of the skin to ultra-violet light. He has found that it doubles the minimal erythematous dose, and he also states that when the same patients were submitted to six minutes' exposure before, during, and after cortisone therapy the effect of cortisone was to promote pigmentation and, as one might therefore expect, to diminish the harmful erythematous and vesicular reaction.

From these simple and precise observations Dr. Järvinen draws the somewhat surprising conclusion that in this respect cortisone is not increasing the resistance of the skin to the injurious effect of ultra-violet light, but rather suppressing the normal protective mechanism by which this resistance is augmented and maintained. This can be true only if we regard erythema and vesiculation as a protective mechanism and pigmentation as an injurious effect. Since the opposite is a more prevalent teleological interpretation of the phenomena of photosensitivity, I would like to submit that his experiments indicate a true increase in the resistance of the skin to ultra-violet light as exemplified by the doubling of the minimal erythematous dose and that they also suggest a stimulation of the protective mechanism if we are entitled to regard pigmentation in this light.—I am, etc.,

Merck and Co., Ltd.,
Montreal.

J. H. LAURIE,
Medical Director.

Night Pain with Fractured Clavicle

SIR,—Within the last 10 weeks I have had two cases in children under 5 of fracture of the outer third of the clavicle. Clinically they have been misleading in that there is no deformity; there is practically no loss of function—the child has been able to dress and undress itself apparently without pain, including pushing the affected arm into a jersey, etc.; there is no apparent general disturbance. There has, however, been one feature common to both cases, and that is pain at night in bed. I suppose the anatomical structure maintains position while erect, but on lying down and turning over in bed pressure is brought on the fracture, or is it relaxation of muscles while asleep? Both cases were found on x-ray examination.

I wonder if any other people have found this pain-in-bed story connected with fracture of the outer third of the clavicle in young children.—I am, etc.,

Hadlow, Kent.

J. B. MARSHALL.

Treatment of Anthisan Poisoning

SIR,—Your report of a further two cases of "anthisan" poisoning in children (December 22, 1951, p. 1530) prompts me to take out of their context some of the results of an investigation into the cerebral effects of histamine. This investigation, which will be published eventually, necessitated the administration of anthisan in toxic doses to a large number of animals. The findings were so uniform in all the species examined (mouse, rat, guinea-pig, and rabbit) as to favour the view that they might also apply to human beings, especially as the clinical features of anthisan poisoning are very similar in man and animals.

Anthisan is a central convulsant—i.e., the convulsions seen in poisoning are not a secondary effect of interference with respiration, as is sometimes suggested, but depend on a direct action of the drug upon nervous centres. The average convulsive dose is very near the average lethal dose, and the gravest view must therefore be taken of any case presenting convulsions. Death is the result of respiratory depression, which occurs after the animal has passed through the convulsive stage. With slow absorption of the drug the central nervous system shows successively depression, excitement and increased reflex activity, tonic-clonic convulsions, coma, and respiratory depression. These stages correspond to the severity of the intoxication, and all four stages are therefore only seen with fatal or near fatal doses. Anthisan may be classified with atropine as a "deliriant narcotic," and their similarity of action is not fortuitous.

Orthodox anticonvulsant drug therapy is likely to prove disastrous in anthisan poisoning. The administration of ether, chloroform, soluble barbitone, or "nembutal" to experimental animals, while leading to a prompt cessation of the convulsions, greatly diminishes the survival rate by hastening and deepening the

stage of respiratory depression. It should be remembered that convulsions, unless of great severity and long duration, are not a life-threatening symptom in themselves. Their abolition is therefore not usually a legitimate therapeutic aim unless it is achieved by means which relieve rather than deepen the underlying intoxication of the central nervous system.

The effect of histamine on anthisan poisoning is markedly diphasic. In relatively small doses it has an important anticonvulsant and life-saving action, while in larger doses it increases mortality. With simultaneous administration the greatest life-saving effect is produced by an anthisan:histamine acid phosphate ratio (weight for weight) of 4:1 in the guinea-pig and 1:1 in the mouse, using average lethal doses of anthisan. To translate this finding into terms of human therapy is extremely difficult, not only because of species difference but also because poisoning in human cases is usually by mouth and the amount swallowed is rarely known. Moreover, animal experiments suggest that it is very difficult to dislodge anthisan from its central receptors, and histamine therapy becomes successively less effective as the interval between anthisan and histamine administration grows. In spite of this, a cautious trial of histamine in these desperate cases can be recommended, especially as absorption of anthisan is often still proceeding when they are first seen by a physician. If histamine is tried as an antidote, steps must be taken to protect the patient from the acute and severe hyperchlorhydria which will ensue.

Morphine occupies theoretically an ambivalent position in the treatment of anthisan poisoning. As a respiratory depressant it would seem to be contraindicated, as a histamine-releasing drug it might be an ideal therapeutic agent. Preliminary trials in mice have not yet given an unequivocal answer, but I think that a clinical trial of its efficacy as an antidote would be justifiable. Judging from animal experiments, it is certainly preferable as a sedative to barbiturates in these cases.

Adrenaline and atropine hasten death from anthisan poisoning in experimental animals.

On these imperfect data we may base the following scheme of treatment:

1. Wash out the stomach.
2. Treat the patient in a darkened room and avoid all unnecessary stimulation.
3. Do not administer inhalation anaesthetics or barbiturates.
4. If drug therapy seems desirable, try morphine or histamine, the latter in doses no greater than the amount (weight for weight of histamine acid phosphate) thought to have been absorbed by the patient.
5. Watch for respiratory depression, and give respiratory stimulants if it supervenes.
6. Take any supportive and eliminative measures which are not in conflict with the above.

An improved outlook in anthisan poisoning will result from the conscientious reporting of all cases with full notes on the treatment, even if unsuccessful. Meanwhile a certain number of lives may be saved by attention to these (largely negative) injunctions.

These observations probably apply to a greater or lesser extent to all antihistamine drugs. They are all central convulsants in toxic doses, and it is to be assumed that the mechanism of production of toxic manifestations is the same. I cannot conclude these remarks without making reference to the great help which I have received from Dr. Roy Maxwell, of May and Baker, Ltd., both in the supply of drugs and in the giving of expert advice.—I am, etc.,

Edinburgh.

ERICH GEIRINGER.

Discovery of the Formol Gel Reaction

SIR,—I am very much indebted indeed to Colonel W. C. Spackman for his letter (October 13, p. 911) about the discovery of the formol gel reaction, as it provides a very good opportunity for me to give a short account of the history of this discovery in the light of real facts, and not as presented in some publications.

In September, 1920, while I was a medical student and assistant at the Diagnostic Laboratory of Dr. Gaté, of the Bacteriological Institute of Lyons (France), there was a violent explosion that destroyed part of the Institute, including the refrigerator in which I used to keep the mixture of positive and the mixture of negative

serums of the previous week's Wassermann tests. Being at that time responsible for these tests and wondering where to keep the serum-controls each time used, I thought of adding to them a few drops of formol.

When I next wanted to use these serum-controls I observed that the positive mixture had jellified and was stuck to the bottom of the test-tube, while the negative mixture remained fluid, with no change whatsoever. This phenomenon seemed strange to me, and made me wonder whether, if repeated, it could not be used as a specific reaction for the diagnosis of syphilis. I tested immediately with formol some serum specimens, syphilitic or not, that I had available, and next day I observed that the former became jellified while the latter remained unchanged. I communicated this to Dr. Gaté, who during the succeeding days sent me from the Antiquaille Hospital of Venereal Diseases, in which he was assistant, a great number of syphilitic blood specimens for testing them comparatively with formol and at the same time by the Wassermann reaction.

The experiment was simple: To 1 ml. serum in an ordinary test-tube I added two drops of formol. Within 24–30 hours most of these sera jellified, and the results corresponded with Wassermann results in 85% of cases. The findings of this research were presented to the Société de Biologie at its meeting of November 15, 1920, and the relevant communication, entitled "Une nouvelle réaction des sérums syphilitiques: Formol-Gélification," appeared in the *Comptes rendus de la Société de Biologie*, 1920, 83, 1432.

The reaction being easy to carry out, there followed a great number of publications, from which, as well as from our own, it was proved that the formol gel test is not a specific syphilis reaction, but occurs in various diseases and is due to some abnormality of one or more constituents of the blood serum. The reaction was naturally tested both by us and many other research workers in connexion with various diseases. It was also tested, for the first time, in kala-azar by Colonel Spackman,¹ who observed that its occurrence in that disease was very quick, and that besides getting jellified the serum also became turbid. He therefore suggested that the formol gel reaction might also be strongly positive in trypanosomiasis.

A month later² it was reported that Napier "has discovered a test which promises to be of great value in the diagnosis of kala-azar . . ." and that "the test is a modification of that described by Gaté and Papacostas, who found that the serum of syphilitic patients becomes jellified in 24 to 30 hours when to 1 ml. clear serum two drops of commercial formalin solution are added. When this test is applied to the serum of kala-azar patients an immediate white opacity develops and the serum jellifies within half an hour."

There followed almost immediately³ a communication by Fox and Mackie, stating that they were studying the Gaté-Papacostas reaction in kala-azar from July 21, 1921, and reporting the results of their research.

The findings of Napier's study were published by him seven months later.⁴ In addition to kala-azar, he reports a number of cases of other diseases in which he tested the reaction. In his study he states that in carrying out the test he used the technique described by Gaté⁵ and Papacostas. Owing, however, to the quickness with which kala-azar patients' sera become jellified and turbid, he deemed it advisable to redesignate the formol gel test of Gaté and Papacostas as the "aldehyde test" or "Napier test,"⁶ and has since used this reference for the formol gel reaction in all his papers, as well as in his book *The Principles and Practice of Tropical Medicine* (1946).

Let us now see how far this redesignation of the reaction can be justified.

As is known, when speaking of any chemical reaction whatever we mean "the action set up by one substance on another" (*Concise Oxford Dictionary*). Therefore for any chemical reaction two things are necessary—the reagent and the substance on which it reacts. In the case of the formol gel reaction, the two interacting substances are formol and blood serum.

Both Spackman and Napier used the same reagent as we did—i.e., formol—and on the same substance—the serum. In addition, they used the same technique—namely, 1 ml. serum, two drops of formol, and the ordinary laboratory temperature. The test, therefore, used both by Spackman and Napier is exactly the same as we first described and is as now universally used. And if in some diseases the reaction somewhat varies in regard to time and turbidity, this, we believe, can by no means justify a special redesignation of the reaction in each particular case. Furthermore, according to Napier the two specific features of the formol gel reaction whereby he justifies its redesignation to "Napier test" are not encountered exclusively in kala-azar cases. Numerous writers have noted that the quickness of reaction and turbidity do not constitute a rule in kala-azar, nor do they represent exclusive characteristics of this disease. In this con-

nexion we would refer, among others, to the relevant study of Froilano de Mello and Baretto,⁷ who observed the same opalescence in sera of malaria patients, lepers, and dysenteric and syphilitic persons. Napier himself,⁴ in his first study, reports kala-azar cases in which solidification occurred without complete opacity. I also, having studied kala-azar reactions for years in Greece, observed a great number of cases where reaction developed many hours later, and in others there was no turbidity. I sometimes noted these phenomena in the same patient at different times.

We now know some more morbid conditions in which the formol gel test appears as in kala-azar. This especially applies to Kahler disease (multiple myeloma), which was thoroughly studied by Bing,⁸ E. Delbarre,⁹ and others. In that disease jellification of serum occurs within a few minutes, and is followed by an intensive turbidity. According to Delbarre, in the above disease formol gel reaction is a fundamental symptom. But neither Bing nor Delbarre ever thought of changing the name of the reaction.

In one of our later studies, in 1922,¹⁰ on the formol gel reaction in various diseases we drew the conclusion that "the reaction is not specific for syphilis, and that it seems to act as a control of unknown humoral changes, possibly caused by general chronic morbid conditions," and in another communication¹¹ we stated: "Like so many other humoral reactions or blood tests, such as eosinophilia, which no one claims to be specific for a certain disease, but the theoretical and practical diagnostic value of which in many diseases no one questions, the formol gel reaction—a new blood serum test—though not specific for one disease, maintains its value for many morbid conditions. . . ."

At present, from numerous researches made by various workers, it appears that the formol gel reaction is due to the disequilibrium of serum proteins and particularly to the reversal of the albumin-globulin ratio. According to many writers, this is due to an increase in the globulin fraction, but several others think that, for its occurrence, some other secondary, but necessary, unknown factors are required.

Regarding the use of formol gel reaction in surra (trypanosome disease of camels), to which Colonel Spackman refers in his letter, priority in its application pertains to the French Plantureux,¹² who published his relevant study eight months before Colonel Spackman's publication.¹³

I have thought it necessary to set forth the foregoing details in order to put an end, once for all, to the confusion appearing in some publications, especially English and American, about the history and origin of formol gel reaction.

I wish to thank Colonel Spackman again for the opportunity he offered me by his communication, as well as the Editor of the *British Medical Journal* for his courtesy in publishing this long letter.—I am, etc.,

School of Hygiene,
Athens.

GEORGE PAPACOSTAS,
Professor of Public Health and Social Medicine

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- ⁴ *Indian J. med. Res.*, 1922, 9, 830.
- ⁵ *Bull. Soc. Path. exot.*, 1926, 19, 127.
- ⁶ *Acta med. scand.*, 1937, 91, 336; 1940, 103, 547.
- ⁷ *Congrès Français de Médecine*, 18e session, Genève, 1949, Paris, Masson, 1951, p. 145.
- ⁸ *C.R. Soc. Biol.*, Paris, 1922, 87, 543.
- ⁹ *Clinique*, Paris, 1923, p. 73.
- ¹⁰ *C.R. Soc. Biol.*, Paris, 1923, 88, 1189.
- ¹¹ *British Medical Journal*, 1923, 2, 1257.

Gastric Carcinoma and Acute Perforation

SIR,—I read with great interest the article on acute perforation of gastric carcinoma by Mr. T. L. Kennedy (December 22, 1951, p. 1489), and it recalled to my mind a case which I operated upon about two years ago which showed some unusual features.

On October 28 a man aged 41 was admitted with a very severe epigastric pain of three hours' duration. There was a five-year history of epigastric pain which came on about two hours after meals and showed periods of remissions and exacerbations. In the last month before admission the pain had become very severe, but it was still related to meals. His appetite was good except in the week previous to admission, when he had taken very little