Conclusion

I can picture Thomas Huxley, if he could still be with us, refurbishing his armament, not perhaps without a certain zest, in expectation of a new encounter. He would know, however, that any real hope for the ultimate solution of this problem, in the interests of all humanity, must depend upon the degree to which it can be lifted into the clear light of scientific discussion, out of the range of irrelevant beliefs and furtive superstitions, beyond the reach of any suspicion of racial rivalry or patronage. He would know that any permanent solution must come from the spread of enlightenment, and thus from a patient and persistent effort of education. I can imagine him proclaiming, in the noble words with which he concluded his address to the British Association in 1870, that "mankind will have one more admonition that the people perish for lack of knowledge; that the alleviation of the miseries and the promotion of the welfare of men must be sought by those who will not lose their pains, in that diligent, patient, loving study of all the multitudinous aspects of Nature, the results of which constitute exact knowledge or Science."

FLEA INFESTATION AS A CAUSE OF PAPULAR URTICARIA

A PRELIMINARY INVESTIGATION

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A parasitic cause for the distressing and persistent eruption of papular urticaria in young children has been suspected for some time past. Evidence in support of this theory, which was suggested by Jonathan Hutchinson in 1879, has been accumulating in recent years.

Hallam's observations (1927, 1932) on the part played by the home surroundings in the production of papular urticaria are well known in this country. Other writers, such as Gordon (1933), Kinnear (1933), Tate (1935), Hamburger and Dietrich (1937), and Blank *et al.* (1950) have all supported the environmental or parasitic theory. Rook and Frain-Bell (1953) have given us the most complete account of the different writings bearing on this subject and bring strong support to the parasitic origin of papular urticaria based on their observations of 100 cases in South Wales.

We also are convinced that this disease is caused by parasites, and hope to provide one of the final links in the chain of evidence by observations made as a result of visits to the homes of the patients.

Symptoms and Signs

Previous observers have noted the variety of the lesions, ranging through an oval urticarial flare, small solid papules, vesicles, bullae, and crusted impetigo lesions to residual macules and small pigmented areas. The eruption comes out in crops of spots lasting some three days in an active irritable state, and is followed by gradual resolution with healing of the excoriated skin. New lesions keep appearing at intervals, and it is not uncommon for the condition to

last for several years. Irritation is intense, so that child and parents are in genuine distress owing to loss of sleep and constant efforts to relieve the condition.

Mothers very often try to explain the rash as "heat spots from eating too many sweets or oranges" or "too much acid in the system," and the family doctor may encourage this idea by suggesting that the rash is of dietetic origin. Surprise and occasionally indignation are registered by the mother when it is suggested that the trouble may be due to insect bites. The family doctor, on the other hand, is often willing to admit that he had thought that the spots were very like flea-bites.

The eruption of papular urticaria will often show lesions of varied type at the same time, and it is a striking fact that the rash does not resemble urticaria as seen in the adult. The individual spots persist and go through a process of resolution which takes several days. In many cases a central punctum can be seen in the lesion.

FIG. 1.—Vesicular lesions in papular urticaria.

The picture of papular urticaria in a child of 2 might be as follows (see Fig. 1):—*Feet*: Studded with small vesicles on the soles and dorsum. *Legs*: Scattered papules, some with small central vesicles in them. *Buttocks*: Many red macules of small size with an area of freedom from spots coinciding with pressure from the elastic band of the drawers. *Trunk*: More macules above the top of the drawers. Groups of oval flare-like lesions with central punctum. Many excoriations and some crusted infected lesions. *Arms*: Papular lesions on the outer aspect of the forearms and upper arms. *Hands*: A few vesicles, some on the palms, suggesting the possibility of scabies.

History.—The age at onset was 3 months in many instances, and the duration of the disease was two to five years or longer. Most children were 3 years old when first attending hospital, but a smaller group averaged 7 years. In one-third of this series of 30 cases more than one person was affected. Pets were kept in 20 of the houses. In several instances other children in the house were not affected. Severe irritation is the most prominent feature.

Procedure of Home Visiting.—(1) Ask permission to visit. (2) Arrange time of visit so that children will be at home. (3) Inspect living-room and child's bedroom in particular. (4) Inquire where animals lie most often and where they sleep. (5) Collect dust sample after careful inspection with naked eye and hand lens at close quarters. (6) If there is a cat or dog in the house this will often spend much of its time on a particular chair or rug near the fire. This is the place to look at closely. (7) Look around skirting-boards of living-room, pulling up linoleum where necessary. (8) Examine the child's bed for signs of flea droppings, which are reddish brown because of the blood ingested. (9) Where no positive results appear probable after looking at the inside of the house, outside factors should be considered. Birds' nests under the eaves and pigeon lofts near by should be looked for. (10) If none of these sources seem likely to be fruitful, a visit to the grand-

mother's house may yield results if the child is known to go there at regular intervals. (11) Some children who are fond of animals may spend considerable time with the neighbours' pets, and a call at the house next door may prove of value.

Insects Associated with Papular Urticaria

Collection

The work of Rook and Frain-Bell (1953) drew attention to fleas and bed-bugs as the parasites probably responsible. We have not found any cases where bed-bugs appeared to

be responsible for the condition, but fleas certainly are of importance, and our work so far has been concerned with several species of fleas.

There are four distinct stages in a flea's life history—namely, egg, larva, pupa, and adult insect. The pupa is

FIG. 2.—Egg of cat-flea. Actual size, 0.65 mm. in length.

FIG. 3.—Larva of cat-flea. Actual size, 4.5 mm. in length.

sedentary and is enclosed in a small cocoon. It is not readily found in a home visit of short duration. The remaining three stages have all been found in houses (see Figs. 2, 3, and 4). As 15 of our total cases were infested with cat-fleas, the methods of collecting and rearing this species are described, as the other species of flea differ only in detail from the cat-flea.

Adult fleas were occasionally found in the animal's bedding. Examination of the cat itself has not proved useful as a means of getting specimens, but the animal's condition is worth noting. Eggs and larvae can occur in very large numbers in the animal's bedding, and give a sure indication that the animal is infested when, as in most cases, one does not find adult fleas.

The removal of the bedding with its eggs and larvae will at once provide ample material for rearing. However, in many houses (even in those otherwise scrupulously clean) the cat is offered a choice of several chairs and even beds for its sleeping quarters, and here a special collecting device is needed. The sucker (Fig. 5) is run over the seats of chairs, sofas, rugs, etc., where the cat is known to lie, and a high proportion of the eggs and even larvae are taken up. Often the $\times 9$ lens will allow one to recognize the pearly white eggs on the cloth surface. In one case 85 eggs were collected from two chairs on which the cat sat.

Identification

The species of fleas have been determined by using the keys of Rothschild (1915), Wagner (1936), Jordan (1943), and Séguay (1944). The species of flea can be recognized

only from its adult form, as there are no keys existing for flea larvae. Larvae can be recognized as those of fleas, and the same (given the circumstances) can be said for the eggs with much more reservation. An attempt has always been made, therefore, to rear eggs and larvae until they become adult.

The following technique yields about 90% of adult fleas from the eggs collected.

The eggs and larvae are reared in 2 by 1 in. (5 by 2.5 cm.) glass tubes closed with pierced corks, with the hole— $\frac{1}{4}$ in. (1.3 cm.) diameter—covered with nylon gauze. The food of the larvae is part of the debris they are found in, but this needs supplementing in many cases.

Satisfactory results have been obtained by using a mixture of four parts of rolled oats by volume with one part of dried blood (human or ox) by volume. No trials of a further range of foods have been made, but this method appears to work. Temperature and humidity are well known to be important. The tubes have been kept in a large container over saturated sodium chloride solution, which gives 75% relative humidity at the temperature of 25° C. in the constant-temperature room where the container was kept. Under these conditions adult fleas emerge in four to five weeks. Fully saturated air allows mould to grow on the food medium and a lower temperature delays maturity.

The species found are: *Ctenocephalides felis* (Bouché), the cat-flea; *Ceratophyllus gallinae* (Schroeder), the hen-flea; *Ceratophyllus columbae* (Stephens), the pigeon-flea; *Ceratophyllus farreni* (Rothschild), the house-martin-flea; and *Pulex irritans* L., the human-flea. The names of the fleas refer to their most usual host. All of them are, however, found on other hosts less commonly. The hen-flea is particularly non-specific, and has been found infesting a wide range of birds and indeed mammals. In our cases we found this flea twice on cats and once in an infested starling's nest.

If our conclusion is accepted that these fleas can cause papular urticaria, then this attack on human beings is a further example of the low host specificity of fleas. Busvine

FIG. 4.—Female cat-flea. Actual size, 2.5 mm. in length.

FIG. 5.—Sucker for collecting flea eggs.

gives seven species of fleas as sometimes infesting houses, *Ct. felis* and *C. gallinae* among them. It is surprising that the human-flea, *Pulex irritans*, has come to our notice only once in this group of cases. This point is discussed below.

Case Histories

We have selected three cases of special interest.

Case 1.—A girl aged 9 was born at her grandmother's house and has spent much time there over the years. A cat called Tiger is kept at this house. Spots have kept coming out on the child's body since she was a few months old. Her brother has never had any spots. Tiger sleeps in an old clothes-basket on a rug. The most striking feature of the infestation was its intensity. The rug on which the cat slept was covered with eggs (see Fig. 6), while nearly full-grown larvae were to be found wriggling among the materials of the rug.

FIG. 6.—Rug showing eggs of cat-flea. (Arrow points to group of eggs $1\frac{1}{2}$ times actual size.)

Case 2.—A boy aged 7 began to get spots when he was 1 year and 4 months old. He has had persistent attacks since. His sister, aged 5, has had one or two spots lately. A visit to the house revealed that the family spent most of their time in the kitchen. The infestation was centred in the warm kitchen on a stuffed fireside chair from which cat-flea eggs and developing larvae were readily obtained with the sucker. This chair fulfilled a dual role in the household. During the night the cat slept on it and allowed its fleas to deposit their eggs, while during the day it was occupied by the grandmother, whose age and condition made her nearly immobile. Thus, throughout the whole 24 hours the chair was kept warm and so formed a perfect device for rearing cat-fleas. It was in no way surprising that disinfecting the cat and the chair caused a marked and permanent improvement in the condition of the children.

Case 3.—This case was reported to us by a sanitary inspector. The clinical symptoms were slighter than usual and hardly typical, but the case shows another possible source of domestic fleas. Fleas were found crawling down the outside of one of two adjacent new semi-detached council houses. Both of the resident families had complained of being bitten by fleas. The fleas were *C. gallinae*, the so-called hen-flea; but these proved, on tracing them up the walls of the house, to be coming from a last year's starling's nest, situated in the space under the roof. The nest was removed and a total of 267 adult fleas were collected, which must have been only a fraction of the total emerging from the nest while the infestation lasted. Such a number from a single nest is in no way exceptional. Rothschild and Clay (1952) state that 4,000 fleas have been found in a single martin's nest. The fleas from this nest would be the offspring of fleas which fed on the nestlings the year before and passed the winter (probably as pupae) within the materials of the nest. The ordinary course of events would be for starlings to nest again in this site, and so the fleas would have found a bird host. The opening

in the eaves had, however, been covered in without the nest being removed, and the fleas had wandered out in a hungry condition.

Control Measures Against Fleas

We will consider only those measures directed against cat-fleas, as the other species of flea all demand individual treatment.

It is worth pointing out that too great a reliance should not be placed on insecticides alone; rather, the aim should be (a) to use insecticides to clear the animal of fleas and then (b) to encourage the family to arrange the cat's sleeping quarters and general discipline so as to reduce the chances of a flea infestation starting. The first point is met by using one of several proprietary cat dusting-powders made by reputable firms. We have advised one which is pyrethrum without D.D.T. When applied regularly it clears the cat of fleas, and if the treatment is repeated from time to time it will keep it free. The second point is met by urging that the cat has a special sleeping-box with a rug to lie on which is removed regularly and shaken out of doors. Further, this rug can be treated periodically with insecticidal dust and thus any larvae which might develop are killed, while the cat itself gets a slight dusting as it lies on the rug.

No originality is, of course, claimed for any of the control measures adopted; they are such as would be advised by any competent veterinarian, and are described in many works on applied entomology—for example, Busvine (1951), Metcalf and Flint (1951).

Discussion

From the figures shown in the Table it is seen that flea infestation occurred in 21 cases out of 30 and that clinical improvement resulted in 14 of these. However, there were nine cases in which fleas were not actually found. The following questions may be asked (our answers are given below). (1) Are fleas the operative cause in those cases where they were found and clinical improvement followed

Table Showing Details of Present Series of Cases

No. of Cases	No. in which Fleas Found	Species of Flea Found	Fleas Not Found	Clinical Improvement After Control Measures in Cases where Fleas were Found
30	21	Cat-fleas 15 Hen-fleas 3* Pigeon-flea 1 House-martin-flea 1 Human-flea 1 Undetermined 1	9	14

* Includes one infestation mixed with *Ct. felis*.

their removal? (2) Will reinfestation with fleas cause reappearance of the symptoms? (3) What is happening in the nine cases where fleas have not been found? (4) Why has only one case of papular urticaria due to the human flea, *Pulex irritans*, been recorded in this survey so far?

Questions 1 and 2.—The figures must stand for themselves. Control groups are rather hard to evaluate in view of the known intermittent nature of the condition. A further strengthening of the evidence is afforded by some tests with the adult fleas reared in the laboratory. We hope to do more with juvenile papular urticaria patients, but so far have confirmed that all the species of fleas referred to will cause irritating papules on a susceptible subject. Conveniently, one of us is susceptible (R. M. B.) and the other is immune (E. T. B.). For example, the same specimens of *Ct. felis* and *C. columbae* were allowed to feed on us, and produced only a transient minute red patch on E. T. B., but irritating papules on R. M. B. In both cases examination of the fleas showed that blood had been taken into the gut. These observations confirm the well-known marked individual variation in response to flea-bites. They also fit in with the observed fact that certain individuals of a family

group may develop papular urticaria and the others be free. The cause of the irritation is presumably the flea's saliva, which is injected into the wound and prevents clotting of the blood during suction.

Question 3.—The nine cases in which fleas were not found require explanation. It is tempting to explain them as cases where fleas, although present, were missed. It is, of course, quite easy to miss a localized flea infestation. In one case we strongly suspected that a hurried clean-up had preceded our visit, and flea eggs and larvae had been eliminated from an otherwise straightforward case. In two other instances we felt sure that the house next door held the answer to our problem. Cockroaches in great numbers came through the party wall in one case, whereas mice came down the bedroom chimney in the other. Many of our visits were made to very old houses in condemned property. The walls could harbour fleas which might or might not be detected in our comparatively brief search. For the present we are inclined to take this view, and would point out that an infestation with bird fleas might easily be overlooked.

Question 4.—The occurrence of only one case due to human-fleas is puzzling. This may be due to the marked decline in the incidence of the human-flea in recent years referred to by Busvine (1951), who attributes it possibly to the increasing use of the vacuum cleaner. Our use of the sucker shows the effectiveness of a vacuum cleaner on flea eggs. Local sanitary inspectors also refer to the decline in the number of fleas in recent years. It should be mentioned, however, that in two of the cases classed as negative for fleas we found flea-marks on bedclothes, and in one of these cases the mother described how she often caught fleas on her husband, which she described as being got at his work. Further, a thorough treatment of this house with D.D.T. spray, carried out by the sanitary inspector, was followed by marked improvement in the child. We think that further work will increase the number of cases in which the human-flea is found to be the cause of papular urticaria, and its undetected presence may explain some of the negative cases.

If we accept the view that many, if not all, cases of papular urticaria are due to fleas transferring their attacks from an animal to man, then it is worth noting that other diseases owe their incidence to this peculiarity of flea behaviour. The rickettsiae of murine or endemic typhus are transmitted to man from their reservoir in the rat population by the bites of rat-fleas, particularly the species *Xenopsylla cheopis*. Plague, which is of course the classical flea-borne disease, occurs in a wide number of different rodents, being transmitted from one to the other by their fleas, but it reaches man usually from rats by the bite of infected fleas, of which *X. cheopis* is again the most important and widespread species.

Thus the attack of animal fleas, which in the present instance is the cause of chronic irritation, may in other times and places be a matter of graver medical importance.

Summary

Thirty cases of papular urticaria were investigated at hospital and at the homes of the patients.

In 21 cases fleas were found or were hatched out from dust samples (which were collected, examined, and incubated under standard conditions of humidity and temperature). Five different species of fleas were found causing infestation. Measures were suggested for disinfecting the home and the pets. These resulted in a clearance of the irritable eruption and kept 14 out of the 21 young patients free.

The great majority of cases of papular urticaria ("heat spots" in popular terminology) can be explained on the basis of a parasitic infestation even though this may be obscure at first sight.

Careful history-taking and investigations extending to the home are necessary before the true facts can be brought to light and complete relief ensured.

Pets as well as patients must be treated.

We wish to thank our medical colleagues who have referred cases to us, and the Department of Photography, King's College, Newcastle-upon-Tyne, for the photographs.

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SYNTHETIC OXYTOCIN

BY

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The oxytocic hormone of the posterior pituitary when isolated and biologically standardized is commonly known by the trade name "pitocin," but more correctly as oxytocin (*B.P.* and *U.S.P.*). It was synthesized by du Vigneaud and others (1953, 1954). No substantial quantities of this synthetic hormone became available in this country for clinical trial. The synthesis has now been performed by a different method, and Messrs. Sandoz have produced a preparation, "syntocinon" (O.T.S. 68), which they have adjusted by biological assay methods to be equal in potency to the international standard preparations of posterior pituitary powder at 10 international units to 1 ml.

The assay of syntocinon against the standard posterior pituitary powder was carried out in the first place by Konzett on animal preparations, using (*a*) rat uterus by the method of Holton (1948), and (*b*) blood pressure in the chick by the method of Coon (1939). They further made a number of qualitative observations upon the cat uterus (Konzett *et al.*, 1956).

Normal tests for toxicity revealed no adverse effects from syntocinon even when given in large doses.

Following this work, the new drug was tried out clinically by Bösch and Käser (1956) in the Frauenklinik at St. Gallen, and clinical observations there on 152 patients showed that it acted in every way as though it was the natural hormone.

In August, 1955, Messrs. Sandoz supplied us at University College Obstetric Hospital with a quantity of this new synthetic oxytocin for clinical trial. We have