there is a great difference in the physiological action of ordinary carbolic acid melting point 33° , and pure carbolic acid melting point, 40° to 42° . While their antiseptic properties remain the same, the lethal action on animals is twice as great in the impure as when the acid is pure, and I am satisfied that salicylic acid can be obtained pure from carbolic acid which has a melting point of 40° to 42° . So prepared the acid has a melting point of 157° , and its crystalline form is similar to that of the natural acid. Its physiological action is also equally harmless when injected in 15 grains into an animal weighing $2\frac{1}{2}$ lbs. All these researches and experiments have strengthened the view expressed at the Royal Medical and Chirurgical Society on February 11th, 1890, that similarity of crystalline form in the artificial and natural acids seems to be absolutely essential to secure uniform and harmless physiological action when administered to animals in similar doses.

It is gratifying to note, with reference to these remarks, that the new German *Pharmacopœia* has altered the melting point of salicylic acid from about 155° to 157° . Further, the admirable commentary of this *Pharmacopœia* by Haser, Fischer, and Hartrich, states that the crystalline form of the acid should alone be employed in pharmacy. I presume that this acid and the sodium salt prepared from it will alone be supplied to the English market by German manufacturers, for I would be loth to believe that they would sell to us preparations which are not officially sanctioned in their country.

These facts show that our *Pharmacopœia* is not up to date. Its description of acidum salicylicum refers to a bygone period, and now represents neither the characters nor the melting point of the natural or the pure artificial acid.

It is not my intention to prosecute this research further. I close it by stating that sufficient evidence has been adduced to show, that in cases where poisonous symptoms have been evoked by the administration of large and repeated doses of the artificial salicylate of sodium in rheumatism, they are dependent upon its containing the impurities mentioned. Further experiments may be necessary to determine whether the amount of para-cresotic acid contained in some samples of commercial salicylic acid is sufficient to produce poisonous effects on a human subject. My experiments show that when injected into small animals it is poisonous, though in a less degree than the ortho-acid, and that its poisonous effects are

intensified when combined with the ortho-acid, and still more so when incorporated with this acid and salicylic acid.

The question which has been raised as to the therapeutic value of the sodium salt of para-cresotic acid is beyond the scope of this research. The acid from which it is prepared is poisonous, yet its salt, judiciously given, may be of benefit in certain diseases. The information as yet afforded with regard to this is meagre, and requires to be supplemented; but whatever the decision as to its value may be, the presence of para-cresotic acid cannot be desired by anyone who impartially considers the subject from a chemical, a physiological, or a therapeutic standpoint.

A CASE OF ACROMEGALY.¹

By ROBERT RUTTLE, L.M. & S. UNIV. DUB.,
Vice-President Blackburn and District Medical Society.

THE first of the accompanying photographs is that of the patient just before her marriage in 1876; at that time she was 24 years of age. The second, taken recently in the same position, affords a striking contrast.

A. H., 1876.

I saw the patient in May, 1879. She was not then or since, until October 11th, 1890, a patient of mine, but at that casual meeting her face, hands, and feet at once attracted my attention. I thought of cretinism, but the woman was clear, cool, intelligent, though certainly in a peculiar condition, and she let fall the remark that she had been under Dr. Popjoy for a considerable time. She is now 38, has been married fourteen years, has had no family. She had been accustomed to heavy farm service, describes herself as "strong and healthy, with cheeks like roses," up to the time of first symptoms. She had no severe illness nor any irregularity, except that her menstrual periodicity varied slightly, but without pain or any other inconvenience; she menstruated once after marriage, never since then. Soon after she began to experience severe pains about vertex, back of head, and in the cervical region, which increased gradually in intensity; she also complained of a feeling of "numbness" all over her body; the headache became "dreadful," and she then noticed that her hands and feet were "swelling," because No. 7 gloves no longer fitted her

hands, and 5 in boots also became too small. This enlargement went on gradually. When she was twelve months married she was suddenly seized in the mill with an attack of vertigo followed by total loss of consciousness. She was taken to a friend's house, and from there removed home with difficulty, kept her bed for nearly three weeks, hanging apparently between life and death. Her convalescence was slow, alternating with relapses of agonising pain, accompanied by vertigo and loss of consciousness. These attacks seem of late years to have somewhat decreased in severity. Treatment always was powerless to relieve her, rest and quiet alone doing any good; she appeared better when idle in the country.

At the time of the severe explosion her extremities rapidly enlarged, so much so that her left ring finger burst her wedding ring, a moderately stout one. She also began to experience failure of sight at this time, which has gone on to total blindness in the right eye from atrophy of the optic nerve. In the left eye the temporal half of the field of vision is gone, and the activity of the upper limit at the nasal side slightly encroached on; the hemianopsia is very clearly defined; refraction is emmetropic, the pupils always somewhat dilated; the optic axes are divergent.

A. H., November, 1890.

Heart, liver, kidneys, etc., appear sound, no albumen or sugar present; occasionally a slight cloud of phosphates in urine.

Digestion fairly good, bowels inclined to constipation; she eats little, often not till evening. She can sleep well, but wakens often during the night. I might add that her pain now generally comes on at night and wakens her; but sleep and rest afford relief, stimulants rather increase pain. She does not use tea. Coffee gives some slight relief; coffee and cocoa are her usual beverages.

Her face is pale, with skin smooth and few wrinkles, but not very marked; slight puffiness under lower lids certainly varies, while eyes are somewhat divergent and lids large; the cartilages are enlarged, nose long and very large; both lips hypertrophied, especially the lower one; the lower jaw and chin enlarged, prominent, prognathous; teeth separated, tongue large; the face does not appear at all broadened nor the frontal sinuses enlarged. Her head measures 23½ inches in circumference round the brows.

She has become somewhat stooped, and complains of

¹ Shown at the Blackburn and District Medical Society.