external genital organs. Both the testicles and the penis were very much undersized. Mentally the boy appeared exceedingly dull, so that in spite of the presence of a competent interpreter it was impossible to get any history out of him. However, he admitted having frequently used morphin hypodermically for over two years. The keloids, mostly consisting of nodules and plates, were found particularly on the outer sides of the arms and on the anterior and outer surfaces of the thighs (Figs. 4 and 5). They were hard, smooth and shining.

In Cases 2 and 3, pieces of tissue were obtained and at once after removal placed in Zenker's solution. The paraffin sections were stained with hematoxylin and eosin, eosin and alkaline methylene blue and by Weigert's method for elastic fibers.

The sections from the tissue in Case 2 (Fig. 6), removed from the thigh above the knee, show in the outermost portion of the loose subcutaneous areolar connective tissue some remnants of sweat glands. Above these subcutaneous strata are masses of coarse homogeneous fibers, arranged in bands and bundles, which run parallel to the surface of the skin. These bundles interlace with each other in such a manner that in general the deeper layers appear to run at right angle to the upper layers and in the sections the former are cut transversely and the latter longitudinally. Fairly numerous vessels with moderately thickened walls are seen in the innermost layers of the coarse fibers. The outer layers show few vascular lumina. Elastic fibers are entirely absent where the tissue is composed of the coarse, homogeneous, collagenous fibers, but at the margin of the fibrous masses and in one place near the surface of the skin, between two converging fibrous bands, they are encountered. In the keloid tissue proper, sweat and sebaceous glands and hair follicles are absent. The papillary layer is almost entirely obliterated. Only here and there a very short stumpy papilla or two with correspondingly small interpapillary pegs are seen. The epidermis in general is almost completely flattened out. The Malpighian layer is normal in extent, no karyokinetic figures are seen in its cells. The stratum granulosum is narrow and its keratohyalin scanty. The stratum lucidum and the stratum corneum are broad. At the margin of the keloid mass proper, hair follicles and glands are again encountered, but the tissue here shows a round-celled subacute inflammatory infiltration, composed of small round lymphoid, embryonal fusiform and a few plasma cells. Bacteria are not encountered in these marginal inflammatory areas.

CASE 3.—A. L., Chinese, aged about 30, had been sent to prison for one month in punishment of a petty theft. He is a medium sized, strong built, fairly well-nourished man. He admitted having used morphin by the aid of the hypodermic syringe for two years. Previously he had been an opium smoker.

Examination.—All parts of his body accessible to the syringe, with the exception of the face, head, hands and feet were covered with keloid nodules and elevations. They were found from the clavicles downward to the ankles, on the inner and outer surfaces of the arms from the shoulders to the wrists, on the sides of the thorax, on the buttocks, on the anterior, inner, outer and partly on the posterior surfaces of the thighs, and over the calves (Figs. 7 and 8). The most profoundly effected surfaces were those of the left arm, most probably on account of having been most frequently used as the site for the morphia injections. Most of the keloids were round or elliptical, very firm elevations. Irregularly stellate ridges were seen, however, on the outer surface of the left arm. The nodules, ridges, etc., were smooth, moderately shining and of a pale reddish hue. Some of them were covered with dried up scabs. Others showed a very shallow, ulcerated surface.

Microscopic Examination.—Pieces of tissue were removed

from the outer surface of the left arm and from the left shoulder. Microscopic examination of the sections shows the following (Fig. 9): In general the tissues are very much like those from Case 2, though some points of difference are to be noted. The keloid fibers are, on the whole, much coarser than in Case 2, more swollen, more homogeneous. In some places they do not reach up to the epidermis, and when they do the papillary layer is fairly well preserved. Here also small remnants of hair follicles are found. All epidermal layers, except the stratum germinativum, are thin. Lymph clefts in the keloid mass are more numerous than in Case 2, but in neither of the cases is a proliferation of lymphatic endothelia demonstrable. The inflammatory zone at the margin of the keloid connective tissue mass is less pronounced than in Case 2. In neither of the cases are the keloid fibers directly traceable to the adventitia of vessels. Elastic fibers are absent in the area of keloid connective tissue fibers. No bacteria are seen in the sections.

CONCLUSIONS.

The most important and most interesting deductions to be drawn from the observation and examination of these three cases are:

1. The great multiplicity of the keloids and the vast areas over which they occurred.

2. Their common etiology, all three unmistakably depending on the habitual use of the hypodermic syringe for the purpose of injecting morphin.

3. The fact that Chinese, when habitually using hypodermic injections of morphin, are apparently liable to development of keloids. This is probably due to a racial predisposition. It is perhaps proper to mention here that, while opium smoking is very widespread among the Chinese, the use of morphin by the aid of the hypodermic syringe is not at all common among these people.

4. The result of the microscopic examination is in accord with what has repeatedly been described as the typical histology of the keloid. Several years ago I examined microscopically several cases of spontaneous keloids. The sections from these cases are not now accessible, but I have the impression that there is no fundamental difference between the histology of so-called spontaneous and acquired keloid. The preservation or absence of the papillæ of the derma, in the two types of keloids in particular, is by no means an invariably present differential feature; on the contrary, transitional stages are occasionally found in either variety.

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ISOPRAL AND HYDRATED CHLORAL.*

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A student of materia medica can not fail to observe that many substances come into notice, rise into popular favor and sink back into obscurity, only to give place to others which follow the same course. This observation should tend to make one conservative, but we are so accustomed to brilliant discoveries, whereby the impossibility of yesterday becomes the accomplished fact of to-day, that many of us have cast conservatism to the winds and accept, with extraordinary credulity, the statements of the charlatan, the falsifier and the self-styled investigator.

We are coming to appreciate the indecency of allowing ourselves to be made the dupes and unpaid agents of

*This article was read at the meeting of the Section on Medicine of the New York Academy of Medicine on April 16, 1907

the makers of worthless compounds, which are forced on our notice in high-sounding, and often meaningless, phrases. We must also be on our guard against accepting the statements of those who may be interested in reporting too "optimistically" on nostrums sold at fancy prices, and we must remember that the investigator who is paid for his report and the enthusiast are prone to accept insufficient evidence as the basis for highly-colored reports.

While the ideal is being sought in every department of medicine, and nowhere more earnestly than in the field of anesthetics and hypnotics, it should be remembered that these remedies, which by their very nature can not be wholly free from danger, should not be used on man before they have been thoroughly tested on animals. The precise dose for man can not be learned by experiments on animals, but such experiments do unquestionably show the mode of action of a substance, and from this its advantages and disadvantages may be compared with those of another substance. Thus, the depression of the vasomotor center in one case, and that of the respiratory center in another, may limit the usefulness of certain agents.

Isopral is being extensively advertised as "The safe hypnotic of the chloral group; isopral acts more efficiently than chloral in one-half the dose, and without depressing effects on the heart and nervous system."

The danger attending the uses of hydrated chloral has long been recognized, and due caution is exercised in its employment. If it can be shown that isopral is fully as dangerous as hydrated chloral, and probably more dangerous, we shall not often have occasion to prescribe the proprietary, of which we know practically nothing in respect to other effects than the production of unconsciousness, and which costs about twenty times as much as the official hydrated chloral.

The use of isopral by clinicians is apparently based on the pharmacologic investigation of Impens,¹ who gave figures purporting to show that isopral is much safer than chloral. It does not seem to me that his conclusions are in any way justified, and the table taken from his article is given for comparison with results obtained myself in experiments on eight cats, thirteen dogs and two guinea-pigs.

Impens determined the effective and the lethal doses of isopral and hydrated chloral for cats, dogs and rabbits respectively, and, dividing the lethal by the effective dose, obtained indices of their safety. It will be seen that the margin of safety given for isopral is about three and a half times that of hydrated chloral in the case of cats. I am at a loss to understand how any conscientious observer could come to such a conclusion in the light of my own observations given in the protocols immediately following the table of Impens.²

TABLE TAKEN FROM IMPENS' ARTICLE.

(All doses are expressed in grams per kilogram of body weight.)

		Isopral.	Hydrated chloral.
CAT:	Effective.....	0.09	0.2
	Lethal.....	0.4	0.25
	Quotient.....	4.4	1.25
RABBIT:	Effective.....	0.2	0.356
	Lethal.....	0.9	1.54
	Quotient.....	4.5	4.2
DOG:	Effective.....	0.093	0.25
	Lethal.....	0.6	1.0
	Quotient.....	6.4	4.0

1. Therap. Monatsb., 1903, ix, 459; x, 533.

2. Impens gave the drugs by the mouth. I gave them by the rectum, from which absorption is somewhat more rapid, but this does not affect the ratio of toxicity.

CATS.

March 13. CAT 1.—WEIGHT 4.56 KG.³

11:15 A. M.—0.1 isopral.
 11:17 —Some incoördination.
 11:30 —Doses a minute or two and then struggles to rise.
 11:44 —Less incoördination.
 11:55 —Constantly in motion.
 12:27 P. M.—Very restless; gait nearly normal.
 12:50 —Becoming quiet.

March 13. CAT 2.—WEIGHT 4.4 KG.³

11:23 A. M.—0.1 hydrated chloral.
 11:32 —Some incoördination.
 11:52 —Dozed about half an hour.
 12:23 P. M.—Nearly normal.
 12:50 —Sleeping in middle of floor (habitually seeks corner).

March 13. CAT 3.—WEIGHT 2.57 KG.

2:08 P. M.—0.3 isopral.
 2:11 —Wild excitement.
 2:17 —Fully extended, sphincter ani relaxed.
 2:30 —Deep narcosis; respiration, 60, shallow.

March 14. —Sitting up, awake nearly all day; some incoördination.

March 15. —Extremely irritable; much depressed.

March 16. —Sleeps most of the time; rolled over on side after leaping from table 77 cm. in height.

March 13. CAT 4.—WEIGHT, 2.6 KG.

2:00 P. M.—0.3 hydrated chloral.
 2:14 —Some incoördination.
 2:25 —Fully extended; respiration 35.
 3:40 —Narcosis not so deep as in 3; reflexes more easily elicited.

March 14. —Very sleepy all day.

March 15. —Nearly normal.

March 16. —Falls gracefully to feet when dropped 1 meter.

March 14. CAT 5.—WEIGHT, 3.5 KG.

11:24 A. M.—0.35 isopral.
 11:55 —Respiration 100, very irregular.
 1:00 P. M.—Reflexes abolished.
 5:00 —Respiration 38.
 March 15.
 10:00 A. M.—Respiration, 14.
 5:00 P. M.—Respiration, 12.
 March 16.
 11:00 A. M.—Respiration, 10; reflexes obtained on pinching toes.
 March 17.
 7:30 A. M.—Respiration, 23.

March 18. —Rolls on side after leaping from table.

March 23. CAT 6.—WEIGHT, 3.0 KG.

9:37 A. M.—0.35 hydrated chloral.
 11:37 —Respiration 90, irregular; reflexes from toes.
 3:20 P. M.—Respiration, 51; reflexes from toes.

March 24. 8:00 A. M.—Respiration, 27.

March 25. 7:30 A. M.—Respiration, 21; dozing all day.

March 26. —Very sleepy all day.

March 26. CAT 7.—WEIGHT, 4.51 KG.

10:15 A. M.—0.375 isopral.
 11:00 —Died.

March 26. CAT 8.—WEIGHT, 4.62 KG.

11:05 A. M.—0.375 hydrated chloral.
 11:35 —Struggles to escape from cage.
 5:20 P. M.—Very restless; respiration, 22.

March 27. 10:00 A. M.—Respiration, 18; restless; frequently struggles to feet.

March 28. —Some incoördination.

March 29. —Normal.

The dose of isopral in Experiment 1 exceeds that claimed by Impens to be effective by more than 10 per cent., but except for a few minutes of dozing it caused only excitement and incoördination, while the same amount of hydrated chloral, which is just half that claimed by Impens to be effective, caused a considerably greater degree of hypnosis. In Experiment 7 a dose of 0.375 gm. per kg. proved fatal, while Cat 8 survived the same amount of hydrated chloral, which is 50 per cent. greater than the fatal dose given by Impens. Furthermore, sublethal doses of isopral cause more profound depression of the respiratory center and more lasting incoördination than does hydrated chloral in equal doses.

Cushny says⁴ that the soporifics, or narcotics (of the chloral group) have the same general action as the anesthetics, which, as is well known, paralyze the respiratory center, and we may feel sure that the relative

3. Cats 1 and 2 are thoroughly accustomed to the laboratory, having been kept there for four months. Neither is wild, but 2 is naturally more quiet than 1.

4. Pharmacology and Therapeutics, third edition, p. 188.

danger of the different members of the chloral group may be measured by their depressant action on the respiratory and vasomotor centers.

A number of experiments on dogs were, therefore, made with a view to determining the relative effects of isopral and hydrated chloral on the respiratory and vasomotor centers. Especial care was observed in the different experiments to have the same degree of anesthesia, which was just sufficient to prevent pain during the short operation preliminary to taking tracings. The protocols of Experiments 8 and 9 will serve to illustrate the relative action of the two drugs. The same results are shown more graphically in the tracings of Experiments 12 and 13.

Fig. 1.—April 1, 1907. Fox terrier; excellent condition, weight 7.0 kg. At 11:05 ether; cannulas inserted. At 11:25 ether withdrawn. At 11:41 tracing. At 11:42 1/3, injected 0.1 gm. isopral per kg. of weight. At 11:45 2/3 injected 0.1 gm. isopral per kg. of weight. A, respirations; B, blood pressure; C, lines showing times of injection; D, time record in seconds. (Less than half a dozen heart beats, not shown on tracing, occurred after the heart had apparently stopped.)

March 20. DOG 8.—MALE, WEIGHT, 5.3 KG.

9:55 A. M.—Ether cannulas inserted into the carotid artery, femoral vein and trachea.
10:15 —Ether withdrawn.
10:25 —Dog awake.
10:33 —Blood pressure⁵ 140, respiration 48, heart rate 96.
10:34-10:36 1/2 —0.1 gm. per kg. isopral, vein.
10:35 —Blood pressure 134, respiration 21, heart rate 90.
10:36 —Blood pressure 108, respiration 36, heart rate 126.
10:36 1/2 —Blood pressure 50, respiration 48, heart rate 114.
10:44 —Blood pressure 100, respiration 23, heart rate 125.
10:44-10:47 —0.1 gm. per kg. isopral, vein.
10:45-10:47 —Blood pressure 40, respiration stopped, heart rate 96.
10:47 1/4 —Blood pressure 18, heart rate 84.
10:48 —Blood pressure 0, heart stopped.

Fig. 2.—April 1, 1907. Mongrel, excellent condition, weight 6.6 kg. At 11:57 ether; cannulas inserted. At 12:17 ether withdrawn. At 12:30, tracing. At 12:31-12:34:20, injected 0.2 gm. hydrated chloral per kg. of weight. At 12:36-12:39:20 injected 0.2 gm. hydrated chloral per kg. of weight. At 12:41 tracing in seconds interrupted 50 seconds while changing drums. A, respirations; B, blood pressure; C, lines showing times of injection; D, time in seconds; Y, X, places where writing point failed to record heart beats.

DOG 9.—FEMALE, WEIGHT, 6.8 KG.

12:40 P. M.—Ether; operation as in preceding experiment.
1:00 —Ether withdrawn.
1:27 —Blood pressure 140, respiration 65, heart rate 130.
1:29 —Blood pressure 140, respiration 65, heart rate —.
1:30-1:32 1/2 —0.2 gm. per kg. hydrate chloral, vein.
1:32 —Blood pressure 115, respiration 66, heart rate —.
1:33 1/2 —Blood pressure 92, respiration 66, heart rate 120.
1:40 —Blood pressure 120, respiration 45, heart rate 144.
1:40 1/4-1:43 1/2 —0.2 gm. hydrated chloral, vein.
1:44 —Blood pressure 70, respiration 24 shallow, heart rate 120.
1:47 —Blood pressure 93, respiration 31, heart rate 132.
1:51 —Blood pressure 76, respiration 21, heart rate 160.
1:53-1:54 —0.1 gm. hydrated chloral, vein.
1:54 1/4 —Blood pressure 80, respiration 16, heart rate 140.
1:55-1:56 —0.1 gm. per kg. hydrated chloral, vein.
1:56 1/4 —Blood pressure 66, respiration stopped, heart rate 115.
1:58 —Blood pressure 70, heart rate 110.
1:58 1/2 —Blood pressure 50, heart rate 65.
1:59 —Blood pressure 0, heart stopped.

5. The blood pressure is given in millimeters of mercury.

It is seen by the protocols of these experiments that 0.1 gm. of isopral per kg. of weight caused a much greater fall in blood pressure (vasomotor depression) and a more profound depression of the respiratory center than did twice as much hydrated chloral, three times as much hydrated chloral as isopral being required to produce paralysis of the respiratory center, at which time the vasomotor center was less affected after hydrated chloral than after isopral, as indicated by the asphyxial rise occurring after chloral, but not after isopral.

The deep respirations shown in the isopral tracing are due to struggling; the normal respiration is shown at the very beginning of the tracing. It is seen that the respiration stopped before a third of the second dose of isopral had been injected, and that the heart was rapidly failing, as shown by the short excursions, while the vasomotor center was soon completely paralyzed, for no asphyxial rise of blood pressure occurred, the heart stopping within three minutes after the respiration ceased. In the case of hydrated chloral more than three-fourths of the second dose had been injected before the respiration ceased, at which time the heart beats were much stronger, the heart continuing to beat vigorously for seven minutes; the vasomotor center was still active, as shown by the asphyxial rise of blood pressure. The ratio of toxicity of isopral to that of hydrated chloral, as shown in several of my experiments on dogs, in which the drug was injected intravenously, is as ten to four; this is confirmed in the present experiments, since respiration was paralyzed by less than half as much isopral as of chloral, but Impens gives the ratio of toxicity as ten to six, or a relative toxicity for chloral 50 per cent. greater than I was able to show.

A guinea-pig was given 0.4 gm. of isopral per kg., and another was given 0.8 gm. of hydrated chloral per kg., the latter being somewhat more deeply narcotized. Both were able to sit up in about four hours and were recovering apparently, but both died during the night—a result which might be attributed in part to the lowered temperature of the building at that time.

The results obtained in these experiments and confirmed in a number of others do not agree with the figures given by Impens for the relative toxicity of the two drugs.

Cats and dogs are so prone to fall asleep at any time in those places to which they are accustomed that it is evidently impossible to fix the minimal hypnotic dose with accuracy for these animals, hence but little value attaches to Impens' conclusions as to the exact effective dose for them. Rabbits usually remain awake during the day, and they, therefore, afford a better opportunity for comparing the effectiveness of hypnotics, and the indices of safety of isopral and hydrated chloral for these animals given by Impens are so nearly the same

that the difference may be considered as coming well within the limits of error. The figures given by Impens for this animal accord fairly well with the results obtained by myself in experiments on ten rabbits made before I had read Impens' paper.

From those experiments I had concluded that 25 parts of isopral equaled in effectiveness and toxicity 40 parts of hydrated chloral. It is not necessary to give the protocol, as I am willing to accept Impens' figures for rabbits with the reservations mentioned.

Wassermeyer⁶ reports that he used isopral in doses varying from 0.5 gm. to 2.5 gms. If we accept 40 to 25 as the ratio of toxicity of isopral to that of hydrated chloral, 2.5 gms. of isopral is equivalent to 4 gms. of hydrated chloral or, if the ratio be 2 to 1, 5 gms. of hydrated chloral, an amount which no careful clinician would venture to employ.

Kress⁷ used isopral in doses of from 0.5 gm. to 0.75 gm., and particularly advises caution in its use in cases of disease of the heart and vessels, urging that it be employed only occasionally, because we know nothing of the injury resulting from its continued use or from its decomposition products.

In conclusion, I wish to reiterate my belief that my experiments on rabbits and cats and Impens' experiments on rabbits show that there is no essential difference between the action of isopral and hydrated chloral in effective doses on the respiratory centers, while my experiments on dogs show that isopral is more than twice as active in depressing the vasomotor and respiratory centers and the heart, my figures for the relative toxicity almost precisely corresponding to those given by Impens for the relative effectiveness of the two drugs for the dog.

Cautious clinicians will not experiment with isopral except in carefully selected cases.

It seems almost superfluous to add that isopral, like hydrated chloral, is wholly unsuited for use in those cases in which sleeplessness is due to pain, since it is an anesthetic only in extremely dangerous doses.

My thanks are due to two of my students, Messrs. Rulison and Flagg, for assistance in certain of these experiments.

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PARANOIA, ITS VARIETIES AND MEDICO-LEGAL IMPORTANCE.*

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Psychiatry is the most backward of the sciences. This is not surprising because it deals with the most complex problems and has received but little aid from psychology, the study of the normal mind. So long as we are ignorant of the processes of normal thought and of the relation of brain to mind our knowledge of the processes of morbid thought must remain far from complete. The study of each, however, will help the other, and one of the most encouraging signs of the times is that psychologists, or some of them at least, are now studying the matter clinically and comparing the normal with the abnormal.

6. Berlin klin. Wochschr., xlii, 1180.

7. Berlin klin. Wochschr., xlii, 487.

*An address read at the meeting of the Philadelphia County Medical Society, April 10, 1907.

As a result of our comparative ignorance, the classification of the types of mental disease is most unsatisfactory. This is to be expected, for science is nothing other than classified knowledge. At present, classification is not scientific and accurate, but unscientific, inaccurate and necessarily in some degree untrue. The use of the same word to mean different things and of different words to mean the same thing increases the difficulty of classification. There is no authoritative and accepted nomenclature. Thus, the word *paranoia*, which when introduced into modern medicine was given a fairly clear and definite meaning, has come to be vague or, if you prefer a gentler word, wide in its significance. A learned English writer has pointed out that if it be accepted in all its meanings and *dementia præcox* in all its meanings, then all men suffering from any form of alienation have either *paranoia* or *dementia præcox*. The difficulty of classification is further increased because there are at present two divergent streams of psychiatric thought: one tries to simplify matters by proving the unity of all mental disease or at least by classifying all types of insanity under a few heads, the other attempts to clarify knowledge by multiplying types and separating from each other forms of disease, which, while identical in essentials, differ in non-essential symptoms. The final outcome will doubtless be increase of knowledge, but the present temporary result is confusion.

Unsatisfactory as classification is, every one admits that all forms of mental disease may be divided into two great types: first, the accidental insanities, so-called, in which heredity plays a smaller part and stress of life and bodily disease are the predominating causative influences; second, the insanities of degeneration, in which heredity is the one great cause, and the disease the inevitable result of the conjunction of a germ cell bearing the potentialities of certain qualities with a sperm cell bearing certain other abnormal potentialities. The disease begins with conception and the result, in the biologic not the theologic sense, is predestined, and comes to pass independently of the presence or absence of external stress or bodily disease.

Paranoia is one of the most interesting examples of the degenerative insanities. Owing to confusion in classification, the opinions of authors vary much as to just what should be included under the term, and all that I can do is to describe, briefly, *paranoia* as I have seen it and to trust that I shall not add to the already existing confusion. Since *paranoia* is a disease of personality and character, its description is difficult because the symptoms vary as the congenital temperament varies, and, since no philosopher has ever succeeded in classifying the numerous types of normal men, the classification of diseased men is not easy.

The *paranoiac*, then, is the product not of environment, but of heredity. He is the victim, not of external stress or bodily disease, but of internal, inherent, congenital weakness. The inheritance is rarely direct; that is to say, a *paranoiac* parent rarely has *paranoiac* offspring, but always there is a bad strain in the family; some form of insanity, marked eccentricity, pseudo-genius, epilepsy, hysteria, alcoholism, or criminality. Statistics from hospitals do not agree with this statement, but hospital data as to family histories, as a rule, are incomplete.

In private practice it is much easier to obtain correct histories and I have never known a true *paranoiac*, whose lineage I knew, who did not show some ancestral defect.