Current Practice

Leptospirosis

L. H. TURNER,* M.D.

Brit. med. J., 1969, 1, 231-235

Leptospirosis became a notifiable disease throughout England and Wales with effect from 1 October 1968. Now is a suitable time to summarize various aspects of the subject, with special reference to the United Kingdom. It is hoped that the following account, which is based on a recent article (Turner, 1967), will be useful to clinicians, public health workers, and clinical pathologists in their attempts to comply with this new regulation.

Leptospirosis is not synonymous with Weil's disease; other febrile syndromes may be mimicked, or the illness may be a pyrexia of unknown origin (P.U.O.), and the presumptive diagnosis is often wrong. Laboratory investigations are required to confirm or establish the diagnosis; these are very useful provided that suitable specimens and information are submitted. Serological tests can be carried out in many peripheral laboratories and are likely to be included by the pathologist even when they are not directly requested by the clinician. Rats are by no means the only reservoir hosts of leptospires in this country. The range of indigenous pathogenic serotypes is much wider than is generally realized. Suitable treatment is effective. Leptospiral infections are now less prevalent. Viral hepatitis, however, is much more common than leptospirosis and it is hoped that the available laboratory resources will not be overwhelmed by requests to exclude leptospirosis in such cases. These points are further discussed below.

Classification

The notion that only serotypes *icterohaemorrhagiae* (formerly designated *icterohaemorrhagiae* A), *copenhageni* (formerly designated *icterohaemorrhagiae* AB), and *canicola* occur in the United Kingdom is no longer tenable. At least five other serogroups are also represented (see below and Table I).

TABLE I.—Sources of Strains of *Leptospira* in the United Kingdom

Serogroup	Serotype	Hosts
<i>icterohaemorrhagiae</i>	<i>copenhageni</i>	Man, rats (wild, laboratory), dogs, cattle
<i>javanica</i>	<i>icterohaemorrhagiae</i>	Rats
<i>canicola</i>	(Not determined)	Hedgehogs
<i>ballum</i>	<i>canicola</i>	Man, dogs, pigs (Scotland)
<i>autumnalis</i>	(Not determined)	White mice, field-mice, voles
<i>australis</i>	<i>erinacei-auriti</i>	Water vole
<i>hebdomadis</i>	<i>bratislava</i>	Hedgehog
	(Not determined)	Hedgehogs, voles, field-mice
	(Not determined)	Field-mice, voles, cattle

The genus *Leptospira* is currently arranged in one species, *L. interrogans* (Stimson, 1907; Noguchi, 1928), and two complexes designated *interrogans* and *biflexa*. The *interrogans* complex happens to comprise most of the pathogenic and parasitic strains. The *biflexa* complex consists mainly of the so-called saprophytic strains with no known hosts; but it also

includes a few serotypes, reputed to be pathogenic, which are not known to occur in this country. The two complexes differ in their biological (physiological) characters as well as in some of their antigenic content. Within each complex strains are classified by cross-agglutination and cross-agglutinin-adsorption studies—with antisera prepared in rabbits—into serogroups and serotypes. Serotype is the basic taxon in this genus, familiar examples of which are *icterohaemorrhagiae*, *copenhageni*, and *canicola*. The leptospiral serotype is regarded, in the strict sense of the International Code of Nomenclature of Bacteria, as an infrasubspecific form or category; it is not synonymous with species and should not, therefore, be designated by the binomial convention—for example, *L. canicola*—which is reserved under the rules of the Code for designating species.

The *interrogans* complex now consists of about 130 serotypes arranged in 16 serogroups (World Health Organization, 1967). These serogroups, with the number of serotypes which they contain, are as follows, and those which are known to be represented in the United Kingdom are indicated in bold type: ***icterohaemorrhagiae*** (13), ***javanica*** (6), ***celledoni*** (2), ***canicola*** (11), ***ballum*** (3), ***pyrogenes*** (9), ***cynopteri*** (3), ***autumnalis*** (13), ***australis*** (10), ***pomona*** (6), ***grippotyphosa*** (2), ***hebdomadis*** (28), ***bataviae*** (8), ***tarassovi*** (syn. *hyos*) (10), ***panama*** (2), and ***shermani*** (1).

Course of Leptospiral Infections

Knowledge of the basic course of leptospiral infections is needed for understanding the clinical syndromes which may be evoked, the likely results of treatment, the epidemiology and enzootiology, and last, but certainly not least in importance, the sort of specimens and information which the laboratories require in order to render the maximum help in any investigations.

Two overlapping phases follow an incubation period of 7 to 12 days (range 2 to 20 days): the first is characterized by leptospiroemia, and the second by leptospiruria and increasing concentrations of antibodies (see Fig. 1).

Phase of Leptospiroemia.—This phase persists from some time during the incubation period to about days 7 or 8 (rarely longer) from the onset of illness. The leptospires circulating in the blood may reach, and therefore affect, any tissue or organ. This accounts for the wide variety of clinical symptoms and signs which may be evoked.

Phase of Leptospiruria and Immunity.—Leptospires are removed from the blood and tissues by phagocytosis aided by increasing concentrations of specific antibodies. The kidney is the exception: here the leptospires tend to reach the convoluted tubules in the cortex, where they may settle and multiply for a time—sometimes even forming colonies in the lumina—whence they are shed into the urine and then into the outside environment. This carrier-shedder state may be of short duration, persisting for one or two months—a convalescent state—

* Director, Leptospirosis Reference Laboratory (Public Health Laboratory Service, W.H.O./F.A.O.). Secretary, Taxonomic Subcommittee on *Leptospira* (International Committee on Nomenclature of Bacteria); member of the W.H.O. Expert Group on Leptospirosis.

as in most human infections. However, when there is a suitable host-serotype relationship, the shedder state may persist for years without detriment to the host. Such hosts are important reservoirs of infection for the serotype concerned, in the particular region.

FIG. 1.—Leptospirosis: phases and relevant diagnostic procedures. (Reproduced with slight modifications from Turner, L. H., *Trans. roy. Soc. trop. Med. Hyg.*, 1967, 61, 842.)

Natural History of Leptospirosis

Survival of Leptospirae

Environmental conditions which favour the survival of virulent leptospirae outside the bodies of susceptible vertebrates are moisture, warmth, and pH values of soil and surface waters around neutrality—as in the summer and autumn months in temperate climates. Adverse factors include salinity and chemical pollution—for example, hypochlorites, detergents—as well as desiccation and pH values outside a range of about 6.2 to 8.0.

Modes of Transmission

Indirect contact with an environment contaminated with virulent leptospirae originating from a convalescent or reservoir host (urinary shedder) is the most important. Such environments include soil, mud, water, vegetation, foodstuffs, and so forth. The leptospirae enter the body through the skin (especially if this is wounded, macerated, or diseased), the nose or muzzle (important in grazing animals and dogs), the mouth, conjunctiva, or genitalia.

The bites of animals may provide a portal of entry for the organisms, but in themselves are not important because leptospirae are not excreted in the saliva. Transplacental infection is quite common among animals, when it can result in abortion, stillbirths, or sickly offspring—as in livestock. Venereal transmission occurs in some rodents. Both these two modes may occur in humans. Various blood-sucking arthropods, especially ticks, can harbour leptospirae; but they are of little practical importance as vectors. Leptospirae survive only a short time in undiluted milk, and they are readily destroyed by heating above about 60° C.

Reservoir Hosts

The natural reservoirs of pathogenic strains of *Leptospira* are wild animals, mainly mammals; but though other vertebrates—birds, reptiles, amphibians, fish—may be infected they are much less important.

Among mammals the order Rodentia is the most important. The role of rats is well known; but strains have also been isolated from field-mice, voles, and laboratory white mice in this country; and house-mice and coypus are potential hosts (the latter had a high seropositivity rate in East Anglia, unpublished data). Among Insectivora, hedgehogs are notorious hosts in Europe, the U.S.S.R., and in this country; shrews are also involved. Other orders which are important locally in various parts of the world are Carnivora (dogs, foxes, jackals; mongoose; civets; skunks; racoons) and Marsupialia (bandicoots, opossums). Cheiroptera (bats), Artiodactyla (deer), and Lagomorpha (hares, rabbits) are less important.

Domesticated animals—especially cattle, pigs, and dogs—can maintain enzootic leptospirosis in the herd or kennels. Their infections are apt to be transmitted to other animals, wild or domesticated, and to man. Laboratory colonies of white rats and mice can also maintain enzootic leptospirosis without any signs of ill effects. Often the first clue to such a state has been severe illness in a member of the staff who handles these animals.

The interrelationships of the principal reservoir hosts are shown in Fig. 2. The sources of strains of *Leptospira* isolated in the United Kingdom are given in Table I: these are provisional data because definitive typing of many strains has not been completed.

FIG. 2.—Relationships of the principal reservoir hosts of *Leptospira*. (Reproduced with slight modifications from Turner, L. H., *Trans. roy. Soc. trop. Med. Hyg.*, 1967, 61, 842.)

Principal Hazards for Man

The epidemiological pattern in this country has changed over the last 30 years. The rate of infection among sewer workers and fish cleaners, once risky occupations, is now low. Hygienic measures—personal and environmental, including rodent control—have probably been effective. One wonders, however, to what extent the widespread use of detergents, in home and industry, may have affected the situation in the sewers.

Certain occupations are still risky. These include: agriculture (farm work, market gardening); animal contacts (veterinary, livestock attendants (cattle; pigs in Scotland), kennel personnel, rodent exterminators); meat handlers (abattoirs, meat packing and processing); construction works

(drains, canals, roads, gravel pits) ; forestry, surveying, military exercises or service, as well as sewer work and fish cleaning when control measures break down.

Recreational pursuits become more important as people can more easily reach the countryside and therefore the habitats of reservoir hosts. Swimming, camping, picnicking, fishing, boating, and nature study may lead to contact with a contaminated environment.

Incidence of Leptospirosis

Until now the only systematized information available comes from laboratory identifications reported to the Epidemiological Research Laboratory (Central Public Health Laboratory, Colindale). These may certainly not be taken as representing the whole picture, because notification has not been compulsory and the figures are likely to be an understatement (see Table II).

TABLE II.—*Leptospiral Infections in Humans, England and Wales (Reported to the Public Health Laboratory Service)*

Year	Serogroup Involved				All Cases
	Ictero-haemorrhagiae	Canicola	Hebdomadis	Unknown	
1955	99	25	0	16	140
1956	28	12	0	5	45
1957	51	16	0	7	74
1958	48	18	0	5	71
1959	42	11	0	3	56
1960	46	26	0	5	77
1961	60	15	1	6	82
1962	32	11	0	2	45
1963	32	9	1	9	51
1964	19	8	0	8	35
1965	18	7	0	12	37
1966	24	6	0	5	35
1967	8	9	0	6	23
1968*	15	6	11	1	33

* Figures for 1968 are provisional.

Until 1960, agglutination tests were carried out with suspensions of *copenhageni* (syn. *icterohaemorrhagiae* AB) and *canicola* only, even in this unit. Then we added *ballum*, *bratislava*, and *sejroe* or *saxkoebing* to represent serotypes which were suspected to occur in this country (strains had been isolated). From mid-1962 an extended battery of suspensions, to include representatives of all recognized serogroups, has been used: this is arranged so that pools of antigens represent serogroups of *Leptospira*. Until recently most of the laboratories which undertake leptospira agglutination tests have used only the first two serotypes; but *wolffii* has been added to cover the part of the large hebdomadis serogroup which has attracted notice (see below).

The items listed under "serogroup unknown" have not been analysed in detail, but most are probably examples of two or more antigens giving the same titres. In such cases the extensive agglutinin-adsorption studies which are necessary for further definition of the serotype which is likely to be involved are too burdensome for routine application (Turner, 1968).

We have been asked whether there is much likelihood that leptospiral infections are being overlooked. The answer is probably few, if any; and these are likely to be the mild or very mild infections from which the patient may quickly recover without having been investigated. We have found very little evidence of residual agglutinins in the specimens which are submitted to us. Some laboratories have used a "genus-specific" antigen in a complement fixation test without disclosing more than a few leptospiral infections from among the sera submitted for leptospiral agglutination tests and sera sent for "virus tests" and other investigations.

The reasons for the recent increase in infections with strains in the hebdomadis serogroup are not yet known. Such strains have been isolated from various animals (Table I). For years

we have noted that a large proportion of sera from grazing animals contain agglutinins to serotypes in this large serogroup; foxes and foxhounds have also reacted. But until recently there have been very few human infections and the cattle have seemingly not been sickened by their infections. During the current year human infections have been detected in various parts of the country; most have been sporadic cases, but a small outbreak occurred among cattle men on a farm in Surrey. The illness in these patients has been aseptic meningitis or P.U.O. No strains have been isolated, but the antigen suspensions which react to highest titres are *medanensis*, *wolffii*, *hardjo*, *sejroe*, and *saxkoebing*. The latter three are known to occur in Europe, and the isolates which we are studying could belong to these three serotypes.

Clinical Manifestations

The severity of leptospiral infections ranges from the sub-clinical to the fatal. The manifestations can be many and varied; and jaundice is not an invariable feature. Other febrile syndromes may be mimicked, and sometimes leptospirosis is merely another P.U.O. Leptospirosis should therefore be considered in the differential diagnosis of the following types of illness.

- (1) Influenza, especially sporadic cases.
- (2) Aseptic meningitis. (Four series of patients have been reported in this country; the average incidence of leptospirosis—*icterohaemorrhagiae* (*copenhageni*) and *canicola* antigens were mainly used—was about 5%.)
- (3) Other febrile illnesses with involvement of the nervous system (encephalitis, poliomyelitis).
- (4) Rickettsiosis.
- (5) Glandular fever, especially in small outbreaks unconfirmed by laboratory tests for infectious mononucleosis.
- (6) Brucellosis, unconfirmed.
- (7) Enteric, unconfirmed.
- (8) Jaundice with fever and other suggestive signs.
- (9) P.U.O. of 3 to 12 days' duration, especially if a secondary rise of temperature occurs within a few days of the original febrile phase and is associated with meningeal symptoms and signs.
- (10) Pneumonitis of undiagnosed aetiology.
- (11) Acute abdominal emergencies when laparotomy fails to disclose the cause.

A few additional points may help in suggesting that leptospirosis should be considered in the differential diagnosis of such illnesses. Many systems and organs may be involved without definite localizing symptoms and signs. Prostration may be more marked than the clinical signs would seem to warrant. Conjunctival injection is quite common—the small vessels are engorged and the appearance is not that of inflammation. The cerebrospinal fluid is often under increased pressure; the cell count is usually raised (predominantly neutrophils at first, lymphocytes later); protein is increased, but chloride and glucose contents are normal. The sputum may be faintly blood-tinged. The erythrocyte sedimentation rate is often markedly raised. The total white blood cell count may be within normal limits or below 5,000/cu. mm., but even then the proportion of neutrophils is often in the range 75–90%. Albuminuria, especially if associated with other suggestive signs of leptospirosis, should not be dismissed as "febrile albuminuria" (Mackay-Dick and Robinson, 1957); and microscopical examination of the urinary deposit will often show red cells, white cells, and casts (mainly granular).

In leptospirosis, jaundice, if it occurs, ensues while the patient is febrile and the general condition is deteriorating. In viral hepatitis, particularly the infectious hepatitis type, albuminuria is uncommon, and by the time jaundice appears the patient is usually afebrile and the general condition is improving. Moreover, the available data suggest that in leptospirosis the

serum transaminase levels are within normal limits or only slightly raised. In viral hepatitis, by contrast, the levels are markedly raised.

Treatment

Treatment does not depend on the identity of the infecting strain of *Leptospira* and is of three sorts: antibiotic, supportive, and symptomatic.

Antibiotic Treatment

Penicillin is the antibiotic of choice because it has fewer undesirable side-effects than most; but tetracyclines or other broad-spectrum antibiotics (except chloramphenicol, which is the least effective) may be used. In mild illnesses the patient will recover without antibiotic therapy (see, for example, Kocen, 1962). Though some authors have been unfavourably impressed with the efficacy of penicillin, the current view is that *large doses given early* in the course of a suspected leptospiral illness are indeed advantageous.

Dosage depends on the duration of the illness, on its severity, and on the general condition of the patient. Gsell (1966) recommends penicillin 2.4 mega units per day if treatment is started before day 4 of illness; but the initial dose should be 6 to 10 mega units if treatment is started on day 4 or later. In each case the succeeding doses should be 2.4 mega units per day for a further six days. Tetracycline may be given as an alternative in dosages of 2 g. per day for seven days. In very ill patients the initial dosage of penicillin should be up to 40 mega units in the first day, given with fluids in an intravenous drip; subsequent dosage depends on the patient's response. The larger dosages are also indicated in enfeebled patients.

Mackay-Dick and Robinson (1957) gave 600,000 units of penicillin every four hours for the first 24 hours, then six-hourly. They confirmed a report that penicillin treatment may provoke Herxheimer reactions—a sharp rise in temperature, marked fall in blood pressure, precipitation or aggravation of symptoms and signs. Such reactions occurred in 83% of all their patients. They regarded the reactions as a sign of effective therapy and also as a "diagnostic penicillin-leptospira response."

Gsell (1966) has emphasized the correlation between the duration of illness and the effects of adequate antibiotic treatment. If treatment is started on day 5 of illness complications will usually be prevented, existing symptoms and signs will usually be modified, and the febrile relapse will be prevented. The earlier treatment is started, the more likely are these modifications of the basic course to be induced. Another important effect concerns the peak titres of the antibodies. If adequate treatment is started on day 5 the peak titres are likely to be low; they will be lower when treatment is started on days 3 or 4; and if treatment is started on days 1 or 2 there may be no detectable antibody reaction during the ensuing weeks. This effect on the production of antibodies stresses the need for obtaining a specimen of blood *before antibiotic treatment* is given; the only means of diagnosing leptospirosis may be by isolating the strain from this specimen.

Supportive Treatment

Impairment of hepatic and renal function is dealt with conventionally. Gsell (1966) recommended giving prednisone 20 to 40 mg. with laevulose in an intravenous drip and 30 mg. orally for jaundice. Moreover, because renal failure is the commonest cause of death, recourse to peritoneal dialysis or the artificial kidney should not be delayed; these measures have saved lives. There is also evidence that renal function is not permanently impaired (Simpson *et al.*, 1967).

Symptomatic Treatment

Analgesics and hot compresses will relieve the pains in muscles and joints. Lumbar puncture, by reducing pressure, may be the only means of relieving headache; and leptospirae may be isolated from the cerebrospinal fluid thus obtained.

Specific Treatment

Leptospira antiserum is seldom considered at this time because the effective valency is likely to be restricted to strains belonging to the homologous serotype or perhaps, and to a lesser degree, to strains in the particular serogroup. An antiserum (horse) prepared against *L. icterohaemorrhagiae* is still available (Burroughs Wellcome). Because the severely ill, jaundiced patients in this country are probably infected with strains belonging to this serogroup, the administration of the antiserum might be useful on occasions. The results of serum therapy are generally good if the course of treatment is started before the fifth day of illness, even in the presence of deep jaundice (Parish and Cannon, 1961). Some fatal cases of presumed icterohaemorrhagiae infection have shown little reaction in the agglutination test, even at low dilutions of serum. The severe course of the illness may have been due partly to poor antibody response and it might have been modified by the administration of antiserum. The dosage recommended is 20 to 40 ml., intravenously in severe cases, repeated daily if necessary; in less severe cases the serum should be injected intramuscularly.

Prevention

Personal Hygiene and Care.—Protective clothing (gloves, boots), washing, and first-aid facilities, as well as advice not to use or drink untreated water can be offered, but may not be adopted.

Environmental Hygiene.—Control of potential reservoir hosts should be attempted. Surfaces such as floors and work benches can be washed down regularly with hypochlorite solution (1 in 4,000) or with detergents.

Prophylactic Vaccination.—In circumstances where control of the reservoir hosts is impracticable and the infection rate is high, vaccines prepared from local strains have proved to be effective.

Abortive Treatment.—When a person has been exposed to a serious risk of infection through contact with material known to contain virulent leptospirae, a course of penicillin (2.4 mega units per day for seven days) should be given. When the risk is less, active treatment may be postponed until the patient develops fever within four to five weeks, then a specimen of blood is taken and a course of penicillin given.

Laboratory Investigations

Laboratory investigations will rarely help the patient because they can seldom confirm the diagnosis in time to influence treatment. However, retrospective diagnoses are not to be despised; at least they are enlightening, and they may be of epidemiological importance.

This subject cannot be set forth in a few lines. Published accounts are available (Babudieri, 1961; Galton *et al.*, 1962; Yager *et al.*, 1963).

The appropriate specimens which are required from the clinicians are indicated in Fig. 1. A few points need to be stressed. (1) Blood should always be obtained as early as possible after the onset of a febrile illness and *before* antibiotic treatment is started. The infecting strain of *Leptospira* may be isolated from the fresh specimen or from the clot; and a negative result in a serological test may be of crucial diagnostic

importance when compared with the findings in a parallel test with a later specimen. (2) All blood specimens should be obtained before meals to avoid a lipaemic sample. (3) The duration of illness and the date (or day of disease) on which the serum was obtained should be clearly stated. The date of admission to hospital is irrelevant. (4) The dosages and dates of any antibiotic treatment should be given to help in deciding whether the results of the tests may have been influenced by such treatment.

A "genus-specific" antigen for use in complement fixation tests is available in most laboratories of the Public Health Laboratory Service. This antigen detects current or recent leptospiral infections in man. The test has already proved to be a most useful screening method, the results of which correlate very well with those of a microscopical agglutination test with suspensions representing all the recognized serogroups.

I am grateful to Sir J. W. Howie, Director of the Public Health Laboratory Service, for commenting on the draft of this article; to Dr. T. M. Pollock and Mrs. E. D. Vernon, of the Epidemiological Research Laboratory, Central Public Health Laboratories (Colindale), for the information presented in Table II; and to Dr. Charles Wilcocks, Editor of the *Transactions of the Royal Society of Tropical Medicine and Hygiene*, for permission to draw freely on the material and figures in a previous publication (Turner, 1967).

REFERENCES

- Babudieri, B. (1961). *Bull. Wld Hlth Org.*, **24**, 45.
Galton, Mildred M., Menges, R. W., Shotts, E. B., jun., Nahmias, A. J., and Heath, C. W. (1962). *Leptospirosis: Epidemiology, Clinical*

- Manifestations in Man and Animals, and Methods in Laboratory Diagnosis*. United States Public Health Service Publication No. 951. Washington, D.C.
Gsell, O. (1966). *Ann. Soc. belge Méd. trop.*, **46**, 203.
Kocen, R. S. (1962). *Brit. med. J.*, **1**, 1181.
Mackay-Dick, J., and Robinson, J. F. (1957). *J. roy. Army med. Cps.*, **103**, 186.
Noguchi, H. (1928). In *The Newer Knowledge of Bacteriology and Immunology*, edited by E. O. Jordan and I. S. Falk, p. 485. Chicago.
Parish, H. J., and Cannon, D. A. (1961). In *Antisera, Toxoids, Vaccines and Tuberculin in Prophylaxis and Treatment*, 5th ed. Edinburgh.
Simpson, B., Cook, A. T., Dimond, A. H., Brown, M., and Thin, R. N. T. (1967). *Brit. med. J.*, **3**, 472.
Stimson, A. M. (1907). *Publ. Hlth Rep. (Wash.)*, **22**, 541.
Turner, L. H. (1967). *Trans. roy. Soc. trop. Med. Hyg.*, **61**, 842.
Turner, L. H. (1968). *Trans. roy. Soc. trop. Med. Hyg.*, **62**, 880.
World Health Organization (1967). *Wld Hlth Org. techn. Rep. Ser.*, No. 380.
Yager, R. H., Alexander, A. D., Gochenour, W. S., jun., Reinhard, K. R., Stavitsky, A. B., and Ward, M. K. (1963). In *Diagnostic Procedures and Reagents* 4th ed., p. 544. New York.

B.M.J. Publications

The following are available from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1. The prices include postage.

<i>The New General Practice</i> ...	Price 16s.
<i>B.M.J. Cumulative Index, 1967</i> ...	Price 30s.
(15s. to B.M.A. members)	
<i>Porphyria—a Royal Malady</i> ...	Price 13s. 6d.
<i>Is There an Alternative?</i> ...	Price 7s. 6d.
<i>Treatment of Common Skin Diseases</i> ...	Price 10s.
<i>Charles Hastings and Worcester</i> ...	Price 3s. 6d.

TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Vitamin P

In 1936 Szent-Györgyi described the properties of an extract of lemons which he named "citrin." He claimed that it could prolong the lives of animals dying of scurvy and markedly reduce their haemorrhagic symptoms. The active ingredient, which he also prepared from red peppers, was christened vitamin P ("in honour of permeability and paprika"), and it was thought that a petechial syndrome corresponding to deficiency of the new vitamin would soon be established; or possibly that scurvy would prove redefinable as a combined deficiency of vitamins C and P.

Subsequent experience failed to substantiate these suggestions. No condition representing lack of vitamin P has ever been satisfactorily demonstrated. The original preparation of citrin probably influenced the survival of scorbutic animals because of contaminating traces of ascorbic acid.

All compounds having vitamin P activity were soon identified as flavone derivatives; the title "vitamin P" has long been abandoned. Today the generic term "bioflavonoids" is universally accepted for these substances, of which at least two were probably present in Szent-Györgyi's original citrin. They are yellow pigments, extensively distributed in fruit and green leaves. Particularly high concentrations occur in blackcurrants, rose-hips, and citrus fruit. Rutin, hesperidin, and quercetin have been the most widely studied. All bioflavonoids show a tendency for the ring structure to open at a specific position, when chalcones are formed. These compounds, like ascorbic acid, act as powerful reducing agents. One theory maintains that flavonoids are active only after this conversion, and the soluble stable chalcone, hesperidin methyl chalcone, has been studied and used therapeutically.

Pharmacology

Though not essential for the normal function of capillary vessels the bioflavonoids can apparently affect their behaviour. How this influence is exerted and its magnitude are both disputed. After parenteral administration they have a weak vasoconstrictor action on the capillary bed; it has been suggested, but never convincingly demonstrated, that this is due to inhibition of adrenaline oxidation. In addition they decrease capillary permeability and fragility both under normal conditions and after damage by various physical and chemical agents. This effect may be secondary to vasoconstriction.

Miscellaneous other effects include partial inhibition of tissue inflammatory response and protection against the effects of anaphylaxis and histamine administration.

Clinical Applications

Ever since Szent-Györgyi claimed to have successfully treated a bleeding disorder with citrin there has been much interest in the possible therapeutic potential of the bioflavonoids. In 1967 the *American Drug Index* listed more than 70 proprietary preparations containing either rutin or hesperidin; this reflected the large number of therapeutic successes with bioflavonoids reported in the past 30 years. Unfortunately more scrupulous investigations have so frequently failed to justify initial optimism that there is today no clinical field in which drugs such as rutin and hesperidin are authoritatively recommended. The continued promotion of bioflavonoid derivatives makes it worth briefly reviewing past attempts to find a therapeutic niche for these drugs.