the injection of magnesium sulphate would appear to vary, the above cases being the extremes in the present series.

A study of the literature available to us suggests that only two groups of workers have undertaken the necessary control observations—namely, examination of the bile aspirated at operation from the gall-bladder and common duct in patients who had previously been intubated, concentrated magnesium sulphate being the biliary stimulant employed. Knott and Bowell (1924) investigated five cases, and their reports do not show any constant parallelism between the findings in the bile removed at operation and that obtained by medical drainage. In parenthesis it should be noted that Venables and Knott (1924) introduced into the duodenum only 10 c.cm. of a 25% solution of magnesium sulphate instead of 75 c.cm. of a 33% solution as recommended by Lyon. It is not surprising, therefore, that they were unable to confirm Lyon's claim that three distinct types of bile could be recovered (Bile A, B, and C). The small amount of the stimulant used may also explain why the number of cells present in the specimens was often much less than was found by us. Mateer and Henderson (1926) could not find any leucocytes or epithelial cells in the bile aspirated direct from the gall-bladder at operation in 54 cases, though in 51% of the same group they found bile-stained cells in the bile recovered by duodenal drainage after the administration of magnesium sulphate before operation. They regarded these cells as evidence of inflammation of some part of the biliary tract other than the gall-bladder; but this assumption lacks proof, since they did not examine bile obtained from the common or hepatic ducts.

The work of the above authors strongly supports our contention regarding the local irritating effect of magnesium sulphate on the duodenal mucosa and that the cells do not come from the gall-bladder. It should be noted that the necessary comparison of the cytological effects of other biliary stimulants with that of magnesium sulphate in the same patients was not undertaken as an additional control. Our repeated failure to find cells in the bile removed by intubation after the administration of peptone and olive oil, in cases in which many cells were present in the bile obtained after magnesium sulphate, suggested at once a possible fallacy in this diagnostic method.

Summary and Conclusions

A study has been made of the cellular content of: (a) bile removed by duodenal intubation after the administration of magnesium sulphate, peptone, and olive oil in patients with and without disease of the biliary tract; (b) bile aspirated at operation from the gall-bladder and common duct in patients suffering from cholecystitis and cholelithiasis; (c) fluid removed from the mucosa of the human stomach, duodenum, jejunum, and ileum, exposed at operation, which had been submitted to the local effect of saline, peptone, and magnesium sulphate.

From the above experiments it is concluded that the cells present in the bile obtained by duodenal drainage after the administration of magnesium sulphate may be produced by local irritation of the duodenal mucosa, and hence do not necessarily indicate pre-existing inflammatory disease of the biliary tract. Attention is drawn to the fact that the degenerating oval or cuboidal duodenal epithelial cells may closely simulate pus cells.

We wish to express our thanks to our surgical colleagues in the Royal Infirmary for permission to investigate their cases, and in particular to Prof. J. R. Learmonth for his advice and help in the experiments connected with the action of magnesium sulphate on the exposed mucous membrane of the alimentary tract. One of us (J. I.) was in receipt of the McCosh Bursary and Crichton Scholarship in Medicine during the period of this investigation.

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[NOTE.—Since the completion of this paper for publication we asked some of our medical colleagues on the staff of the Edinburgh Royal Infirmary to select patients in their own wards who were not suffering from disease of the gastro-duodenal or biliary tracts, in order that we might demonstrate the irritant effects of magnesium sulphate as used in duodenal intubation. Our colleagues watched the technique being carried out and personally made a microscopical examination of the specimens of bile recovered. The results obtained were similar to the findings shown in Table I.]

OBSERVATIONS ON SOME NORMAL AND INJURIOUS EFFECTS OF COLD UPON THE SKIN AND UNDERLYING TISSUES

III. FROST-BITE

BY

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Frozen Skin

Skin can be frozen in the living subject very readily by bringing it into contact with sufficiently cold metal or by allowing a jet of very cold air to impinge upon it. These methods I used extensively to study the effects of freezing (Lewis and Love, 1926). Freezing of the skin in a current of cold air is recognized by an observer the instant it happens. The patch of skin affected seems at once to become pale, dull, opaque, and of a yellowish colour. The attentive subject recognizes freezing at once when it is due to metallic contact, the formation of ice crystals in the skin being accompanied by a very definite pricking sensation. In a jet of cold air freezing may happen without subjective sensation; or it may be signalled by a little short stinging pain that is felt abruptly in the part. All these observations of the laboratory conform with the experience of sufferers from frost-bite in the open air. Skin that is frozen without involvement of the subcutaneous tissue forms a hard plaque in the skin, with edges which are sharply defined and by which the plaque can be lifted. It feels like a coin embedded in the skin. When the frost extends deeply the frozen tissues are solid and immovable.

Freezing-point of Skin

Although very accurate determinations of the living skin's freezing-point have never been made, this point is known accurately enough for our purposes. It is certain that it lies below the freezing-point of water, and it is equally certain that it is not far from -1° C. The freezing-point of blood serum is -0.53° C., from which that of skin is unlikely to be far removed. If metal bars at exactly known temperatures are applied to the human skin, freezing can be shown to occur on occasion at a surface temperature as high as -2° C. (Lewis and Love, 1926). Such an observation fixes a temperature between which and 0° C. the actual freezing-point of skin lies.

Supercooling

It is now to be said that skin when cooled very rarely freezes at its true freezing-point. It exhibits in very

remarkable degree the property called supercooling (Lewis and Love, 1926). If the skin is cooled by contact with cold metal it is unusual for it to freeze unless its surface temperature is reduced below -5°C. , and it often happens that this temperature is lowered to as much as -10°C. , and sometimes to -15° or even to -20° , without the occurrence of freezing. It is not merely a matter of surface temperature; the whole thickness of the skin may at times be reduced to -10°C. and remain unfrozen. Freezing will generally occur between -5° and -10°C. if such temperature is maintained; but the actual temperature required and the time for which cold metal must be applied vary greatly, not only from one skin to another, but from point to point of the same skin, and even in successive observations on one and the same small area. Freezing begins with difficulty, but once started it spreads rapidly throughout all the chilled tissue, progressing the more quickly the lower the point to which preliminary cooling has been carried. As in the case of a cooled vessel of water, the formation of the first ice crystals encourages the formation of more, and so water or skin that has already been supercooled quickly becomes solidified once freezing starts.

This power to supercool is normal; it is a very important protection against freezing and the injurious effect that would arise out of this physical change. It has been found that supercooling displays itself in greater degree in skin that remains unwashed. Washing the skin encourages, while rubbing the skin with spirit and anointing it with oil discourages, freezing. The capacity to supercool greatly would seem to be connected with relative dryness of the horny layers of the skin. It is well known that Arctic explorers leave their skins unwashed.

The level of temperature at which skin freezes does not seem to be influenced appreciably by the presence or absence of a blood flow to it; but, naturally, blood flow according to its degree will affect the rate at which the preliminary cooling of the skin occurs.

Natural Frost-bite

The conditions under which natural frost-bite occurs are known to us from the observations of those who have lived in very cold climates. When atmospheric temperature is below 0°C. the air contains no moisture. Frost-bite occurs only when the air is dry and when the ground is snow-clad or frozen. It is frequent in people moving about out of doors when the temperature is as low as -30°C. (-22°F.). The radiant heat of the sun protects against frost-bite. Wind favours its occurrence, for in a still atmosphere the skin tends to become enveloped in a layer of air which the skin itself has warmed; thus Brahdy (1935) speaks of frost-bite as frequent with a temperature of -13°C. (8°F.) if there is wind. Natural frost-bite occurs chiefly in parts of the skin that are exposed and in those parts of such skin that cool most readily. When both are exposed the hands cool more readily than does the face; the fingers, the ears, and the nose cool fastest, and in the order stated. It is customary to give special protection to hands and ears; consequently frost-bite of the nose is relatively more frequent than it otherwise would be. Frost-bite of the feet is relatively unusual, for circulation in the feet is generally maintained active by walking; the feet will suffer if they are kept still in very cold air or in snow for long periods, for when still the feet cool as quickly as the hands. Tight coverings of legs or feet by interfering with circulation encourage cooling and increase the chance of frost-bite. Freezing of feet while immersed in sea-water can hardly occur; for the temperature of the water cannot fall below -1.9°C. , its own freezing-point.

Effects of Freezing

These lesser effects have been described in full detail in my original article with Love (Lewis and Love, 1926). When the skin has been frozen its invariable response when thawed is a state of hyperaemia. The local redness of the skin, due to dilatation of all its small blood vessels, occurs after the lightest freezing. If the skin has been frozen harder—namely, at -10° to -15°C. for about twenty seconds—the local redness is shortly followed by itching and by swelling, and a full wheal develops precisely over the area frozen. This wheal is surrounded on all sides for some centimetres by a bright red flare, the result of reflex vasodilatation. The local reddening, the wheal, and the flare compose what I have called (Lewis, 1927) the “triple response.” They are due to the release of a histamine-like substance or substances from the cells of the skin, the release resulting from the injury caused to the skin cells by the ice crystals formed in it; and they together constitute a simple acute inflammation, the typical immediate reaction to physical injury. The wheal gradually subsides within a period of a few hours, leaving behind it an area of local redness. This redness persists, and next day at latest the corresponding skin is a little swollen, is tender to friction, and gives pain when warmed. Sections of the human skin taken twenty-four hours after the injury display a little oedema of both epidermis and dermis, and a perivascular infiltration of the superficial layers of the dermis with lymphocytes, extravasated red blood cells, and some polymorphonuclear cells (personal observations). This infiltration may in some instances be intense enough within a few days to give to the affected skin a yellow colour. Within about a week the tenderness of the skin has subsided and the epidermis has proliferated and presents a crinkled pigmented surface, which soon peels. After peeling, the redness of the skin gradually fades, though pigmentation often persists for many weeks or even months.

Such are the simplest reactions to freezing in the human skin. If freezing has continued at -15°C. for thirty to sixty seconds, or at -20°C. for fifteen or thirty seconds, then the lesion that follows is more severe. Usually the wheal which at first forms gives place within an hour or two to blister, which, curiously, is predicted in the stage of thawing by the occurrence not of itching but of burning pain. Such blisters are associated with a more pronounced exudative inflammation than that described as following the wheal.

Still greater damage occurs when freezing is more severe and more prolonged, for the skin is frozen harder and the frost penetrates more deeply. Corresponding lesions are well illustrated by the effects of freezing the skin with CO_2 snow (the temperature of which is about -57°C.) and by severe frost-bite in man (Hodara, 1896a, 1896b). The results of such freezing have also been extensively investigated in animals, especially in the rabbit's ear, by Cohnheim (1873) and others (Brahdy, 1935; Fuerst, 1898; Hodara, 1896a, 1896b; Kriege, 1889), observations that have enlightened us particularly as to the train of events leading up to loss of tissue. The end-result of severe freezing, where there is deep penetration of the tissues, is necrosis. The blood flow in the milder lesions is not interrupted, but there is general agreement that necrosis is brought about largely through injury to the blood vessels of the skin and subjacent tissues; it is the rule to find thrombi within them* (Kriege, 1889; Hodara, 1896a, 1896b). These are of various kinds—platelet, hyaline, and

* Recklinghausen (1883) is cited to the same effect, but it is not clear that the gangrene in this case followed directly on frost-bite. Rischpler (1900) believes that necrosis can occur without thrombosis.

fibrinous in both the smaller arterioles and the larger arteries and veins—and appear within a few hours of freezing; they have been found in human frost-bite not only in tissue in the process of undergoing necrosis but in tissue on the border of such necrosis, and in tissue where necrosis is threatened.

It is clear from past observation and experiment that freezing at such temperatures as -15° to -20° C. must be continued for a matter of minutes if necrosis of the frozen tissues is to follow. But it is not clear that damage to a given tissue progresses beyond a certain point when freezing in it is prolonged. It would seem probable that freezing brought about at -15° or -20° C. soon enters a stable condition so far as a given small group of cells is concerned, and that damage to the cells concerned is full for that temperature and does not increase steadily with time. It is known in general that lesions become severer with lengthening exposure. But the increased severity of damage to skin as freezing is prolonged is probably due, once a hard frost has been ensured, to extension of freezing to deeper layers of skin and to subjacent tissues, rather than to progressive damage of individual cells. There is, at all events, no evidence to show that a severely frozen limb in which freezing has after a time ceased to extend becomes subsequently damaged in proportion to the time which it remains frozen. Some progress there may be, but almost certainly the chief factors governing the degree of damage are the hardness of the frost and its extent: time, apart from its influence in increasing the freeze, is not known to be a material factor.

Secondary Injury.—There is some evidence that when the skin has been frozen the damage sustained may be added to in the stage of the reaction itself by the rapid outpouring of fluid between the tissue elements (Lewis and Love, 1926). If the venous return from a limb on which a small area of skin has been frozen is obstructed during the stage of thawing and for five minutes afterwards, subsequent whealing is much diminished and seemingly the return of the tissues to a normal state afterwards is expedited (Lewis and Love, 1926).

Treatment of Frost-bite

Our knowledge of frost-bite and the manner in which the skin reacts to it suggests certain measures in its treatment, which will be dealt with briefly.

When the patient is seen at a stage at which the tissues are frozen the first step will be to induce thawing. There are two reasons why this should not be done too rapidly. First, rapid thawing will be followed by intense swelling of the tissue, and this is probably in itself injurious. Secondly, the more rapid the warming the greater will be the pain, and following thawing it may be very severe. The long-established custom of rubbing the frozen part with snow will ensure slow thawing, and its reputed effectiveness probably depends on this fact. But friction is not to be recommended in itself: thawing will not occur unless friction is brisk, and such friction will tend to damage the skin and to increase the reaction. It would seem preferable, when it is practicable, to apply warmth of reasonable amount. It should be no more than suffices to induce thawing under strict control. Thus if the skin is unbroken, cold water, rising to no higher temperature than 10° or 15° C., may be applied safely and will answer the purpose, precaution being taken then and subsequently to prevent the return of a full circulation to the damaged tissues. In the case of a limb, its arteries may be compressed until thawing is complete, and the compression then be relaxed gradually to allow the blood to return to the limb little by little. The temperature of the part that has been frozen can in

this way be raised very slowly, as is desirable, and warmth mainly allowed to come to it through the returning blood. If in the process pain becomes severe it can be moderated by cooling the part once more as the circulation returns to it. The object should be to restore the blood flow and warmth gradually and thus restrain vascular and accompanying reactions.

When this has been effected the limb may be protected by wrapping it lightly with cotton-wool or lint, covering it with a cradle, and maintaining around it a reasonably cool temperature. Further treatment will be demanded by blisters and by necrosis with ulceration. From this standpoint it should be recognized that between the lesions following freezing and those following heat there is no fundamental distinction. All such lesions are the result of greater or lesser injury of cells of the skin and of deeper integuments, injury which brings partial or complete disintegration of the cells. The reactions that follow are not properly regarded as reactions to frost or to heat, but to tissue injury. The heating and the freezing are transient, and the reactions we see are the reactions to what heat and frost leave behind them. In both instances the reaction is a response to substances released largely from living cells and in part from killed cells. It is true that heat differs from frost in that it has the power to coagulate the tissues and in the end to consume them; but the important fact remains that the reactions, as we trace them through different grades of severity and compare equal grades, are fundamentally alike: local redness, wheal, flare, blister, cellular exudate, vascular thrombi, and necrosis appear in each, as do the appropriate processes which isolate and separate off dead tissue and lead to repair.* The presence of incinerated tissue in the case of injury by fire is the only notable difference and one that has no high importance; this difference does not exist in a comparison of freeze and scald.

It follows from what has been said that the rational treatment of the lesions of frost-bite and scald have much in common. The appropriate routine treatment of one or other state must of course be governed ultimately by one consideration only—namely, by its proved effectiveness. But in considering new means of treating, theoretical considerations can guide. A guide to the treatment of lesions following frost-bite which I would strongly recommend is that they should be dealt with in the same way as are similar lesions resulting from heat, in respect of the treatment of which we possess much recent experience.

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* For detailed evidence of this similarity a number of papers may be consulted (Cohnheim, 1873; Gans, 1925; Lewis, 1927; Lewis, Grant, and Marvin, 1927; Lewis and Love, 1926; Samuel, 1868; Uschinsky, 1893).

S. B. Lovelady, J. R. McDonald, and J. M. Waugh (*Amer. J. Obstet. Gynec.*, 1941, **42**, 309) made a study of thirty-four benign growths of the vulva which had been removed at the Mayo Clinic from 1906 to 1939 inclusive. The commonest types were fibromas, lipomas, and haemangiomas. Two neurofibromas, two leiomyomas, a ganglioneuroma, and a lymphangioma were also encountered. A striking feature was the lack of symptoms produced by the tumour in the majority of cases.