

In spite of this, Hatcher did not take the trouble to find out what were the minimum effective and fatal doses of isopral for intravenous injection into the dog. In the hands of an expert and experienced pharmacologist like Professor Mayor the intravenous method may sometimes yield satisfactory results, as we have seen, but in the hands of less experienced investigators it becomes a source of gross mistakes, and may even furnish results diametrically opposed to the actual state of affairs. And this is what has happened to Hatcher. If he had administered his drugs by the mouth he would not have worked in the dark, and he would have been able to see that the hypnotic dose of isopral lowers the blood pressure but slightly and does not affect the heart or arrest respiration. As I have shown, isopral does not retard the latter more than corresponds to the diminished consumption of oxygen during rest and sleep. The frequency of the respiratory movements is diminished, the amplitude increased. The exchange of air, therefore, is more complete for each respiration.

Even here Hatcher placed himself in conditions which prevented him from taking account of the various effects of isopral.

In conclusion, I do not think that the experiments of this author can alter in any degree the opinion which I have given on isopral, an opinion which has been strengthened by the work of Schmitt and Mayor.

The deductions which Hatcher has drawn concerning the clinical application of the drug naturally crumble to pieces. I may recall the circumstance that isopral apparently does not decompose in the system, but changes into a compound of glycuronic acid which I have isolated and analyzed, and described.⁵ Hatcher need, therefore, have no fear as regards the effects of products of decomposition of isopral on the system.

I have finished with what I have to say on the main points. It remains for me to make an observation regarding the style of the article. I do not lay any stress on the exaggerations contained in the introduction, but I protest most decidedly against the insinuations which accompany the criticisms.

ISOPRAL AND CHLORAL HYDRATE.

COMMENTS ON THE ABOVE CRITICISM BY IMPENS.

REID HUNT, M.D.

Chief of Division of Pharmacology, Hygienic Laboratory, U. S. P. H.
and M.-H. S.; Member Council on Pharmacy and Chemistry,
American Medical Association.

WASHINGTON, D. C.

Impens brings forward nothing new in this communication. Nearly half the article is taken up with quotations from other writers to support his previous contentions; the remainder is devoted to a criticism of Hatcher's methods. A very little examination suffices to show that Impens presents the matter from a most prejudiced point of view. By selecting only the parts favorable to his side and ignoring everything unfavorable his quotations of certain authors give an entirely erroneous impression of their attitude toward some of the chief points under discussion; he attributes experiments to one author (Frey) when there is evidence that this author never performed such experiments. He accepts without question other experiments, apparently favorable to his contentions, although a very little examination shows that they were made in such an unscientific way that no conclusions can safely be drawn from them. His

discussion of Hatcher's results is likewise one-sided and in some cases amounts to actual misquotation; he criticises Hatcher for certain omissions, although many of his own experiments are open to precisely the same criticism. The article appears to be for the most part a hasty highly-prejudiced, ill-considered production which contributes little to the elucidation of the subject under consideration.

That these criticisms of Impens's paper are justified is shown by the following considerations:

SCHMITT'S RESULTS.

Impens quotes Schmitt as having confirmed his results as to the "toxic quotient" of isopral. To a certain extent that is true, but a closer examination of Schmitt's figures shows that the confirmation is not as complete as Impens' words would lead one to suppose. Moreover, the criterions for judging the "effective" dose can not be so definite that they would be interpreted alike by all observers, so that this seriously impairs the availability of Schmitt's conclusions. Table 1 of Impens' article, taken from Schmitt, is a composite table made up partly from Impens' figures and partly from those of Schmitt. With one exception, all the figures for chloral are taken from one of Impens' previous papers. Schmitt determined the toxic quotient for isopral for frogs, rabbits and dogs and compared these with Impens' figures for chloral. In every case Schmitt's figures are less favorable to isopral than are Impens', as is shown by the following:

	Impens.	Schmitt.
Frogs	4.7	4.0
Rabbit	4.5	4.25
Dog	6.4	6.0

Schmitt adopted Impens' figures for chloral; if these figures are as low as those of Impens for isopral are high, then the differences between the two drugs disappear in the case of the frog and rabbit and are materially reduced in the case of the dog. As regards the latter animal, Impens¹ admits that his figures as regards isopral are extremely uncertain, and Mayor, whom Impens quotes so extensively, states (p. 833) that he abandoned the attempt to determine the hypnotic dose of chloral for dogs on account of the great irregularities (varying from 0.17 to 0.55 gm. per kilo. intravenously). Under these circumstances the experiments on the dog may be disregarded. Schmitt's figures for the toxic quotient of isopral in the case of the guinea-pig (4.7 as compared with 3.4 for chloral) are favorable to isopral, but they were obtained in an unsatisfactory way, viz., by subcutaneous injection. Impens records no figures for this animal. Schmitt reports no experiments on cats; this is to be especially regretted, for Hatcher obtained results widely different from those of Impens with this animal. A marked and definite difference in the toxic quotient therefore exists only for the cat as determined by Impens, and Hatcher's results throw doubt on the value of these. Granting that Impens is correct, however, the results with the cat are so peculiar that they should be classed as idiosyncratic, and there is no reason for assuming that the human organism would exhibit the same idiosyncrasy.

Before leaving the subject of the toxic quotient it is of interest to see what Mayor (whom Impens calls an "expert and experienced pharmacologist") has to say on this subject; on page 855 of the article quoted by Impens, Mayor states: "But this range of dosage (— toxic quotient) estimated for the rabbit seems to us

⁵ Internat. Arch. of Pharmacodynamics and Therap., Vol. 13.

1. Therap. Monatshft., 17, p. 474.

to give no serious information as to human therapeutics" (*"Mais cette zone maniable, appréciée chez le lapin, ne nous paraît donner aucun renseignement sérieux quant à la thérapeutique humaine."*) And, after giving some illustrations, he concludes (p. 856): "It is then indeed difficult to draw a positive conclusion from the fact that the toxic quotient of isopral is the larger." (*"Il est donc bien difficile de tirer une conclusion ferme du fait que la zone maniable de l'isopral est la plus large."*)

Impens' paper would undoubtedly lead the reader to suppose that Schmitt shared the former's views as to the superiority of isopral to chloral. That this is by no means the case, however, is shown by the following quotations from Schmitt: "If one examines in detail the action of isopral on the different mechanisms, it is found that this action does not differ sensibly from that of chloral" (p. 658). "On the heart the action of isopral has appeared to me identical to that of chloral in so far as it is difficult for me to find a difference in the cardiograms furnished by the heart of the frog after the administration of the two substances" (p. 660). "Another fact which identifies the action of isopral on the circulation with that of chloral is the vasodilatation" (p. 661). "I have not found, for my part, the diuresis described by Impens" (p. 661). "Résumé: from the experimental point of view, on animals, isopral acts exactly as chloral; the only differences I have found are (1) a more rapid action, (2) a greater activity with equal doses, (3) a more considerable range between the active and the toxic dose" (p. 661). Impens ignores all parts of Schmitt's paper except the last part quoted above. As we have seen, most of Schmitt's figures can not be accepted as satisfactorily showing that isopral has a more favorable toxic quotient.

An impartial account of Schmitt's paper would include such sentences as the following relating to the therapeutic use of isopral (*italics mine*): "Thus isopral succeeds in those cases where chloral succeeds and fails in those where chloral fails, so that up to the present at least one is not able to attribute to the new hypnotic any special indications" (p. 664). "The contraindications of isopral appear to be the same as those of chloral" (p. 665), and finally Schmitt's concluding sentence (p. 666), "*Dormiol is only a succedaneum inferior to chloral. Isopral is the equivalent of the latter; if slight advantages over chloral can be claimed for it, it has, on the contrary, all of its disadvantages*" (*"Le dormiol n'est qu'un succédané inférieur du chloral. L'isopral est l'équivalent de celui-ci; s'il peut revendiquer sur lui de légers avantages, il en a par contre tous les inconvénients"*).

MAYOR'S EXPERIMENTS.²

We have seen that Impens ignores all of Schmitt's paper except the small part more or less favorable to isopral. Mayor's paper is used in exactly the same way. Almost the only thing in Schmitt's paper which supports Impens' claims relates to the toxic quotient, and we have already seen that Mayor holds that little importance can be attached to this.

Impens quotes Mayor extensively as having shown that hypnotic doses of isopral are less depressing to the circulation than are similar doses of chloral, but a closer examination of Mayor's paper makes it doubtful if such a conclusion can be drawn from his experiments. In the

first place, there is a curious series of changes in certain figures. Impens quotes Mayor as saying that the hypnotic doses of isopral and chloral are

Chloral0.1 gm.
Isopral0.06 gm.

per kilo of animal when injected into the marginal vein of the ear. Mayor himself (p. 829) gives the following figures:

Chloral 0.12 gm.
Dormiol 0.13 gm.
Hedonal0.07 to 0.08 gm.
Isopral 0.06 gm.

These figures are taken from the theses of three of Mayor's pupils; he states that they have been modified from those originally published. Mayor then proceeds to quote the figures found in the thesis by Romanovitch.³ Romanovitch, however, used in every recorded experiment the figure 0.05 gm. per kilo as the hypnotic dose of isopral for the rabbit. Mayor evidently recognized later that this figure was too small and adopted 0.06; but the experiments which he quotes to show that the hypnotic dose of isopral is less depressant to the circulation than chloral are taken from Romanovitch's paper, where a figure which Mayor admits is too small was used. Is it to be wondered at that he found less depression? Romanovitch injected hypnotic doses of isopral (— 0.05 gm. per kilo according to him) and determined the effects on blood pressure and heart rate. He then prepared a table (one quoted by Impens) in which he summarized these results and compared them with experiments with chloral, performed not by himself (p. 80) but by Mayor and Nutriziano. The latter authors injected chloral in hypnotic doses (0.12 gm.). Thus 2.4 times as much chloral was injected as of isopral and the former was stated to produce a slightly greater depression of the circulation (see table quoted by Impens).

The method by which these figures, quoted by Impens, were arrived at by Mayor and Romanovitch is open to criticism; they represent the average blood pressure and pulse rate before the injection of the drug and two and twenty minutes after the injection. An examination of Romanovitch's tables shows what an imperfect picture such figures give. For example, in one experiment (33) the blood pressure twenty minutes after the injection was 90 mm. mercury, forty-seven minutes later it was 100 mm.; in the experiment immediately preceding (32) the blood pressure twenty minutes after the injection was 60, forty-five minutes later it was 46.

Considering that these figures represent the effects of 2.4 times as much chloral as of isopral and that the differences in the effects are not so very striking, it seems to me that we are justified in concluding that isopral is about twice as toxic to the circulatory system as is chloral. Impens finds the toxicity of isopral for the entire animal (rabbit) to be 1.7 times as great as that of chloral. In other words, the high toxicity of isopral as compared with chloral applies to the circulatory system also.

At first sight Mayor's experiments on dogs seem more conclusive, but a closer examination shows that they are open to even more criticism. Mayor abandoned the attempt to determine the hypnotic doses for dogs by intravenous injection, but states that he injected one drug until the corneal reflex disappeared, and then fifteen days later injected the other drug into the same dog until a similar effect was produced. The doses of chloral were almost invariably much larger than those of isopral. Nine of the twelve experiments cited by

2. Mayor's experiments were published in the *Revue medicale de la Suisse Romande*, Dec. 20, 1905; they have recently been republished in *Therap. Monatshefte*, May, 1907.

3. *Recherches expérimentales sur l'Isopral*, Geneva, 1905.

Impens are taken directly from Romanovitch's theses (p. 97); this author states (p. 84) that he determined the figures for isopral, but that he is indebted to Mayor for the figures for chloral. Apparently one person determined one figure and another the one for comparison. As is well known, the point at which the corneal reflex disappears in a dog is not very sharp; experienced observers would differ. There is thus introduced into most of Mayor's experiments an error (a personal equation), and it is probable that this is for the most part in one direction; it may be high or low, but in any case a person must hesitate to accept the results. These tables are far from giving a true picture of the experiments themselves; the figures are for the blood pressure and pulse rate before the drug was given, when the corneal reflex disappeared and again when this reappeared. All other figures are disregarded; the figures for the minimum depression (which might as well have been selected) would probably have presented a different picture. The "normal" figures were obtained on animals operated on without anesthesia, probably by different persons; the appearance and disappearance of the corneal reflex was also determined (as far as can be judged from the papers) by different persons in most of the experiments.

In any case the differences were not very great, as is shown by the table (p. 854) of Mayor immediately following the part quoted by Impens; in seven of the eleven experiments the greater depression varied from 3 to 8 per cent., in three from 16.5 to 27 per cent., while in one case isopral caused a greater depression by 3 per cent. Considering the sources of error, not much importance is to be attached to these differences.

It would be interesting to know what doses of the hypnotics were administered; Romanovitch gives them for isopral in the protocols of his experiments, but I can not find the corresponding ones for chloral. The doses for isopral varied from 0.09 to 0.17 gm. per kilo body weight; the average was 0.14. Mayor states (p. 833) that the minimum dose for chloral was 0.17 gm., the maximum 0.55 gm.; he refers to three experiments in which the doses were 0.17, 0.32 and 0.47 respectively. The average of the four figures actually given is nearly 0.38 or nearly three times that for isopral; it is certainly not unreasonable to suppose that the average for chloral was more than twice that for isopral (in similar experiments on rabbits it was 2.4 times). The effects of these doses on the blood pressure were not markedly different; in seven of ten experiments the difference was but from 3 to 8 per cent. If we are justified in drawing any conclusions from Mayor's experiments, it is that isopral is at least twice as toxic to the vascular system of the dog as is chloral; Hatcher found it to be more than twice as toxic. Impens⁴ gives the lethal dose of isopral for the dog as 0.6 gm. per kilo; that of chloral was 1 gm. or it required 1.7 times as much chloral to kill as of isopral. In other words, isopral seems to be relatively more toxic to the circulatory system than to the organism as a whole. It should be emphasized, however, that no satisfactory conclusions can be drawn from Mayor's experiments; the above seem to be more reasonable than any others.

Attention may also be called to what seems to be a deliberate distortion by Impens of part of Mayor's paper. In the latter part of his article Impens criticises Hatcher severely for anesthetizing his animals; he does not do Hatcher the justice of stating that the anesthesia was

very light and that the ether was withdrawn some time before the chloral or isopral was administered, and that these were then administered not in hypnotic doses but in fatal doses, so that it is very unreasonable to suppose that their action was appreciably influenced by the small amount of ether. In discussing Mayor's results Impens says Mayor "warns against the use of ether as an anesthetic." Mayor simply states that he did not use ether because he thinks that an animal with such a sensitive nose as the dog suffers more from the ether than from the slight operations necessary for the insertion of the cannulas. This sentence of Impens seems to be an effort to prejudice the reader against Hatcher.

Thus we find that Impens is silent concerning Mayor's unfavorable attitude toward the "toxic quotient," that he gives an entirely false impression concerning Mayor's remarks about the use of ether, and that finally in quoting from Mayor's papers he ignores the serious and very obvious objections to this author's methods. Those familiar with Impens' previous writings (the one in which he discussed the product of a rival firm, chloretone, for example) will be struck by this sudden loss of critical ability.

Impens says: "Frey made comparative experiments with chloral hydrate . . . and isopral . . . and came to the same conclusions, viz., that isopral showed the greatest interval between the minimum physiologic dose and the lethal dose." In the only paper on this subject by Frey⁵ I have been able to find this author states perfectly plainly that he has taken the figures for isopral from Impens. There is nothing to indicate that he experimented with this drug himself; if there are other papers on this subject by Frey, Impens should have given the reference.

I have not yet been able to obtain Carusi's paper.

HATCHER'S EXPERIMENTS.

In his discussion of Hatcher's experiments Impens again exhibits a very one-sided way of looking on the subject. He is most critical of Hatcher, but apparently forgets that his own experiments are open to precisely the same criticisms. Thus he arraigns Hatcher severely for reporting but "one experiment on one single cat" with a small dose of isopral. Yet Impens⁶ placed the lethal dose of isopral at 0.4 gm. because "one single cat" recovered from 0.35 gm. isopral and another died from 0.4. He reported no experiments with doses between 0.1 gm. and 0.35 gm. The "single cat" which recovered from 0.35 gm. evidently had a narrow escape; it received the drug one morning, the respiration sank to 11 per minute and the cat slept all of that and the following day. There is as much reason to suppose that this experiment with 0.35 gm. is an exceptional case as that Hatcher's one experiment was exceptional.

Impens says Hatcher has not a clear idea of what is meant by a minimum effective dose and expresses a desire to "refresh his memory" and says the minimum effective dose is "the smallest possible quantity which may induce sleep." This is not consistent with an earlier expression of Impens. For instance, in choosing the effective dose of chloral for rabbits, he says:⁷ "From all the experiments which I have made we may conclude that the effective dose of chloral hydrate for rabbits is 0.356 gr. per kilo. One would even say 0.334 gr., but with that quantity the effect is not certain, and I prefer to accept the former dose." Impens attributes to Hatcher

5. Arch. int. de Pharm. et de Ther., 13, p. 464, 1904.

6. Therap. Monatshft., 17, p. 472, 1903.

7. Arch. int. de Pharm. et Ther., 8, p. 83.

4. Therap. Monatshft., 17, p. 474.

an admission of his inability to distinguish between medicinal and natural sleep. What Hatcher actually said was that it was difficult to fix accurately the minimal hypnotic dose. Evidently Impens himself experienced this difficulty, for it is very plain from a perusal of his protocols that he did not even try to determine the minimal *hypnotic* dose, but chose rather the *narcotic* dose, which is indeed much easier.

Impens is also very remiss in not giving any of the experiments on which he bases the toxic quotient for chloral for cats. As Impens' results with cats were very different from those obtained by himself and others (see Schmitt's tables, quoted by Impens) with other animals, and in such direct conflict with Hatcher's results, he might well have devoted some of the space occupied with a criticism of Hatcher to giving at least a few experiments on this subject.

If Hatcher is at fault in not reporting more experiments on the minimal hypnotic dose of isopral, Impens is at fault in not reporting more experiments on the lethal dose of isopral and in not reporting in detail any experiments on either the hypnotic or the lethal dose of chloral for cats.

Every word of criticism Impens directs against Hatcher on this score is equally applicable to Impens' own work.

The question whether the results of the rectal injection of these drugs gives results comparable to those when they are given *per os* can be easily determined by experiment. Impens argues that the absorption from the rectum is slower; Hatcher states that it is somewhat more rapid. Slow absorption might explain the fact that Hatcher placed the hypnotic dose of isopral higher than did Impens, but it would not explain why Hatcher found the toxic dose for isopral lower and that for chloral higher than did Impens. Impens himself stated in a previous paper⁸ that the absorption of chloral from the intestine (the author quoted, Walton, says "rectum") is much more rapid than from the stomach.

Impens criticises Hatcher's blood pressure experiments chiefly from a point of view different from that which prompted Hatcher to make them. Impens says: "If he (Hatcher) had administered his drugs by the mouth . . . he would have been able to see that the hypnotic dose of isopral lowers the blood pressure but slightly." Hatcher was not determining the effect of a hypnotic dose on the blood pressure—he was determining the relative danger of the two drugs "by their depressant action on the respiratory and vasomotor centers." Surely no one could suppose that if Hatcher were experimenting with hypnotic doses he would have injected the drugs until they killed the animals.

Impens also says: "Hatcher did not take the trouble to find out what were the minimum effective and fatal doses of isopral for intravenous injection into the dog," and then refers to Mayor. If Impens had read the papers of Mayor and Romanovitch carefully he would have known that these authors thought it useless to try to make such determinations. It seems to me that Hatcher's blood pressure experiments simply afford further evidence that isopral is at least twice as toxic as chloral to the vascular system; this also seemed to be the only conclusion that could be drawn from Mayor's experiments with hypnotic doses.

Impens states: "Hatcher need have no fear as regards the effects of products of decomposition of isopral on the system." This is an inexcusable misquotation.

Hatcher had simply quoted Kress as stating that "we know nothing of the injury resulting from its continued use or from its decomposition products." Incidentally, Impens rather contradicts himself in saying: "Isopral does not decompose in the system." In the paper⁹ from which he quotes he states: "About 60 per cent. of the product was excreted by the kidney. The rest must have been oxidized after the displacement of the chlorin atoms."

Viewed from an impartial standpoint, or rather from the standpoint of one who is anxious to find good in the products of a firm which has the great merit of endeavoring to discover something really new, it is impossible to resist the conclusion that this article of Impens weakens rather than strengthens the position of isopral. If the promoter finds it necessary to pass over in silence much of the work of Schmitt, selecting from it only the small part favorable to isopral; to ignore Mayor's criticism of the value of the "toxic quotient," but to quote in extenso experiments of very questionable value from this author; to distort Mayor's remarks about the use of ether anesthesia, and apparently to misquote Frey; to engage in abusive language concerning Hatcher, although his own experiments are for the most part open to precisely the same criticisms that he makes on Hatcher's experiments—the impartial reader can not avoid the suspicion that if isopral offers advantages over chloral they are so slight as not to be easily detected. And in this connection the claims made by the manufacturers for isopral should not be forgotten; for example, they claim that it is "the safe hypnotic of the chloral series," that it is "much freer than chloral from depressing effects on the heart and nervous system," etc.

It would seem better to confine the claims to the more rapid action which is universally conceded and which might be of distinct advantage, for instance, in convulsive conditions, and to the advantages which may come from the smaller doses necessary to produce a given effect.

Hatcher's experiments, although by no means complete and exhaustive, amply justify the warning he uttered against accepting without question the optimistic and enthusiastic statements of even the best firms—firms which are making almost yearly additions to the list of really useful drugs.

HUMAN MYIASIS FROM THE SCREW-WORM FLY.

(*Comptosmyia macellaria*—Fab.).

C. E. YOUNT, M.D.

Former Instructor in Pathology in Georgetown University.
PRESCOTT, ARIZONA.

AND

M. T. SUDLER, Ph.D., M.D.

Dean of the Scientific Department, School of Medicine, University
of Kansas.
LAWRENCE, KAN.

The attacks of the screw-worm fly or *Comptosmyia macellaria* (Fab.) on man and domestic animals have been observed for many years in the southern and west central parts of the United States. The disease is not rare, and in man its results are always serious or fatal if not recognized and actively and properly treated. The twenty-three cases reported occurred during a single

8. Arch. int. de Pharm. et de Ther., 8, p. 84.

9. Arch. de Pharmacodyn., xiii, p. 40.